Royal College of
Obstetricians and Gynaecologists
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Ectopic pregnancy and miscarriage: Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage

December 2012

NICE Clinical Guideline

National Collaborating Centre for Women's and Children's Health

Update information

For the current recommendations, see the main version of the guideline at: www.nice.org.uk/guidance/NG126.

June 2026: We have reviewed the evidence and made new recommendations on anti-D immunoglobulin prophylaxis. These recommendations are marked **[2026]**.

In some cases, minor changes have been made to the guideline to bring the language and style up to date, without changing the meaning.

August 2023: We have reviewed the evidence and made new and updated recommendations on the medical management of miscarriage. These recommendations are marked **[2012, amended 2023]** or **[2023]**.

September 2022: We have corrected the references to anti-D immunoglobulin prophylaxis.

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National Collaborating Centre for Women's and Children's Health

Commissioned by the National Institute for Health and Clinical Excellence

December 2012

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This guideline has been fully funded by NICE. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.

Implementation of this guidance is the responsibility of local commissioners and/or providers.

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1 Guideline summary

1.1 Guideline development group membership, NCC-WCH staff and acknowledgements

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Wahab Bello, Julie Hodge Allen, Juliet Kenny, Edmund Peston and Wendy Riches at the NCC-WCH

1.2 Care pathway

A. Providing women with information and emotional support

Treat all women with early pregnancy complications with dignity and respect. Be aware that women will react to complications or the loss of a pregnancy in different ways. Provide all women with information and support in a sensitive manner, taking into account their individual circumstances and emotional response. (For further guidance about providing information, see Patient experience in adult NHS services [NICE clinical guidance 138, 2012]).

Healthcare professionals providing care for women with early pregnancy complications in any setting should be aware that early pregnancy complications can cause significant distress for some women and their partners. Healthcare professionals providing care for these women should be given training in how to communicate sensitively and breaking bad news. Non-clinical staff such as receptionists working in settings where early pregnancy care is provided should also be given training on how to communicate sensitively with women who experience early pregnancy complications.

Throughout a woman's care, give her and (with agreement) her partner specific, evidence-based information in a variety of formats. This should include (as appropriate):

- When and how to seek help if existing symptoms worsen or new symptoms develop, including a 24-hour contact telephone number.
- What to expect during the time she is waiting for an ultrasound scan.
- What to expect during the course of her care (including expectant management), such as the potential length and extent of pain and/or bleeding, and possible side effects. This information should be tailored to the care she receives.
- Information about the likely impact of her treatment on future fertility.
- Information about post-operative care (for women undergoing surgery).
- What to expect during the recovery period – for example, when it is possible to resume sexual activity and/or try to conceive again, and what to do if she becomes pregnant again. This information should be tailored to the care she receives.
- Where to access support and counselling services, including leaflets, web addresses and helpline numbers for support organisations.

Ensure that sufficient time is available to discuss these issues with women during the course of their care and arrange an additional appointment if more time is needed.

After an early pregnancy loss, offer the woman the option of a follow-up appointment with a healthcare professional of her choice.

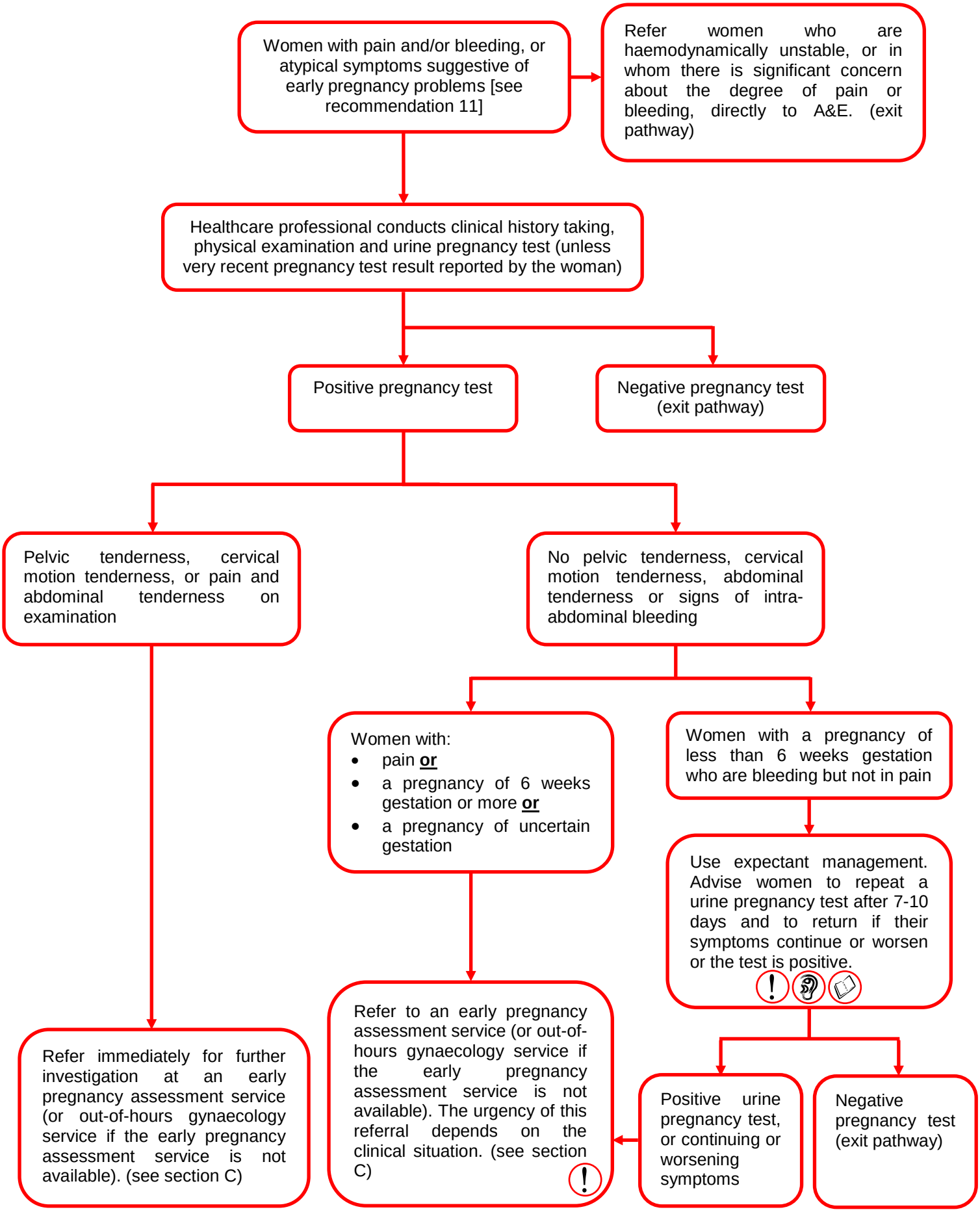
Throughout the care pathway, where these symbols appear, refer back to section A and provide women with information about:

Where to seek help in an emergency

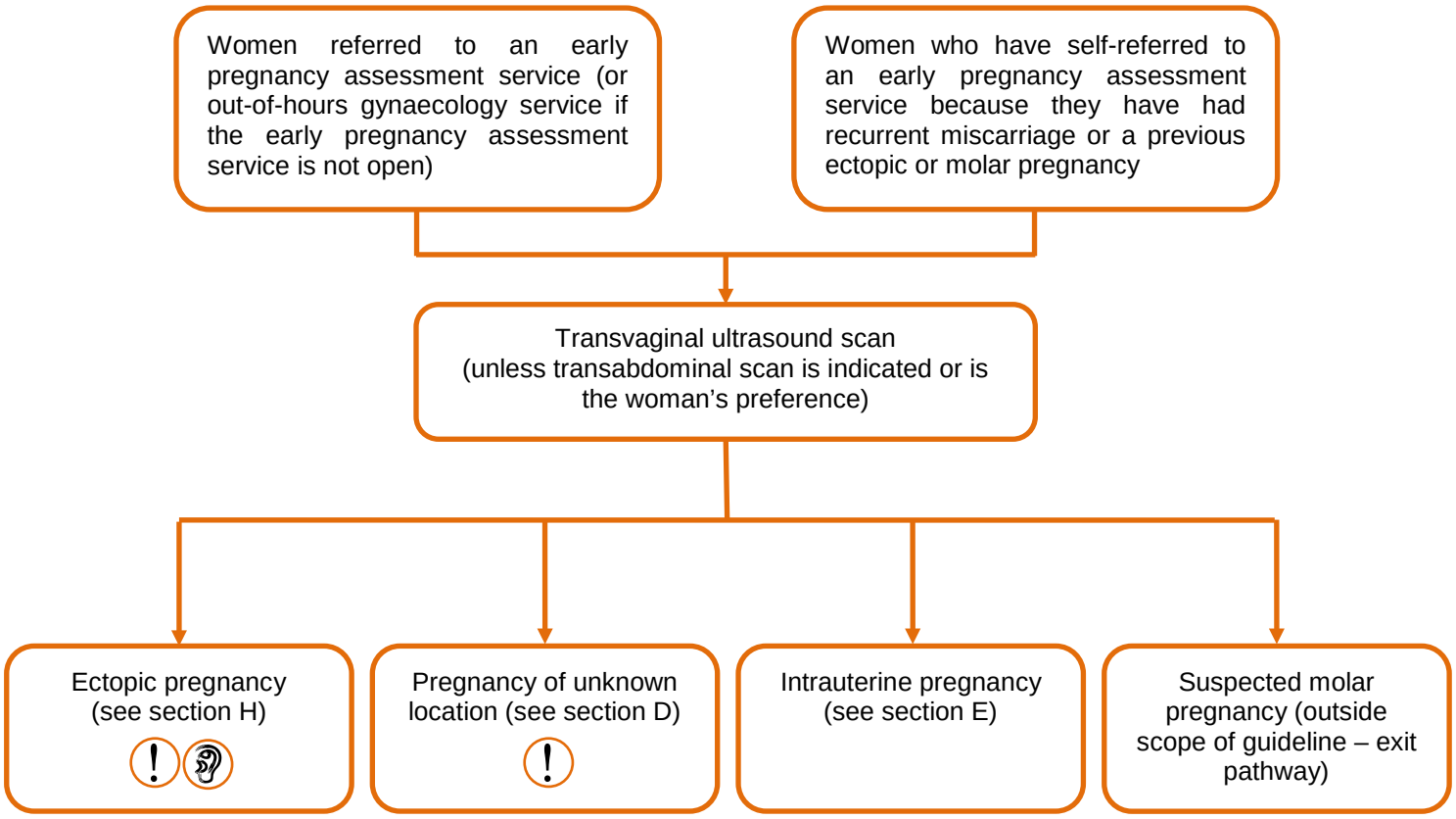
Where to access support and counselling services

The recovery period

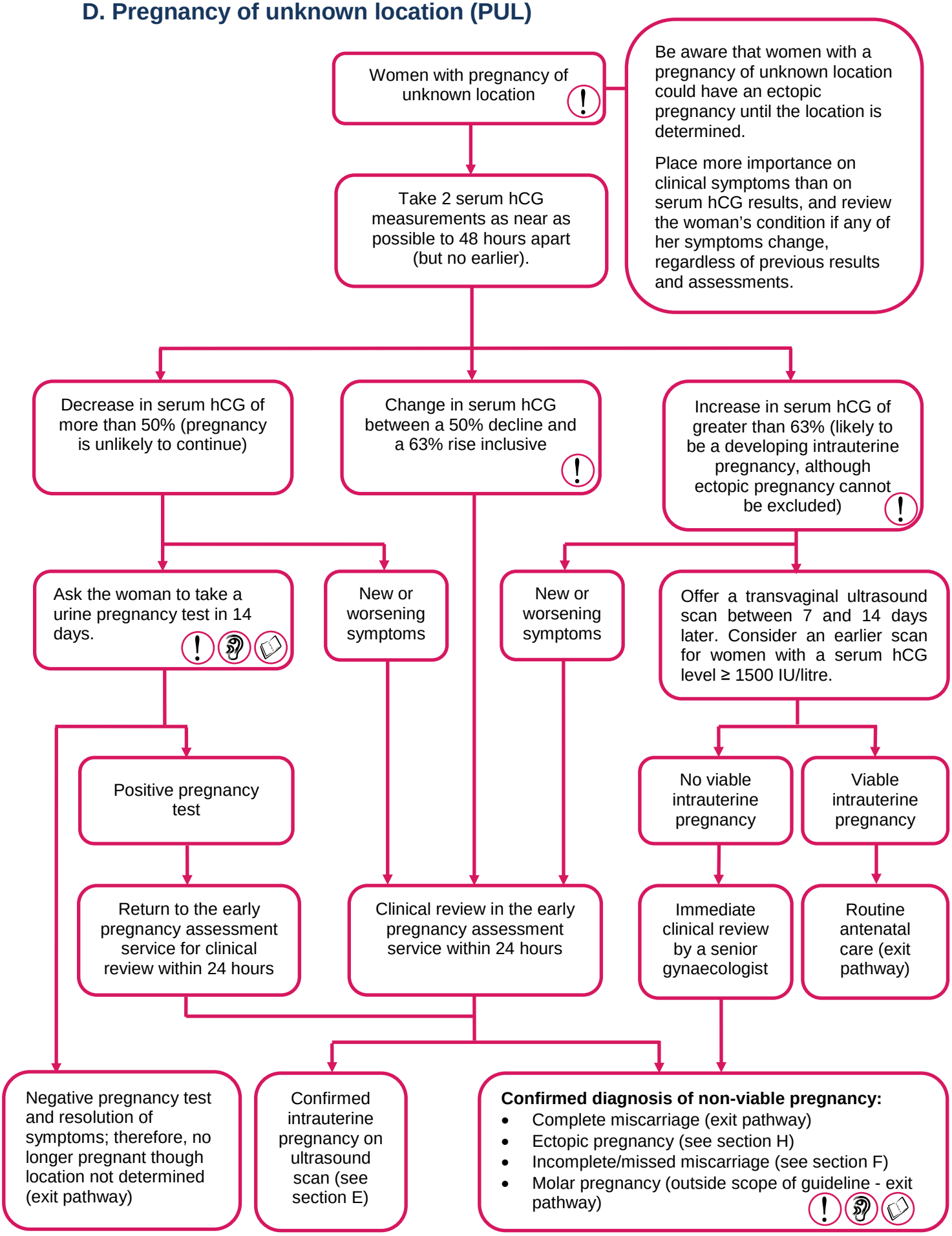
B. Initial clinical assessment



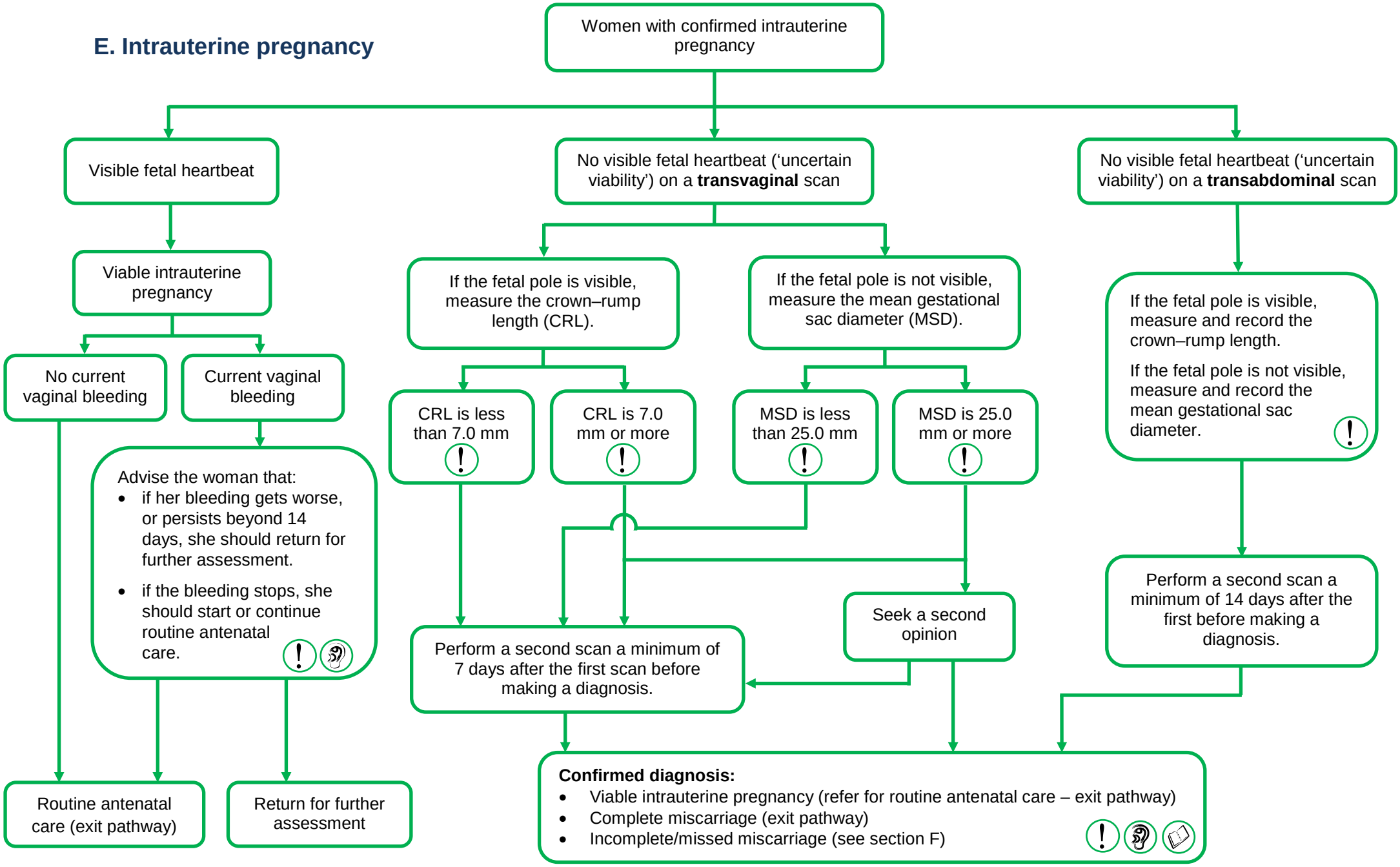
C. Initial ultrasound scan



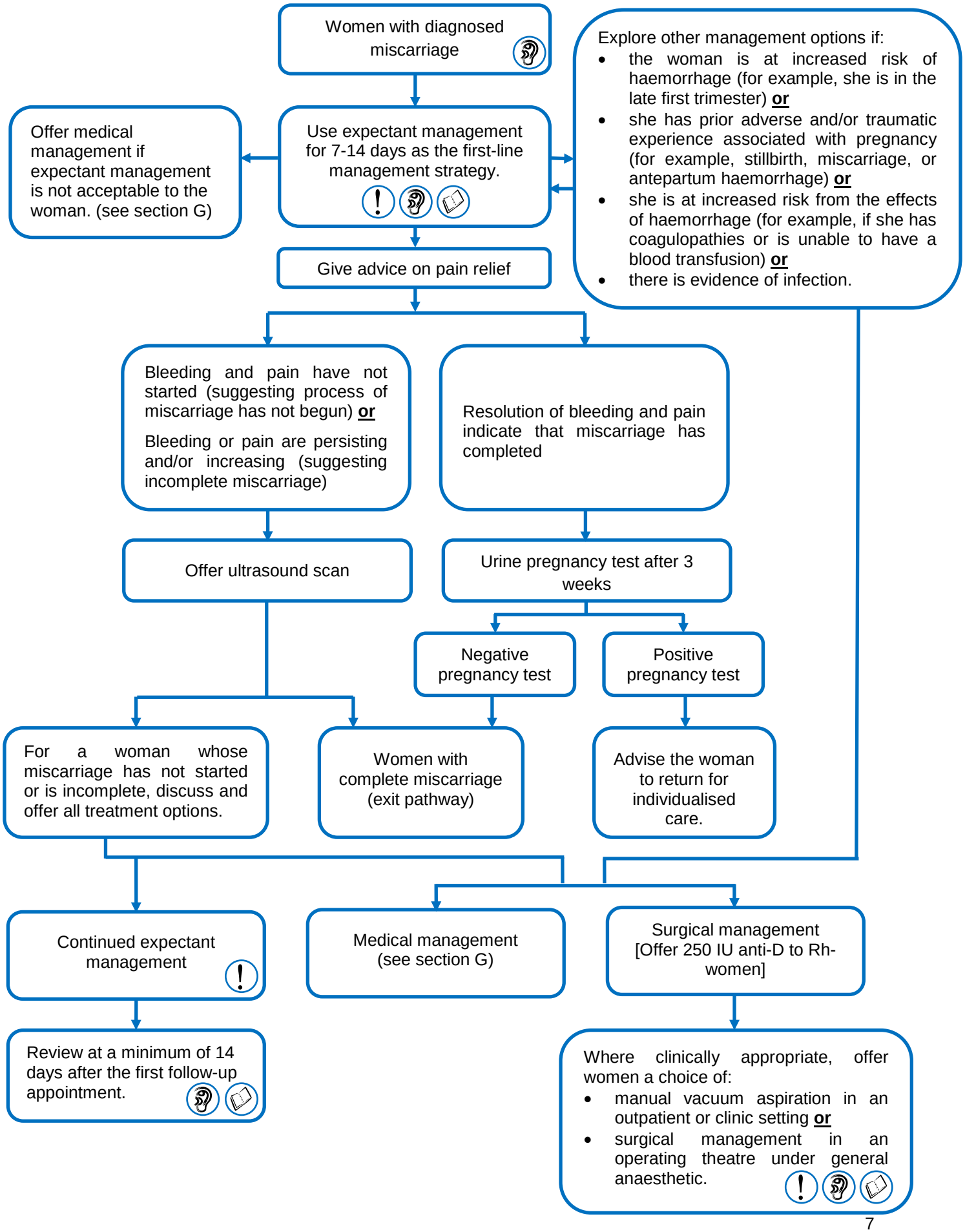
D. Pregnancy of unknown location (PUL)



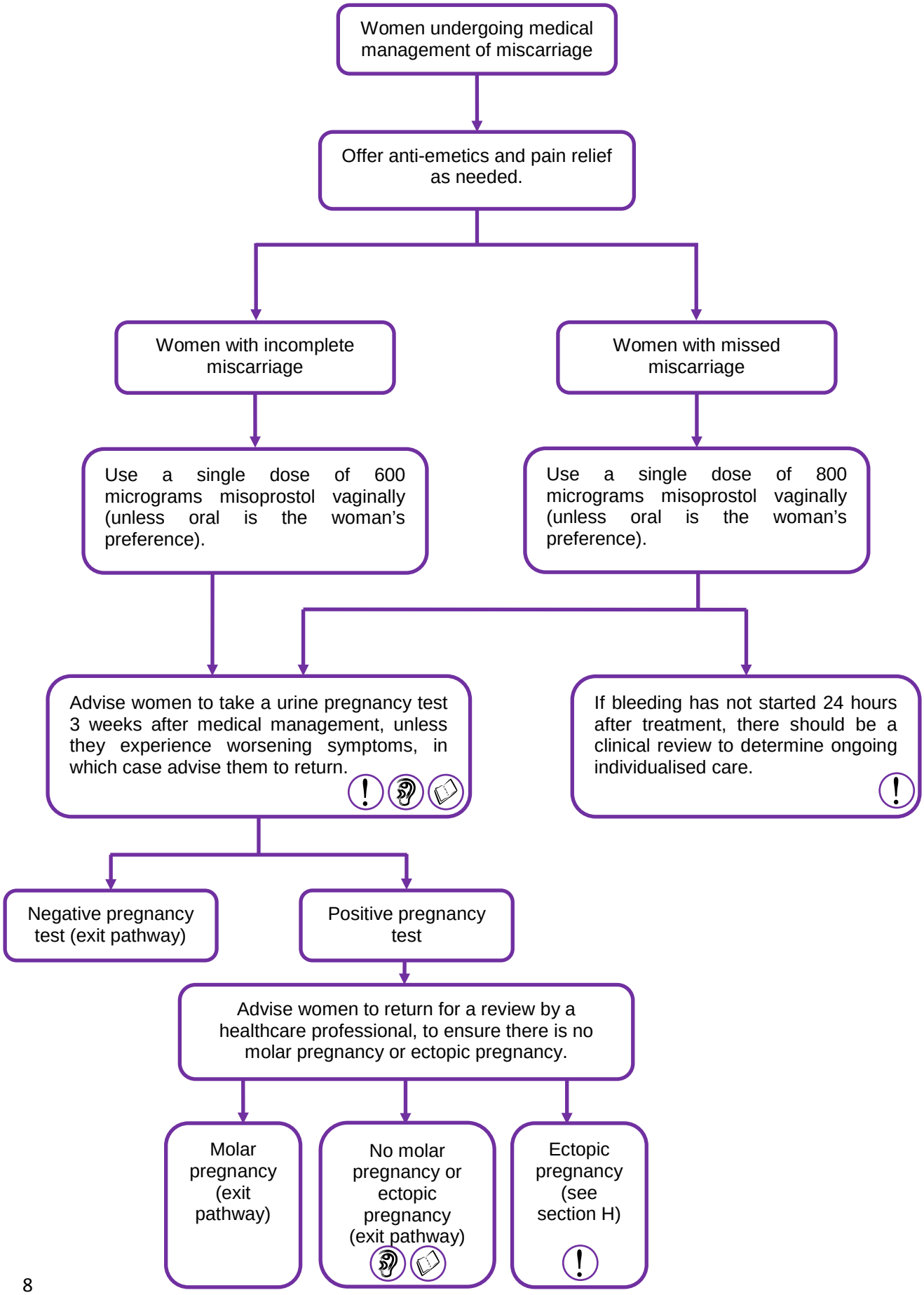
E. Intrauterine pregnancy



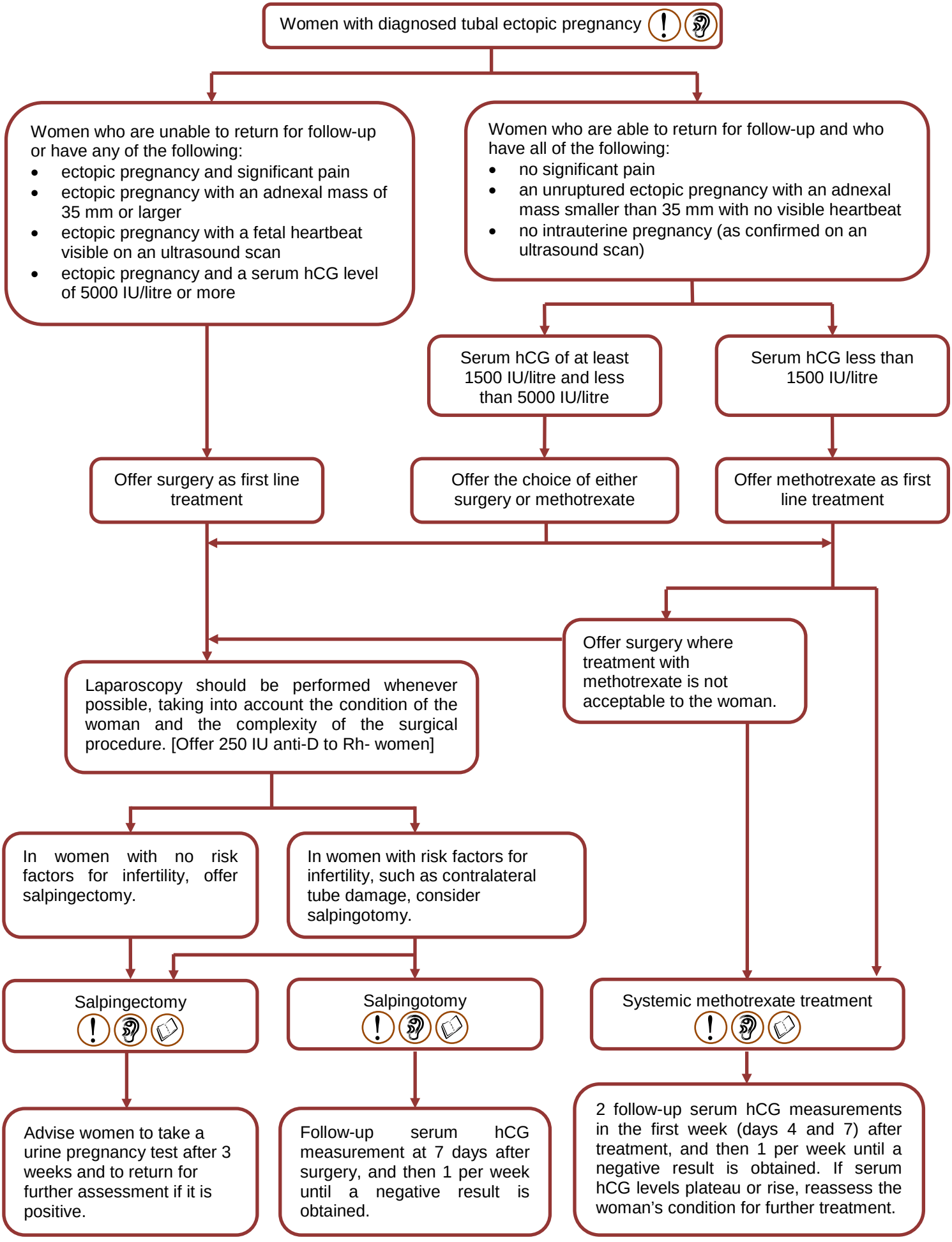
F. Management of miscarriage



G. Medical management of miscarriage



H. Ectopic pregnancy



This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. Many drugs do not have a license for use specifically in pregnant women, reflecting the fact that this group is often excluded from studies. Unlicensed drugs are indicated with a footnote.

1.3 Key priorities for implementation

Number	Recommendation	See section
	Emotional support and information giving	
3	Throughout a woman's care, give her and (with agreement) her partner specific evidence-based information in a variety of formats. This should include (as appropriate): • When and how to seek help if existing symptoms worsen or new symptoms develop, including a 24-hour contact telephone number. • What to expect during the time she is waiting for an ultrasound scan. • What to expect during the course of her care (including expectant management), such as the potential length and extent of pain and/or bleeding, and possible side effects. This information should be tailored to the care she receives. • Information about post-operative care (for women undergoing surgery). • What to expect during the recovery period – for example, when it is possible to resume sexual activity and/or try to conceive again, and what to do if she becomes pregnant again. This information should be tailored to the care she receives. • Information about the likely impact of her treatment on future fertility. • Where to access support and counselling services, including leaflets, web addresses and helpline numbers for support organisations. Ensure that sufficient time is available to discuss these issues with women during the course of their care and arrange an additional appointment if more time is needed.	4.2
	Early pregnancy assessment services	
5	Regional services should be organised so that an early pregnancy assessment service is available 7 days a week for women with early pregnancy complications, where scanning can be carried out and decisions about management made.	5.3
	Signs and symptoms of ectopic pregnancy	
13	During clinical assessment of women of reproductive age, be aware that: • they may be pregnant, and think about offering a pregnancy test even when symptoms are non-specific **and** • the symptoms and signs of ectopic pregnancy can resemble the common symptoms and signs of other conditions – for example, gastrointestinal conditions or urinary tract infection.	6.1

Number	Recommendation	See section
14	All healthcare professionals involved in the care of women of reproductive age should have access to pregnancy tests.	6.1
	Ultrasound for diagnosis	
21	Offer women who attend an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) a transvaginal ultrasound scan to identify the location of the pregnancy and whether there is a fetal pole and heartbeat.	6.3
	Human chorionic gonadotrophin measurements in women with pregnancy of unknown location	
38	Be aware that women with a pregnancy of unknown location could have an ectopic pregnancy until the location is determined.	6.7
	Management of miscarriage	
49	Use expectant management for 7–14 days as the first-line management strategy for women with a confirmed diagnosis of miscarriage. Explore management options other than expectant management if: • the woman is at increased risk of haemorrhage (for example, she is in the late first trimester) **or** • she has previous adverse and/or traumatic experience associated with pregnancy (for example, stillbirth, miscarriage or antepartum haemorrhage) **or** • she is at increased risk from the effects of haemorrhage (for example, if she has coagulopathies or is unable to have a blood transfusion) **or** • there is evidence of infection.	7.4
	Setting for surgical management of miscarriage	
65	Where clinically appropriate, offer women undergoing a miscarriage a choice of: • manual vacuum aspiration under local anaesthetic in an outpatient or clinic setting **or** • surgical management in a theatre under general anaesthetic.	7.6
	Performing laparoscopy	
73	When surgical treatment is indicated for women with an ectopic pregnancy, it should be performed laparoscopically whenever possible, taking into account the condition of the woman and the complexity of the surgical procedure.	8.3
	Salpingectomy and salpingotomy	
76	Offer a salpingectomy to women undergoing surgery for an ectopic pregnancy unless they have other risk factors for infertility.	8.4

1.4 Recommendations

Number	Recommendation	See section
	Emotional support and information giving	
1	Treat all women with early pregnancy complications with dignity and respect. Be aware that women will react to complications or the loss of a pregnancy in different ways. Provide all women with information and support in a sensitive manner, taking into account their individual circumstances and emotional response.*	4.2
2	Healthcare professionals providing care for women with early pregnancy complications in any setting should be aware that early pregnancy complications can cause significant distress for some women and their partners. Healthcare professionals providing care for these women should be given training in how to communicate sensitively and breaking bad news. Non-clinical staff such as receptionists working in settings where early pregnancy care is provided should also be given training on how to communicate sensitively with women who experience early pregnancy complications.	4.2
3	Throughout a woman's care, give her and (with agreement) her partner specific evidence-based information in a variety of formats. This should include (as appropriate): • When and how to seek help if existing symptoms worsen or new symptoms develop, including a 24-hour contact telephone number. • What to expect during the time she is waiting for an ultrasound scan. • What to expect during the course of her care (including expectant management), such as the potential length and extent of pain and/or bleeding, and possible side effects. This information should be tailored to the care she receives. • Information about post-operative care (for women undergoing surgery). • What to expect during the recovery period – for example, when it is possible to resume sexual activity and/or try to conceive again, and what to do if she becomes pregnant again. This information should be tailored to the care she receives. • Information about the likely impact of her treatment on future fertility. • Where to access support and counselling services, including leaflets, web addresses and helpline numbers for support organisations. Ensure that sufficient time is available to discuss these issues with women during the course of their care and arrange an additional appointment if more time is needed.	4.2
4	After an early pregnancy loss, offer the woman the option of a follow-up appointment with a healthcare professional of her choice.	4.2

* For further guidance about providing information, see Patient experience in adult NHS services (NICE clinical guidance 138)

Number	Recommendation	See section
	Early pregnancy assessment services	
5	Regional services should be organised so that an early pregnancy assessment service is available 7 days a week for women with early pregnancy complications, where scanning can be carried out and decisions about management made.	5.3
6	An early pregnancy assessment service should: • be a dedicated service provided by healthcare professionals competent to diagnose and care for women with pain and/or bleeding in early pregnancy **and** • offer ultrasound and assessment of serum human chorionic gonadotrophin (hCG) levels **and** • be staffed by healthcare professionals with training in sensitive communication and breaking bad news.	5.3
7	Early pregnancy assessment services should accept self-referrals from women who have had recurrent miscarriage† or a previous ectopic or molar pregnancy. All other women with pain and/or bleeding should be assessed by a healthcare professional (such as a GP, accident and emergency [A&E] doctor, midwife or nurse) before referral to an early pregnancy assessment service.	5.3
8	Ensure that a system is in place to enable women referred to their local early pregnancy assessment service to attend within 24 hours if the clinical situation warrants this. If the service is not available, and the clinical symptoms warrant further assessment, refer women to the nearest accessible facility that offers specialist clinical assessment and ultrasound scanning (such as a gynaecology ward or A&E service with access to specialist gynaecology support).	5.3
	Signs and symptoms of ectopic pregnancy	
9	Refer women who are haemodynamically unstable, or in whom there is significant concern about the degree of pain or bleeding, directly to A&E.	6.1
10	Be aware that atypical presentation for ectopic pregnancy is common.	6.1

11	Be aware that ectopic pregnancy can present with a variety of symptoms. Even if a symptom is less common, it may still be significant. Symptoms of ectopic pregnancy include:
	• common symptoms:
	  o abdominal or pelvic pain
	  o amenorrhoea or missed period
	  o vaginal bleeding with or without clots
	• other reported symptoms:
	  o breast tenderness
	  o gastrointestinal symptoms
	  o dizziness, fainting or syncope
	  o shoulder tip pain
	  o urinary symptoms
	  o passage of tissue
		6.1

† Although additional care for women with recurrent miscarriage is not included in the scope of the guideline, the Guideline Development Group recognised that it is common clinical practice to allow these women to self-refer to an early pregnancy assessment service and wished this to remain the case.

Number	Recommendation	See section
	o rectal pressure or pain on defecation.	
12	Be aware that ectopic pregnancy can present with a variety of signs on examination by a healthcare professional. Signs of ectopic pregnancy include: • more common signs: o pelvic tenderness o adnexal tenderness o abdominal tenderness • other reported signs: o cervical motion tenderness o rebound tenderness or peritoneal signs o pallor o abdominal distension o enlarged uterus o tachycardia (more than 100 beats per minute) or hypotension (less than 100/60 mmHg) o shock or collapse o orthostatic hypotension.	6.1
13	During clinical assessment of women of reproductive age, be aware that: • they may be pregnant, and think about offering a pregnancy test even when symptoms are non-specific **and** • the symptoms and signs of ectopic pregnancy can resemble the common symptoms and signs of other conditions – for example, gastrointestinal conditions or urinary tract infection.	6.1
14	All healthcare professionals involved in the care of women of reproductive age should have access to pregnancy tests.	6.1
15	Refer immediately to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) for further assessment women with a positive pregnancy test and the following on examination: • pain and abdominal tenderness **or** • pelvic tenderness **or** • cervical motion tenderness.	6.1
16	Exclude the possibility of ectopic pregnancy, even in the absence of risk factors (such as previous ectopic pregnancy), because about a third of women with an ectopic pregnancy will have no known risk factors.	6.1
17	Refer to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) women with bleeding or other symptoms and signs of early pregnancy complications who have: • pain **or** • a pregnancy of 6 weeks gestation or more **or** • a pregnancy of uncertain gestation. The urgency of this referral depends on the clinical situation.	6.1

Number	Recommendation	See section
18	Use expectant management for women with a pregnancy of less than 6 weeks gestation who are bleeding but not in pain. Advise these women: • to repeat a urine pregnancy test after 7–10 days and to return if it is positive • a negative pregnancy test means that the pregnancy has miscarried • to return if their symptoms continue or worsen.	6.1
19	Refer women who return with worsening symptoms and signs that could suggest an ectopic pregnancy to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) for further assessment. The decision about whether she should be seen immediately or within 24 hours will depend on the clinical situation.	6.1
20	If a woman is referred to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available), explain the reasons for the referral and what she can expect when she arrives there.	6.1
	Using ultrasound for diagnosis	
21	Offer women who attend an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) a transvaginal ultrasound scan to identify the location of the pregnancy and whether there is a fetal pole and heartbeat.	6.3
22	Consider a transabdominal ultrasound scan for women with an enlarged uterus or other pelvic pathology, such as fibroids or an ovarian cyst.	6.3
23	If a transvaginal ultrasound scan is unacceptable to the woman, offer a transabdominal ultrasound scan and explain the limitations of this method of scanning.	6.3
24	Inform women that the diagnosis of miscarriage using 1 ultrasound scan cannot be guaranteed to be 100% accurate and there is a small chance that the diagnosis may be incorrect, particularly at very early gestational ages.	6.3
25	When performing an ultrasound scan to determine the viability of an intrauterine pregnancy, first look to identify a fetal heartbeat. If there is no visible heartbeat but there is a visible fetal pole, measure the crown–rump length. Only measure the mean gestational sac diameter if the fetal pole is not visible.	6.3
26	If the crown–rump length is less than 7.0 mm with a transvaginal ultrasound scan and there is no visible heartbeat, perform a second scan a minimum of 7 days after the first before making a diagnosis. Further scans may be needed before a diagnosis can be made.	6.3

Number	Recommendation	See section
27	If the crown–rump length is 7.0 mm or more with a transvaginal ultrasound scan and there is no visible heartbeat: • seek a second opinion on the viability of the pregnancy **and/or** • perform a second scan a minimum of 7 days after the first before making a diagnosis.	6.3
28	If there is no visible heartbeat when the crown–rump length is measured using a transabdominal ultrasound scan: • record the size of the crown–rump length **and** • perform a second scan a minimum of 14 days after the first before making a diagnosis.	6.3
29	If the mean gestational sac diameter is less than 25.0 mm with a transvaginal ultrasound scan and there is no visible fetal pole, perform a second scan a minimum of 7 days after the first before making a diagnosis. Further scans may be needed before a diagnosis can be made.	6.3
30	If the mean gestational sac diameter is 25.0 mm or more using a transvaginal ultrasound scan and there is no visible fetal pole: • seek a second opinion on the viability of the pregnancy **and/or** • perform a second scan a minimum of 7 days after the first before making a diagnosis.	6.3
31	If there is no visible fetal pole and the mean gestational sac diameter is measured using a transabdominal ultrasound scan: • record the size of the mean gestational sac diameter **and** • perform a second scan a minimum of 14 days after the first before making a diagnosis.	6.3
32	Do not use gestational age from the last menstrual period alone to determine whether a fetal heartbeat should be visible.	6.3
33	Inform women that the date of their last menstrual period may not give an accurate representation of gestational age because of variability in the menstrual cycle.	6.3
34	Inform women what to expect while waiting for a repeat scan and that waiting for a repeat scan has no detrimental effects on the outcome of the pregnancy.	6.3
35	Give women a 24-hour contact telephone number so that they can speak to someone with experience of caring for women with early pregnancy complications who understands their needs and can advise on appropriate care.‡	6.3
36	When diagnosing complete miscarriage on an ultrasound scan, in the absence of a previous scan confirming an intrauterine pregnancy, always be aware of the possibility of ectopic pregnancy. Advise these women to return for further review if their symptoms persist.	6.3

‡ See also recommendation 3 for details of further information that should be provided.

Number	Recommendation	See section
37	All ultrasound scans should be performed and reviewed by someone with training in, and experience of, diagnosing ectopic pregnancies.	6.3
	Human chorionic gonadotrophin measurements in women with pregnancy of unknown location	
38	Be aware that women with a pregnancy of unknown location could have an ectopic pregnancy until the location is determined.	6.7
39	Do not use serum hCG measurements to determine the location of the pregnancy.	6.7
40	In a woman with a pregnancy of unknown location, place more importance on clinical symptoms than on serum hCG results, and review the woman's condition if any of her symptoms change, regardless of previous results and assessments.	6.7
41	Use serum hCG measurements only for assessing trophoblastic proliferation to help to determine subsequent management.	6.7
42	Take 2 serum hCG measurements as near as possible to 48 hours apart (but no earlier) to determine subsequent management of a pregnancy of unknown location. Take further measurements only after review by a senior healthcare professional.	6.7
43	Regardless of serum hCG levels, give women with a pregnancy of unknown location written information about what to do if they experience any new or worsening symptoms, including details about how to access emergency care 24 hours a day. Advise women to return if there are new symptoms or if existing symptoms worsen.	6.7

44	For a woman with an increase in serum hCG concentration greater than 63% after 48 hours:
	• Inform her that she is likely to have a developing intrauterine pregnancy (although the possibility of an ectopic pregnancy cannot be excluded).
	• Offer her a transvaginal ultrasound scan to determine the location of the pregnancy between 7 and 14 days later. Consider an earlier scan for women with a serum hCG level greater than or equal to 1500 IU/litre.
	  o If a viable intrauterine pregnancy is confirmed, offer her routine antenatal care§
	  o If a viable intrauterine pregnancy is not confirmed, refer her for immediate clinical review by a senior gynaecologist.
		6.7

45	For a woman with a decrease in serum hCG concentration greater than 50% after 48 hours: • inform her that the pregnancy is unlikely to continue but that this is not confirmed **and** • provide her with oral and written information about where she can access support and counselling services** **and**	6.7

§ See Antenatal care (NICE clinical guideline 62)
** See recommendation 3 for details of further information that should be provided

Number	Recommendation	See section
	• ask her to take a urine pregnancy test 14 days after the second serum hCG test, and explain that: o if the test is negative, no further action is necessary o if the test is positive, she should return to the early pregnancy assessment service for clinical review within 24 hours.	
46	For a woman with a change in serum hCG concentration between a 50% decline and 63% rise inclusive, refer her for clinical review in the early pregnancy assessment service within 24 hours.	6.7
47	For women with a pregnancy of unknown location, when using serial serum hCG measurements, do not use serum progesterone measurements as an adjunct to diagnose either viable intrauterine pregnancy or ectopic pregnancy.	6.7
	Threatened miscarriage	
48	Advise a woman with vaginal bleeding and a confirmed intrauterine pregnancy with a fetal heartbeat that: • if her bleeding gets worse, or persists beyond 14 days, she should return for further assessment • if the bleeding stops, she should start or continue routine antenatal care.	7.2
	Expectant management of miscarriage	
49	Use expectant management for 7–14 days as the first-line management strategy for women with a confirmed diagnosis of miscarriage. Explore management options other than expectant management if: • the woman is at increased risk of haemorrhage (for example, she is in the late first trimester) **or** • she has previous adverse and/or traumatic experience associated with pregnancy (for example, stillbirth, miscarriage or antepartum haemorrhage) **or** • she is at increased risk from the effects of haemorrhage (for example, if she has coagulopathies or is unable to have a blood transfusion) **or** • there is evidence of infection.	7.4
50	Offer medical management to women with a confirmed diagnosis of miscarriage if expectant management is not acceptable to the woman.	7.4
51	Explain what expectant management involves and that most women will need no further treatment. Also provide women with oral and written information about further treatment options.	7.4
52	Give all women undergoing expectant management of miscarriage oral and written information about what to expect throughout the process, advice on pain relief and where and when to get help in an emergency.[††]	7.4

†† See also recommendation 3 for details of further information that should be provided.

Number	Recommendation	See section
53	If the resolution of bleeding and pain indicate that the miscarriage has completed during 7–14 days of expectant management, advise the woman to take a urine pregnancy test after 3 weeks, and to return for individualised care if it is positive.	7.4
54	Offer a repeat scan if after the period of expectant management the bleeding and pain: • have not started (suggesting that the process of miscarriage has not begun) **or** • are persisting and/or increasing (suggesting incomplete miscarriage). Discuss all treatment options (continued expectant management, medical management, and surgical management) with the woman to allow her to make an informed choice.	7.4
55	Review the condition of a woman who opts for continued expectant management of miscarriage at a minimum of 14 days after the first follow-up appointment.	7.4
	Medical management of miscarriage	
56	Do not offer mifepristone as a treatment for missed or incomplete miscarriage.	7.5
57	Offer vaginal misoprostol for the medical treatment of missed or incomplete miscarriage. Oral administration is an acceptable alternative if this is the woman's preference.[‡‡]	7.5
58	For women with a missed miscarriage, use a single dose of 800 micrograms of misoprostol.[‡‡]	7.5
59	Advise the woman that if bleeding has not started 24 hours after treatment, she should contact her healthcare professional to determine ongoing individualised care.	7.5
60	For women with an incomplete miscarriage, use a single dose of 600 micrograms of misoprostol. (800 micrograms can be used as an alternative to allow alignment of treatment protocols for both missed and incomplete miscarriage.)[‡‡]	7.5
61	Offer all women receiving medical management of miscarriage pain relief and anti-emetics as needed.	7.5
62	Inform women undergoing medical management of miscarriage about what to expect throughout the process, including the length and extent of bleeding and the potential side effects of treatment including pain, diarrhoea and vomiting.	7.5
63	Advise women to take a urine pregnancy test 3 weeks after medical management of miscarriage unless they experience worsening symptoms, in which case advise them to return to the healthcare professional responsible for providing their medical management.	7.5

[‡‡] Although this use is common in UK clinical practice, at the time of publication (December 2012), misoprostol did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Number	Recommendation	See section
64	Advise women with a positive urine pregnancy test after 3 weeks to return for a review by a healthcare professional to ensure that there is no molar or ectopic pregnancy.	7.5
	Surgical management of miscarriage	
65	Where clinically appropriate, offer women undergoing a miscarriage a choice of: • manual vacuum aspiration under local anaesthetic in an outpatient or clinic setting **or** • surgical management in a theatre under general anaesthetic.	7.6
66	Provide oral and written information to all women undergoing surgical management of miscarriage about the treatment options available and what to expect during and after the procedure.[§§]	7.6
	Surgical and medical management of ectopic pregnancy	
67	Inform women who have had an ectopic pregnancy that they can self-refer to an early pregnancy assessment service in future pregnancies if they have any early concerns.	8.2
68	Give all women with an ectopic pregnancy oral and written information about: • how they can contact a healthcare professional for post-operative advice if needed, and who this will be **and** • where and when to get help in an emergency.[§§]	8.2
69	Offer systemic methotrexate[***] as a first-line treatment to women who are able to return for follow-up and who have all of the following: • no significant pain • an unruptured ectopic pregnancy with an adnexal mass smaller than 35 mm with no visible heartbeat • a serum hCG level less than 1500 IU/litre • no intrauterine pregnancy (as confirmed on an ultrasound scan). Offer surgery where treatment with methotrexate is not acceptable to the woman.	8.2
70	Offer surgery as a first-line treatment to women who are unable to return for follow-up after methotrexate treatment or who have any of the following: • an ectopic pregnancy and significant pain • an ectopic pregnancy with an adnexal mass of 35 mm or larger • an ectopic pregnancy with a fetal heartbeat visible on an ultrasound scan • an ectopic pregnancy and a serum hCG level of	8.2

[§§] See also recommendation 3 for details of further information that should be provided.

[***] Although this use is common in UK clinical practice, at the time of publication (December 2012), methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Number	Recommendation	See section
	5000 IU/litre or more.	
71	Offer the choice of either methotrexate[†††] or surgical management to women with an ectopic pregnancy who have a serum hCG level of at least 1500 IU/litre and less than 5000 IU/litre, who are able to return for follow-up and who meet all of the following criteria: • no significant pain • an unruptured ectopic pregnancy with an adnexal mass smaller than 35 mm with no visible heartbeat • no intrauterine pregnancy (as confirmed on an ultrasound scan). Advise women who choose methotrexate that their chance of needing further intervention is increased and they may need to be urgently admitted if their condition deteriorates.	8.2
72	For women with ectopic pregnancy who have had methotrexate, take 2 serum hCG measurements in the first week (days 4 and 7) after treatment and then 1 serum hCG measurement per week until a negative result is obtained. If hCG levels plateau or rise, reassess the woman's condition for further treatment.	8.2
	Performing laparoscopy	
73	When surgical treatment is indicated for women with an ectopic pregnancy, it should be performed laparoscopically whenever possible, taking into account the condition of the woman and the complexity of the surgical procedure.	8.3
74	Surgeons providing care to women with ectopic pregnancy should be competent to perform laparoscopic surgery.	8.3
75	Commissioners and managers should ensure that equipment for laparoscopic surgery is available.	8.3
	Salpingectomy and salpingotomy	
76	Offer a salpingectomy to women undergoing surgery for an ectopic pregnancy unless they have other risk factors for infertility.	8.4
77	Consider salpingotomy as an alternative to salpingectomy for women with risk factors for infertility such as contralateral tube damage.	8.4
78	Inform women having a salpingotomy that up to 1 in 5 women may need further treatment. This treatment may include methotrexate and/or a salpingectomy.	8.4
79	For women who have had a salpingotomy, take 1 serum hCG measurement at 7 days after surgery, then 1 serum hCG measurement per week until a negative result is obtained.	8.4
80	Advise women who have had a salpingectomy that they should take a urine pregnancy test after 3 weeks. Advise women to return for further assessment if the test is positive.	8.4

[†††] Although this use is common in UK clinical practice, at the time of publication (December 2012), methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Number	Recommendation	See section
	Anti-D rhesus prophylaxis	
81	Offer anti-D rhesus prophylaxis at a dose of 250 IU (50 micrograms) to all rhesus negative women who have a surgical procedure to manage an ectopic pregnancy or a miscarriage.	9.3
82	Do not offer anti-D rhesus prophylaxis to women who: • receive solely medical management for an ectopic pregnancy or miscarriage **or** • have a threatened miscarriage **or** • have a complete miscarriage **or** • have a pregnancy of unknown location.	9.3
83	Do not use a Kleihauer test for quantifying feto–maternal haemorrhage.	9.3

1.5 Key research recommendations

Number	Research recommendation	See section
	Early pregnancy assessment units	
RR 2	A national evaluation of early pregnancy assessment unit service provision should be carried out to identify factors affecting outcomes. Factors should include whether care is provided in a dedicated unit, staffing configuration and opening hours of dedicated services. Outcomes should include both process (service) outcomes and pregnancy-related outcomes. Data collected should be used to analyse the cost effectiveness of early pregnancy assessment units compared with other models of care. Why this is important The first report of an early pregnancy assessment unit in England was published over 20 years ago, and prompted the rapid development of centres for the management of problems in early pregnancy. Today there are an estimated 150 early pregnancy assessment units in England and Wales (Association of Early Pregnancy Units, 2012). However, there is considerable variation between centres in access to services and levels of care provided. In addition, there has been very little good quality research on the effectiveness of early pregnancy assessment units in improving physical and emotional health compared with services provided outside of a dedicated unit. A national audit of early pregnancy assessment services would help to make up for this lack of information. Such an audit should be along the lines of the National Caesarean Section Sentinel Audit, a cross-sectional national survey of service configuration and outcomes. Data recorded would include service location, opening hours and the healthcare professionals involved. Outcomes would include time of attendance, length of stay, admission rates, time to treatment and women's experience.	5.3

Number	Research recommendation	See section
	Obtaining some of this information would involve early pregnancy services carrying out more formal follow-up of women than they may do currently, for the duration of the audit. The evaluation should be structured to allow for comparisons between different models of care. Comparative outcome data collected would be used to conduct an analysis of the cost effectiveness of early pregnancy assessment units compared with other models of care.	
	Ultrasound for determining a viable intrauterine pregnancy	
RR 4	How does the timing and frequency of ultrasound examination affect diagnosis and outcomes of early pregnancy complications, including women's experience and cost effectiveness? Why this is important The rationale behind the frequency of ultrasound to improve diagnosis and outcomes of early pregnancy complications addresses the problems associated with pregnancy of unknown location and intrauterine pregnancy of uncertain viability. The evidence base for the timing and frequency of scanning in early pregnancy is limited, and the number of scans is organised by individual units according to capacity and demand. Some healthcare professionals choose to wait 5 days between scans whereas others will wait 10 to 14 days. These decisions are driven by resource availability as well as clinical considerations, but in particular the effect of different strategies on cost and women's experience is not clear. The literature suggests that there is no clear consensus, but there is general agreement that by 14 days a diagnosis will be clear. To establish the most appropriate time for scans, the efficacy of scans taken after 14 days could be compared with scans taken after 7 days for diagnosis of ectopic pregnancy or viability.	6.3
	Progesterone/progestogen for threatened miscarriage	
RR 5	Are progesterone or progestogens effective in treating threatened miscarriage? Why this is important Approximately 20% of pregnancies miscarry in the first trimester and many women will experience some bleeding and/or pain in early pregnancy that does not cause miscarriage. In many countries, women with bleeding and/or pain will be treated with progesterone or progestogens to try and decrease the risk of miscarriage. The evidence for the effectiveness of this treatment has been inconclusive, but data from a meta-analysis of several small studies suggest that progestogens are better than placebo. However, there are theoretical risks to prescribing any treatment in pregnancy and for many practitioners this will be a major	7.2

Number	Research recommendation	See section
	change in practice. The lack of strong evidence makes this a priority area for research. A very large multicentre randomised controlled trial of women treated with either progesterone/progestogen or placebo should be conducted. The trial should be large enough so that it is sufficiently powered to detect differences in long-term outcomes. The population would be women with pain and bleeding and a spontaneous, confirmed, viable, singleton, intrauterine pregnancy between 6 and 12 weeks gestation. Progesterone/progestogen or placebo would be administered from when bleeding starts until the end of the 13th week. Pregnancy proceeding beyond the end of the first trimester might be the primary outcome. Live birth should also be measured, as well as pregnancy outcome, gestation at birth and presence of congenital abnormalities.	
	Management of miscarriage	
RR 6	In women with confirmed miscarriage, does the type of management strategy (expectant, medical and surgical) impact on women's experience, including psychological and emotional outcomes? Why this is important The management of miscarriage in the UK has changed in many ways over the past 2 decades, particularly in the shift from inpatient to outpatient or day case care and the introduction of medical and expectant management as alternatives to surgery. Despite these changes there is a lack of research into the effects of these different approaches from the woman's perspective, in particular their psychological and emotional impact. Miscarriage is distressing for most women, and the type of management itself might affect women's need for counselling, with a resulting cost to the NHS. Because of this it is an important area for research. The deficiency in the literature could be addressed by a comparative study of women having the different management strategies (expectant, medical or surgical) and in a variety of clinical settings (for example, early pregnancy assessment unit, gynaecological ward or gynaecological emergency unit). The data collected could be both quantitative (using validated psychological health questionnaires) and qualitative (focusing particularly on women's experience of the particular type and setting of care).	7.4
	Surgical compared with medical management of ectopic pregnancy	
RR 8	In women with ectopic pregnancy, does the type of intervention (laparoscopy or medical management) impact on women's experience, including psychological and emotional outcomes? Why this is important	8.2

Number	Research recommendation	See section
	Currently there is no evidence exploring the psychological impact of the different treatments for ectopic pregnancy. However, the emotional impact of the condition can be significant, in some circumstances leading to post-traumatic stress disorder. A qualitative comparative study should be carried out to assess how this impact can be reduced. This would help to maximise women's emotional recovery in the short and long term, enable women and clinicians to decide the optimum treatment method and identify what support is needed for women during and after the process. It could also reduce the cost to the NHS of providing long-term counselling for affected women.	

1.6 Research recommendations

Number	Research recommendation	See section
	Psychological support	
RR 1	What interventions improve emotional and psychological outcomes for women following ectopic pregnancy?	4.2
	Early pregnancy assessment units	
RR 2	A national evaluation of early pregnancy assessment unit service provision should be carried out to identify factors affecting outcomes. Factors should include whether care is provided in a dedicated unit, staffing configuration and opening hours of dedicated services. Outcomes should include both process (service) outcomes and pregnancy-related outcomes. Data collected should be used to analyse the cost effectiveness of early pregnancy assessment units compared with other models of care.	5.3
	Signs and symptoms of ectopic pregnancy	
RR 3	Research should be undertaken to design and validate a decision tool for evaluating signs, symptoms and risk factors for correctly identifying ectopic pregnancy	6.1
	Ultrasound for determining a viable intrauterine pregnancy	
RR 4	How does the timing and frequency of ultrasound examination affect diagnosis and outcomes of early pregnancy complications, including women's experience and cost effectiveness?	6.3
	Progesterone for threatened miscarriage	
RR 5	Are progesterone or progestogens effective in treating threatened miscarriage?	7.2
	Management of miscarriage	
RR 6	In women with confirmed miscarriage, does the type of management strategy (expectant, medical and surgical) impact on women's experience, including psychological and emotional	7.4

Number	Research recommendation	See section
	outcomes?	
	Misoprostol and mifepristone for managing miscarriage	
RR 7	Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of miscarriage?	7.5
	Surgical compared with medical management of ectopic pregnancy	
RR 8	In women with ectopic pregnancy, does the type of intervention (laparoscopy or medical management) impact on women's experience, including psychological and emotional outcomes?	8.2
	Anti-D rhesus prophylaxis	
RR 9	Does the administration of anti-D rhesus prophylaxis following pain and bleeding in early pregnancy improve outcomes? Outcomes should include rhesus sensitisation in the woman attributable to the early pregnancy event and morbidity related to rhesus disease in subsequent unborn and newborn babies.	9.3

1.7 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 3 years from the date of publication. Reviewing may begin before 3 years have elapsed if significant evidence that affects guideline recommendations is identified sooner.

2 Introduction

2.1 Early pregnancy complications

Ectopic pregnancy and miscarriage have an adverse effect on the quality of life of many women. Approximately 20% of pregnancies end in miscarriage and these miscarriages can cause considerable distress. Early pregnancy loss accounts for over 50,000 admissions in the UK annually (The Health and Social Care Information Centre, 2012). The rate of ectopic pregnancy is 11 per 1000 pregnancies, with a maternal mortality of 0.2 per 1000 estimated ectopic pregnancies (Cantwell et al., 2011). About two-thirds of these deaths are associated with substandard care. Women who do not access medical help readily (such as women who are recent migrants, asylum seekers or refugees, or women who have difficulty reading or speaking English) are particularly vulnerable. Improvement in the diagnosis and management of early pregnancy loss is thus of vital importance, in order to reduce the incidence of the associated psychological morbidity and avoid the unnecessary deaths of women with ectopic pregnancies.

Women with early pregnancy complications will often seek guidance and help from their GPs or from services within secondary care. These services can include accident and emergency departments or dedicated early pregnancy assessment units (EPAUs). Accessibility of the latter varies from region to region, with wide variation in service provision in terms of staffing structure, opening hours and acceptability of self-referral. Provision of an EPAU is a requirement of the National Service Framework for children, young people and maternity care. However, there has been little discussion on the cost effectiveness of EPAUs and it is not known whether they improve outcomes for women with early pregnancy complications.

The guideline covers diagnosis of early pregnancy loss, including the use of ultrasound scanning and biochemical testing. Investigations incur costs and the use of serial measurements may delay decision making. The guideline includes guidance on when senior and/or specialist advice should be sought in order to avoid errors and unnecessary delay.

Treatment for threatened miscarriage has been offered by many clinicians over the years, although it is not freely available to all women. Even though progesterone/progestogen is not licensed for this purpose in the UK, it is commonly prescribed in many countries. The guideline examines the evidence for the risks and benefits of this treatment.

The clinical and cost effectiveness of expectant, surgical and medical management for miscarriage and surgical and medical treatment of ectopic pregnancy are considered, with reviews looking at both the risks and benefits of each strategy in terms of clinical and psychological outcomes. Cost effectiveness is an extremely important component of any guideline, in order to ensure that the limited resources of the National Health Service are used to maximise health benefits for its users. The final advice and selection of first line treatment takes this into account.

The guideline does not cover pregnancy after the first trimester (after 12 completed weeks of pregnancy). It also does not deal with unusual conditions that present with pain and bleeding, such as hydatidiform mole, which require a different form of treatment. Similarly, it does not consider recurrent miscarriage, as this requires more specific investigation and management.

2.2 For whom is this guideline intended

This guidance is of relevance to those who work in or use the National Health Service (NHS) in England and Wales, in particular:

- GPs and primary care professionals who may encounter pregnant women in the course of their professional duties, for example adult mental health professionals
- healthcare professionals working in accident and emergency departments
- professional groups who are routinely involved in the care of pregnant women, especially early pregnancy care
- those responsible for commissioning and planning healthcare services.

In addition, this guidance may be of relevance to professionals working in social services and education/childcare settings.

2.3 Related NICE guidance

Published guidance

- Antenatal and postnatal mental health. NICE clinical guideline 45 (2007).
- Antenatal care. NICE clinical guideline 62 (2008).
- Diabetes in pregnancy. NICE clinical guideline 63 (2008).
- Fertility. NICE clinical guideline 11 (2004).
- Hypertension in pregnancy. NICE clinical guideline 107 (2010).
- Pregnancy and complex social factors. NICE clinical guideline 110 (2010).
- Routine antenatal anti-D prophylaxis for women who are rhesus D negative. NICE technology appraisal guidance 156 (2008).
- Surgical site infection. NICE clinical guideline 74 (2008).
- Venous thromboembolism – reducing the risk. NICE clinical guideline 92 (2010).
- Patient experience in adult NHS services: improving the experience of care for people using adult NHS services. NICE clinical guidance 138 (2012).

Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Diabetes in pregnancy (update). NICE clinical guideline. Publication date to be confirmed.
- Fertility (update). NICE clinical guideline. Publication date to be confirmed.

3 Guideline development methodology

3.1 Introduction

This guidance was commissioned by NICE and developed in accordance with the guideline development process outlined in the 2009 edition of The Guidelines Manual.

In accordance with NICE's Equality Scheme, ethnic and cultural considerations and factors relating to disabilities have been considered by the guideline development group (GDG) throughout the development process and specifically addressed in individual recommendations where relevant. Further information is available from:
http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp

3.2 Developing review questions and protocols and identifying evidence

The GDG formulated review questions based on the scope (see Appendix A) and prepared a protocol for each review question (see Appendix D). These formed the starting point for systematic reviews of relevant evidence. Published evidence was identified by applying systematic search strategies (see Appendix E) to the following databases: Medline (1950 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards) and three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects). Searches to identify economic studies were undertaken using the above databases, the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database. Four of the 14 searches were limited by date appropriate to the interventions being considered (questions relating to biochemical and ultrasound diagnosis of miscarriage, effectiveness of early pregnancy assessment units and treatment setting for management of miscarriage – see protocols in Appendix D for details). The searches were limited by language of publication (publications in languages other than English were not reviewed). Generic and specially developed search filters were used to identify particular study designs, such as randomised controlled trials (RCTs). There was no systematic attempt to search grey literature (conference abstracts, theses or unpublished trials), nor was hand searching of journals not indexed on the databases undertaken.

For four of the review topics a joint search strategy was developed and run to cover more than one question within that topic. The databases of identified titles and abstracts were then 'weeded' and papers allocated to their individual question before further weeding. This was carried out for the two ultrasound reviews, the four reviews on human chorionic gonadotrophin and progesterone for diagnosing early pregnancy loss, three reviews on the management of miscarriage (expectant compared with active management, medical compared with surgical management, and dose of mifepristone and misoprostol) and two reviews on anti-D rhesus prophylaxis. Following weeding within each individual question full text versions of remaining studies were ordered. Each full text version was then assessed for inclusion/exclusion against pre-defined criteria as detailed in the protocol. Flow diagrams detailing these processes for each question can be found in Appendix F and details of excluded studies in Appendix G.

Towards the end of the guideline development process, the searches were updated and re-executed to include evidence published and indexed in the databases by 8 February 2012.

3.3 Reviewing and synthesising evidence

Evidence relating to clinical effectiveness was reviewed and synthesised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In the GRADE approach, the quality of the evidence identified for each outcome listed in the review protocol is assessed according to the factors listed below, and an overall quality rating (high, moderate, low or very low) is assigned by combining the ratings for the individual factors.

- Study design (as an indicator of intrinsic bias; this determines the initial quality rating).
- Limitations in the design or execution of the study including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating).
- Inconsistency of effects across studies: occurs when there is variability in the treatment effect demonstrated across studies (heterogeneity) (this can reduce the quality rating).
- Indirectness: the extent to which the available evidence fails to address the specific review question (this can reduce the quality rating).
- Imprecision: present when there is uncertainty around the estimate of effect, for example when the confidence intervals are wide or the sample size or event rate is low (this can reduce the quality rating).
- Other considerations including large magnitude of effect, evidence of a dose-response relationship, or confounding variables likely to have reduced the magnitude of an effect (these can increase the quality rating in observational studies, provided no downgrading for other features has occurred).

The type of review question determines the highest level of evidence that may be sought. For issues of therapy or treatment, the highest possible evidence level is a well-conducted systematic review or meta-analysis of randomised controlled trials (RCTs), or an individual RCT. In the GRADE approach, a body of evidence based entirely on such studies has an initial quality rating of high, and this may be downgraded to moderate, low or very low if factors listed above are not addressed adequately. For issues of prognosis, the highest possible level of evidence is a controlled observational study (a cohort study or case–control study), and a body of evidence based on such studies would have an initial quality rating of low, which might be downgraded to very low or upgraded to moderate or high, depending on the factors listed above.

For each review question the highest available level of evidence was sought. Where appropriate, for example, if a systematic review of RCTs or individual RCTs were identified to answer a question directly, studies of a weaker design were not considered. Where systematic reviews of RCTs or RCTs were not identified, other appropriate experimental or observational studies were sought. For the priority outcome of women's experience of care and psychological outcomes, qualitative studies were sought where appropriate. For diagnostic tests, test evaluation studies examining the performance of the test were used if the accuracy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of the condition was required, evidence from RCTs or cohort studies was optimal. For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratios for positive and negative test results (LR+ and LR–, respectively) were calculated or quoted where possible (see Table 3.1).

The GRADE system described above covers studies of treatment effectiveness. However, it is less well established for studies reporting accuracy of diagnostic tests. For such studies, NICE recommends using the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) methodology checklist to assess study quality (see the NICE guidelines manual, 2009).

Some studies were excluded from the guideline reviews after obtaining copies of the corresponding publications because they did not meet inclusion criteria specified by the GDG (see Appendix G). The characteristics of each included study were summarised in evidence tables for each review question (see Appendix H). Where possible, dichotomous outcomes were presented as risk ratios (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), and continuous outcomes were presented as mean differences with 95% CIs or standard deviations (SDs).

The body of evidence identified for each review question (or part of a review question) was presented in the form of a GRADE evidence profile summarising the quality of the evidence and the findings (pooled relative and absolute effect sizes and associated CIs). Summary GRADE tables have been reported in the main text, with the full GRADE evidence profiles reported in Appendix I. Where possible, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled RRs, pooled ORs or weighted mean differences. By default, meta-analyses were conducted by fitting fixed effects models, but where statistically significant heterogeneity was identified random effects models were used. Where quantitative meta-analysis could not be undertaken (for example because of heterogeneity in the included studies or where studies were not RCTs) the range of effect sizes reported in the included studies was presented.

Table 3.1 '2 x 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	**Reference standard negative**	**Total**	
Index test result positive	a (true positive)	b (false positive)	a+b	**Positive predictive value = a / (a + b)**
Index test result negative	c (false negative)	d (true negative)	c+d	**Negative predictive value = d / (c + d)**
Total	a+c	b+d	a+b+c+d = N (total number of tests in study)	
	Sensitivity = a / (a + c)	**Specificity = d / (b + d)**		

3.4 Emotional support

A key component of care for women with early pregnancy complications is the provision of emotional support. The GDG members felt that emotional support for women was best addressed throughout the care pathway to make it clear that it is vital at each stage. This decision was based on the fact that, in their experience, when care is provided in a way that is supportive and sensitive to women's needs, the psychological sequelae of pregnancy loss can be lessened. In order to make explicit the GDG's consideration of women's emotional support when making recommendations a separate sub-section has been created within the 'evidence to recommendations' section for each review. Summaries here will link the evidence from the systematic review, the GDG's interpretation of the evidence and the GDG members' own clinical experience with recommendations aimed at improving emotional support for women.

An overarching recommendation summarising giving of information appears in Chapter 4 following the review for emotional support. This draws on evidence from reviews in subsequent chapters as well as that presented in Chapter 4. These recommendations also appear towards the beginning of the care pathway in order to highlight their importance. In addition, symbols are used throughout the care pathway to illustrate where further specific information should be provided in order to highlight that this is essential throughout all stages of care.

3.5 Incorporating health economics

The aims of the health economic input to the guideline were to inform the GDG of potential economic issues relating to ectopic pregnancy and miscarriage, and to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to

integrate data on benefits (ideally in terms of quality adjusted life years [QALYs]), harms and costs of different care options.

The GDG prioritised a number of review questions where it was thought that economic considerations would be particularly important in formulating recommendations. Systematic searches for published economic evidence were undertaken for these questions. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation. Reviews of the (very limited) relevant published health economic literature are presented alongside the clinical effectiveness reviews.

Health economic considerations were aided by original economic analysis undertaken as part of the development process. For this guideline the areas prioritised for economic analysis were:

- expectant compared with active management of miscarriage
- management of ectopic pregnancy
- progesterone for treatment of threatened miscarriage
- effectiveness of early pregnancy assessment units (EPAUs).

Due to a lack of relevant health economic literature and absence of clinical effectiveness data, it was not possible to undertake economic analysis to determine the cost effectiveness of EPAUs.

3.6 Evidence to recommendations

For each review question recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, the technical team drafted and the GDG agreed short clinical and, where appropriate, cost effectiveness evidence statements which were presented alongside the evidence profiles. Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process. The criteria used in moving from evidence to recommendations were:

- relative value placed on the outcomes considered
- consideration of the clinical benefits and harms
- consideration of net health benefits and resource use
- quality of the evidence
- information giving and psychological support
- other considerations (including equalities issues).

In areas where no substantial clinical research evidence was identified, the GDG members considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on GDG consensus in relation to the likely cost effectiveness implications of the recommendations. The GDG also identified areas where evidence to answer review questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously. The GDG identified 10 'key priorities for implementation' (key recommendations) and five high-priority research recommendations. The key priorities for implementation were those recommendations thought likely to have the biggest impact on the care of women with early pregnancy complications and outcomes in the NHS as a whole: these were selected using two rounds of anonymous voting among the GDG members. In the first round of voting each member was asked to cast 10 votes and the five recommendations that received six or more votes were promoted to become key priorities for implementation. A second round of voting was carried out for all

recommendations that received between three and five votes in the first round. Each GDG member was asked to cast five votes. A further three recommendations received six or more votes in the second round and were added to the list of key priority recommendations. Following consultation with stakeholders, two further recommendations were identified as being key priorities for implementation. The priority research recommendations were selected in a similar way, with one round of voting leading to selection of five key priority recommendations for research.

3.7 Stakeholder involvement

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. The GDG took these comments into account in developing the final document.

4 Emotional support and information giving

4.1 Introduction

Becoming pregnant carries considerable psychological as well as physical and social significance. A miscarriage can mean different things to different women. While some women will adjust without distress, others will experience it as the loss of a baby with all of the sadness and grief that that entails. Others may see it as the loss of a potential relationship or the loss of an opportunity to become a mother, and some may be fearful and concerned that they may not be able to have children in the future. In a minority the miscarriage may precipitate psychological disorder such as anxiety or depression. Pain and bleeding in early pregnancy may be also be distressing if it brings anxiety about the health and viability of the pregnancy, even if it does not end with miscarriage. In addition the experience of the early pregnancy loss, especially if sudden or life-threatening, may generate symptoms associated with traumatic stress. This is particularly relevant following ectopic pregnancy.

Pregnancy loss is not just about physical recovery and being ready to become pregnant again. The guideline development group (GDG) considers that good care includes sensitivity to the psychological impact of miscarriage. Even if women have no extra psychological morbidity following the miscarriage, they do express views about what constitutes good care and preferences about how the condition should be managed to enhance their recovery.

The GDG looked at the literature to determine if there were acceptable studies of interventions to improve women's psychological wellbeing after pain and bleeding in early pregnancy and/or early pregnancy loss. The group also looked at qualitative work which reported women's preferences about their care.

4.2 Psychological and emotional support

Review question

What interventions are the most effective for improving women's psychological and/or emotional health following pain, bleeding or pregnancy loss in the first trimester of pregnancy?

Description of included studies

Eight studies are included in this review (Adolfsson et al., 2006; Lee et al., 1996; Neugebauer et al., 2006; Nikcevic et al., 1998; Nikcevic et al., 2007; Séjourné et al., 2010; Swanson, 1999; Swanson et al., 2009). Six studies are randomised controlled trials (Adolfsson et al., 2006; Lee et al., 1996; Neugebauer et al., 2006; Nikcevic et al., 2007; Swanson, 1999; Swanson et al., 2009), one study is a quasi-randomised controlled trial (Séjourné et al., 2010) and one is an observational study (Nikcevic et al., 1998).

Three studies were conducted in the USA (Neugebauer et al., 2006; Swanson, 1999; Swanson et al., 2009), three studies in the UK (Lee et al., 1996; Nikcevic et al., 1998; Nikcevic et al., 2007), one study in France (Séjourné et al., 2010) and one in Sweden (Adolfsson et al., 2006).

The GDG prioritised anxiety and depression as key outcomes of interest. The interventions included in the studies varied. A brief summary is given here (for further details see the evidence table in Appendix H). Three studies (Lee et al., 1996; Nikcevic et al., 2007; Séjourné et al., 2010) compared a single psychological counselling session with no psychological counselling session and reported on the psychological outcomes of anxiety and depression, and women's views/experiences of care.

Counselling sessions were 50 minutes with a psychologist 5 weeks post-miscarriage (Nikcevic et al., 2007), 60 minutes with a psychologist 2 weeks post-miscarriage (Lee et al., 1996) and a counselling session (mean duration 37 minutes, standard deviation [SD] = 14.38) on the day of surgical treatment for the uncomplicated and unanticipated loss of pregnancy (Séjourné et al., 2010). The professional providing the counselling session was not described in the last study.

One study (Swanson 1999) compared three 1-hour counselling sessions at 1, 5 and 11 weeks after enrolment in the study (mean time from miscarriage to study enrolment = 7.86 days, SD = 7.5) with no counselling sessions and reported on the outcomes of anxiety and depression. Counselling sessions were with the principal investigator or research associate (it was unclear whether these were midwives, nurses, psychologists/psychiatrists or social workers).

One study (Neugebauer et al., 2006) compared a maximum of six counselling sessions with a psychiatric social worker or psychiatrist with treatment as usual, which consisted of whatever lay counselling or professional care women sought on their own initiative. Women receiving the intervention could also seek other lay or professional care. The first counselling session was scheduled for 60 minutes; the subsequent sessions were scheduled for 30 minutes. Women concluded treatment whenever they wished: two women received six sessions and 'no others had more than three sessions'.

One study (Adolfsson et al., 2006) compared a single 60-minute structured follow-up visit with a designated midwife with a single 30-minute standard follow-up with one of five midwives between 21 and 28 days post-miscarriage. The structured visit focussed specifically on emotional health issues.

One study (Swanson et al., 2009) compared 'nurse care' (three 1-hour counselling sessions with a nurse counsellor), 'self-care' (three 18-minute videos featuring couples being coached in ways to practice self and partner caring, plus two workbooks, one for the woman and one for her partner), 'combined care' (one 1-hour counselling session with a nurse counsellor followed by the 'self-care' intervention) or 'control' (no treatment).

One study (Nikcevic et al., 1998) surveyed women who had received a follow-up appointment with their local hospital or general practitioner and women who were not offered a follow-up appointment.

Findings are presented below for each type of intervention.

One counselling session compared with no counselling session

Three studies (Lee et al., 1996; Nikcevic et al., 2007; Séjourné et al., 2010) compared a single psychological counselling session with no psychological counselling session and reported on the psychological outcomes of anxiety and depression, and women's views/experiences of care.

Thirty-six percent of the women in the study by Nikcevic et al. 2007, 23% of the women in Séjourné et al., 2010 and none of the women in Lee et al. 1996 had a history of miscarriage (that is, had at least one prior miscarriage). It was unclear how many of the women with a history of miscarriage had experienced recurrent miscarriage. The majority of women in all three studies had children (51%, 56% and 68% respectively).

Quantitative data for key outcomes are presented in a GRADE profile followed by descriptive findings in a short summary table.

Table 4.1 GRADE findings for comparison of one psychological counselling session with no psychological counselling session

Number of studies	Number of women		Effect	Quality
	One psychological counselling session Mean (SD)	No psychological counselling Mean (SD)	Absolute (95% CI)	
Anxiety at 3 weeks (measured with: Hospital Anxiety and Depression Scale)				
1 study (Séjourné et al., 2010)	Mean 7.21 (SD 3.02) n = 50	Mean 9.06 (SD 3.95) n = 52	MD 1.85 lower (3.21 lower to 0.49 lower)	Moderate
Anxiety at 7 weeks (measured with: Hospital Anxiety and Depression Scale)				
1 study (Nikcevic et al, 2007)	Mean 7.2 (SD 5.2) n = 33	Mean 6.7 (SD 4.1) n = 33	MD 0.5 higher (1.76 lower to 2.76 higher)	High
Anxiety at 10 weeks (measured with: Hospital Anxiety and Depression Scale)				
1 study (Séjourné et al., 2010)	Mean 6.22 (SD 3.52) n = 45	Mean 7.16 (SD 4.25) n = 37	MD 0.94 lower (2.65 lower to 0.77 higher)	Moderate
Anxiety at 4 months (measured with: Hospital Anxiety and Depression Scale)				
2 studies (Lee et al., 1996, Nikcevic et al., 2007)	Mean 7.4 (SD 5.9) n = 21 Mean 5.6 (SD 4.5) n = 33	Mean 8.1 (SD 6.2) n = 18 Mean 7 (SD 4.4) n = 33	MD 1.23 lower (3.1 lower to 0.64 higher)	High
Anxiety at 6 months (measured with: Hospital Anxiety and Depression Scale)				
1 study (Séjourné et al., 2010)	Mean 5.33 (SD 3.42) n = 33	Mean 6.5 (SD 3.49) n = 34	MD 1.17 lower (2.82 lower to 0.48 higher)	Moderate
Depression at 3 weeks (measured with: Hospital Anxiety and Depression Scale)				
1 study (Séjourné et al., 2010)	Mean 3.93 (SD 3.38) n = 50	Mean 5.08 (SD 3.6) n = 52	MD 1.15 lower (2.5 lower to 0.2 higher)	Moderate
Depression at 7 weeks (measured with: Hospital Anxiety and Depression Scale)				
1 study (Nikcevic et al, 2007)	Mean 4.1 (SD 4.2) n = 33	Mean 3.34 (SD 2.9) n = 33	MD 0.7 higher (1.04 lower to 2.44 higher)	High

Number of studies	Number of women		Effect	Quality
	One psychological counselling session Mean (SD)	No psychological counselling Mean (SD)	Absolute (95% CI)	
Depression at 10 weeks (measured with: Hospital Anxiety and Depression Scale)				
1 study (Séjourné et al., 2010)	Mean 3.0 (SD 2.46) n = 45	Mean 3.48 (SD 3.2) n = 37	MD 0.48 lower (1.74 lower to 0.78 higher)	Moderate
Depression at 4 months (measured with: Hospital Anxiety and Depression Scale)				
2 studies (Lee et al., 1996, Nikcevic et al., 2007)	Mean 3.2 (SD 4.2) n = 21 Mean 2.8 (SD 4.1) n = 33	Mean 4.8 (SD 7) n = 18 Mean 3.7 (SD 3.7) n = 33	MD 1.04 lower (2.72 lower to 0.63 higher)	High
Depression at 6 months (measured with: Hospital Anxiety and Depression Scale)				
1study (Séjourné et al., 2010)	Mean 2.24 (SD 2.79) n = 33	Mean 2.44 (SD 2.5) n = 34	MD 0.2 lower (1.47 lower to 1.07 higher)	Moderate

CI confidence interval, MD mean difference, SD standard deviation

Hospital Anxiety and Depression Scale: better = lower values [score of 11 was threshold for 'caseness' in Nikcevic et al., 2007 and Lee et al., 1996]

Table 4.2 Women's views and experiences of care following one counselling session compared with no counselling session

Women's views/experiences of care	
Nikcevic et al., 2007 [Moderate quality]	**Helpfulness of 20-minute medical visit with obstetrician 5 weeks post-miscarriage** (received by women in both intervention and control groups): 100% of women reported a moderate to strong agreement regarding helpfulness of the medical consultation. In a cohort of matched controls who received no medical consultation and no psychological counselling, 30/47 (64%) women expressed that some follow-up would have been helpful. **Helpfulness of 50-minute psychological counselling session 5 weeks post miscarriage**: 94% of women agreed the psychological counselling was at least moderately helpful.
Séjourné et al., 2010 [Moderate quality]	**Helpfulness of one psychological counselling session**: at 3 weeks post-miscarriage 43/50 (86%) women felt that the intervention was helpful. **Need for more support**: at 10 weeks post-miscarriage 9/45 (20%) women felt that the psychological counselling was insufficient and felt the need for more support.

Women's views/experiences of care	
Lee et al. 1996 [Moderate quality]	**Helpfulness of 1 hour psychological counselling session**: women were asked to rate the helpfulness of the counselling session on a 100 mm scale from 'extremely unhelpful' (0) to 'extremely helpful' (100): mean = 74 mm, SD = 21.1, n = 21 **Positive comments on psychological counselling session**: having opportunity to express feelings and thoughts; having someone to talk to who listened to them. **Negative comments on psychological counselling session**: having to relive experience; limited medical knowledge of person carrying out the debriefing. **Medical explanation**: women commented that they would have liked a more medical explanation for their miscarriage, as well as emotional support.

SD standard deviation

Evidence statements

Anxiety

One study found that anxiety at 3 weeks was lower in women who received one psychological counselling session within 4 days of miscarriage compared with women who did not receive psychological counselling. This finding was statistically significant. The evidence for this finding was of moderate quality.

Three studies measuring anxiety at different time points following miscarriage found no statistically significant difference in anxiety in women who received one session of psychological counselling compared with women who did not receive psychological counselling at 7 weeks (high quality), 10 weeks (moderate quality), 4 months (high quality) and 6 months (moderate quality).

Depression

Three studies measuring depression at different time points following miscarriage found no statistically significant difference in depression in women who received one session of psychological counselling compared with women who did not receive psychological counselling at 3 weeks (moderate quality), 7 weeks (high quality), 10 weeks (moderate quality), 4 months (high quality) and 6 months (moderate quality).

Women's views/experiences of care

Helpfulness of psychological counselling

One study found that women moderately or strongly felt that a 20-minute counselling session with an obstetrician at 5 weeks post-miscarriage was helpful. In the same study 94% of women who received the additional 50-minute psychological counselling session felt that the psychological counselling was at least moderately helpful. The evidence for this finding was of moderate quality.

One study found that, at 3 weeks post-miscarriage, 86% of women felt that a 1-hour psychological counselling session on the day of surgical treatment of miscarriage was helpful. The evidence for this finding was of moderate quality.

One study found that women rated the helpfulness of a 1-hour psychological counselling session at a mean of 74 mm on a visual analogue scale that ranged from 'extremely unhelpful' (0 mm) to 'extremely helpful' (100 mm). Women found it helpful to have the opportunity to express feelings and thoughts, having someone to talk to and listen to them. The evidence for this finding was of moderate quality.

Need for more support

One study found that 20% of women who received a 1-hour psychological counselling session felt that the counselling was insufficient and felt the need for more support. The evidence for this finding was of moderate quality.

Need for a medical explanation

One study reported that some women commented on the limited medical knowledge of the person delivering the psychological counselling session and that women would have liked a more medical explanation for their miscarriage, as well as emotional support. The evidence for this finding was of moderate quality.

Three counselling sessions compared with no counselling sessions

One study (Swanson 1999) compared three 1-hour counselling sessions at 1, 5 and 11 weeks after enrolment in the study (mean time from miscarriage to study enrolment = 7.86 days, SD = 7.5) with no counselling sessions and reported on the outcomes of anxiety and depression.

Thirty percent of women in this study (Swanson 1999) had a history of miscarriage. It was unclear how many of the women with a history of miscarriage experienced recurrent miscarriage. The majority of women in the study had children (54%).

This study used a Solomon four-group randomised experimental design: some women were randomised to delayed outcome measurement to address the possibility that early outcome measurement (survey completion) could in itself serve as a form of treatment. The data reported in the GRADE profile below represents those women randomised to early outcome measurement as this is the group for whom the most complete data set is available.

Table 4.3 GRADE findings for comparison of three psychological counselling sessions with no psychological counselling session

Number of studies	**Number of women**		**Effect**	**Quality**
	Three counselling sessions	**No psychological counselling**	**Absolute (95% CI)**	
Anxiety at 6 weeks (measured with: Profile of Mood States)				
1 study (Swanson, 1999)	Mean 10 (SD 5.4) n = 43	Mean 11.5 (SD 7.3) n = 40	MD 1.5 lower (4.28 lower to 1.28 higher)	High
Anxiety at 4 months (measured with: Profile of Mood States)				
1 study (Swanson, 1999)	Mean 10.9 (SD 6.8) n = 43	Mean 11.0 (SD 7.3) n = 40	MD 0.1 lower (3.14 lower to 2.94 higher)	High
Anxiety at 12 months (measured with: Profile of Mood States)				
1 study (Swanson, 1999)	Mean 8.7 (SD 5.6) n = 43	Mean 9.3 (SD 7.3) n = 40	MD 0.6 lower (3.41 lower to 2.21 higher)	High
Depression at 6 weeks (measured with: Profile of Mood States)				
1 study (Swanson, 1999)	Mean 12.1 (SD 11) n = 43	Mean 14.8 (SD 12.7) n = 40	MD 2.7 lower (7.83 lower to 2.43 higher)	High

Number of studies	Number of women		Effect	Quality
	Three counselling sessions	No psychological counselling	Absolute (95% CI)	
Depression at 4 months (measured with: Profile of Mood States)				
1 study (Swanson, 1999)	Mean 9.8 (SD 8.7) n = 43	Mean 12.6 (SD 13.7) n = 40	MD 2.8 lower (7.78 lower to 2.18 higher)	High
Depression at 12 months (measured with: Profile of Mood States)				
1 study (Swanson, 1999)	Mean 8.4 (SD 9.3) n = 43	Mean 11.4 (SD 14.5) n = 40	MD 3 lower (8.28 lower to 2.28 higher)	High

CI confidence interval, MD mean difference, SD standard deviation

Profile of Mood States scale: better = lower values

Evidence statements

Anxiety

One study measuring anxiety at different time points following miscarriage found no statistically significant difference in anxiety in women who received three sessions of psychological counselling compared with women who did not receive psychological counselling at 6 weeks, 4 months and 12 months post-miscarriage. The evidence for these findings was high quality.

Depression

One study measuring depression at different time points following miscarriage found no statistically significant difference in depression in women who received three sessions of psychological counselling compared with women who did not receive psychological counselling at 6 weeks, 4 months and 12 months post-miscarriage. The evidence for these findings was high quality.

Up to six counselling sessions compared with treatment as usual

One study (Neugebauer et al., 2006) compared a maximum of six counselling sessions with a psychiatric social worker or psychotherapist with treatment as usual, and reported on the outcome of depression.

Thirty-seven percent of women in this study (Neugebauer et al., 2006) had a history of miscarriage. It was unclear how many of the women with a history of miscarriage experienced recurrent miscarriage. The number of women with children was not reported.

Table 4.4 GRADE findings for comparison of a maximum of six psychological counselling sessions with treatment as usual

Number of studies	Number of women		Effect	Quality
	Maximum of six counselling sessions	Treatment as usual	Absolute (95% CI)	
Depression at 9 weeks (measured with: Hamilton Rating Scale for Depression-17 item)				
1 study (Neugebauer et al., 2006)	Mean 11.6 (SD 8.2) n = 10	Mean 12.9 (SD 8.3) n = 9	MD 1.3 lower (8.73 lower to 6.13 higher)	Very low

CI confidence interval, MD mean difference, SD standard deviation

Hamilton Rating Scale for Depression (HAM-D-17): better = lower values

Evidence statements

Depression

One study found no statistically significant difference in depression at 9 weeks post-miscarriage in women who received up to a maximum of six sessions of psychological counselling compared with women who received treatment as usual. The evidence for these findings was very low quality.

Structured midwifery follow-up compared with standard midwifery follow-up

One study (Adolfsson et al., 2006) compared a single 60-minute structured follow-up visit with a designated midwife with a single 30-minute standard follow-up with one of five midwives between 21 and 28 days post-miscarriage and reported on the outcome of grief. Although not a priority outcome, this study is included as it is the only study found that investigated the effectiveness of an 'informal' intervention delivered by a nurse/midwife.

Twenty-two percent of women in this study (Adolfsson et al., 2006) had a history of miscarriage. It was unclear how many of the women with a history of miscarriage experienced recurrent miscarriage. The number of women with children was not reported.

Table 4.5 GRADE findings for comparison of structured midwifery follow-up with standard midwifery follow-up

Number of studies	**Number of women**		**Effect**	**Quality**
	Structured follow-up reduction change score (95% CI)	**Standard follow-up reduction change score (95% CI)**	**Absolute (95% CI)**	
Grief at 4 months (measured with: Perinatal Grief Scale – Swedish short version)				
1 study (Adolfsson et al., 2006)	23.5 (11.6 to 35.5) n = 43	17.5 (7.7 to 27.3) n = 45	No significant difference *P* = 0.43	Low

CI confidence interval, n number, *P* probability

Perinatal Grief Scale (total score): better = lower values

Evidence statements

Grief

One study found no statistically significant difference in grief at 4 months post-miscarriage between women who attended a structured follow-up visit with a midwife and women who attended a standard follow-up visit with a midwife. The evidence for this finding was low quality.

Nurse caring, self-caring and combined caring interventions and no treatment

One study (Swanson et al., 2009) compared 'nurse care' (three 1-hour counselling sessions with a nurse counsellor), 'self-care' (three 18-minute videos featuring couples being coached in ways to practice self and partner caring, plus two workbooks, one for the woman and one for her partner), 'combined care' (one 1-hour counselling session with a nurse counsellor followed by the 'self-care' intervention) or 'control' (no treatment). The study included 341 couples (n = 682).

The number of women with a history of miscarriage and the number of women with children was not reported.

Women in all three treatment groups exhibited a faster rate of recovery, measured with the Center for Epidemiological Studies-Depression scale (CES-D), compared with women receiving no treatment. However, only the nurse caring group met the authors' criterion for 'substantial evidence' (Bayesian odds ratio more than 3.2). The self-caring group had the highest proportion of women who did not

return data after baseline (25/172, 14.5%); the nurse caring group had the lowest proportion (1/168, 0.6%).

The study reported change in CES-D scores at 3, 5 and 13 months post-miscarriage (data was extracted from a small graph and so numbers are not accurate). The changes in CES-D scores at 3 months were:

- nurse caring approximately −2.9
- self-caring approximately −2.3
- combined caring approximately −2.3
- no treatment approximately −2.2.

The change in CES-D score at 5 months was:

- nurse caring approximately −5.7
- self-caring approximately −4.9
- combined caring approximately −4.7
- no treatment approximately −4.3.

The changes in CES-D score at 13 months were:

- nurse caring approximately −8.2
- self-caring approximately −7.1
- combined caring approximately −6.9
- no treatment approximately −6.2.

The evidence for this finding was of high quality.

One follow-up appointment compared with no follow-up appointment

One study (Nikcevic et al., 1998) surveyed women who had received a follow-up appointment with their local hospital or general practitioner and women who were not offered a follow-up appointment.

The timing of the follow-up appointment and outcome measurement post-miscarriage was not reported in the study. The healthcare professionals delivering the follow-up appointment were not clearly reported. Findings from the study are summarised in the table below.

Table 4.6 Women's experience of care with one follow-up appointment compared with no follow-up appointment

Women's views/experiences of care	
Nikcevic et al., 1998 [Low quality]	**Desire for follow-up, offer of and attendance at follow-up:** 187/204 (92%) women thought a follow-up appointment was desirable. Such an appointment, with a local hospital or general practitioner, was offered to 61/204 (30%) women. 52/61 (85%) women attended the follow-up appointment. **Content of follow-up**: 22/52 (42%) women reported not being given the opportunity to discuss feelings during the follow-up. **Expectations from a follow-up clinic**: 72% of women suggested clinic should be conducted by a doctor, 28% would have preferred to see a midwife or counsellor. 177/204 (87%) women reported it was 'very' or 'extremely' important to them to have an explanation as to why the miscarriage happened. **Contact with the Miscarriage Association:** prior to discharge from the Harris Birthright Research Centre all women were given an information

	leaflet that included the telephone number of the Miscarriage Association. 18/204 (9%) women had made contact; significantly more so in the group that attended a follow-up clinic. **Emotional counselling**: 73/204 (36%) women reported that they would find emotional counselling helpful. The comparison between women who expressed a wish for emotional counselling and those who did not revealed that those who did not want counselling had significantly lower levels of anxiety *(t* test = −2.44, d.f. = 200, *P* < 0.05*)*, depression (*t* test = −2.51, d.f. = 200, *P* < 0.05) and grief *(t* test = −4.30, d.f. = 199, *P* < 0.001*)*. **Women's opinions about ways to improve support from medical professionals:** many women wanted more information concerning the reasons for their miscarriage and its implications, outlined the importance of a sensitive and sympathetic attitude on the part of medical professionals and emphasised the fact that the surgical removal of pregnancy tissue after miscarriage is a trauma that is too often dismissed as a routine surgical procedure by the medical staff involved.

d.f. degrees of freedom, *P* probability

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG had prioritised anxiety and depression as key outcomes for the review. However, when the evidence was presented it was seen that for the majority of the studies the levels of anxiety and depression being reported were very low and generally within a range considered normal, indicating most women do not experience significant anxiety and depression following miscarriage. In addition, the small differences in scores demonstrated between experimental and control groups were felt not to be clinically significant. In contrast, the qualitative findings from the included studies were thought to be more helpful and more credible. Thus women's reports of what they found helpful, their experience of care and reports of what they would have liked were seen by the GDG as the most important findings from this review.

Consideration of clinical benefits and harms

The provision of additional counselling sessions or other emotional support for women with pain and bleeding in early pregnancy and/or women who experience early pregnancy loss appears not to bestow any clinical benefits as measured by anxiety and depression scales (indeed, some women reported negative experiences following counselling sessions as it involved re-living the experience). It seems from the scores reported in the evidence reviewed that women with pain and bleeding in early pregnancy are not suffering from high levels of anxiety or depression as represented by the consistently low scores seen across studies, so perhaps it is not surprising that additional psychological support has little impact on these parameters. The GDG recognised that the same may well not be true for women with recurrent pregnancy loss or with pain and bleeding at a later stage of pregnancy. The GDG also noted that the number and content of the counselling sessions or psychological support did not appear to make a difference to their effect on anxiety and depression, neither did the timing of such sessions (although a general decrease in scores over time was noted) nor the professional training of the person delivering the sessions (although some women had a negative experience when the person delivering the counselling session had limited medical knowledge).

In contrast it was evident from the descriptive evidence, contained in one observational study, that women who had received a follow-up appointment valued this, and many women who had not had a follow-up appointment would have liked one. Many women expressed a need for an explanation for the pregnancy loss and a preference for a medical follow-up in order to discuss this.

The importance of being treated in a sensitive and sympathetic manner through all stages of care was also emphasised. The GDG cross-referred here to NICE clinical guidance 138 Patient experiences in adult NHS services (2012) which makes a series of recommendations on the importance of good communication and an understanding of patients' responses to events and the care provided.

The GDG considered that the clinical benefits of additional psychological support for women with pain and bleeding in early pregnancy outweighed any potential harms as it appears that women tend to self-select in this respect. Evidence from the literature reviewed and from the GDG's own experience was that women who would benefit from additional support would express a preference for it, while those who preferred not to discuss the experience with a healthcare professional would not request such sessions, or would choose not to attend.

Consideration of health benefits and resource uses

Findings from the descriptive evidence suggest that for some women a follow-up appointment is perceived as valuable, particularly the provision of an opportunity to discuss possible reasons for the pregnancy loss and to help in planning for the future. The GDG members believed that not all women experiencing pain and bleeding in the first trimester of pregnancy would want or need this follow-up; however, they believed that the offer of a follow-up appointment in itself would have a beneficial effect, even for those women who chose not to take it up and thus felt it appropriate that this offer be made to all women. The GDG's experience was that a minority of women would actually make and attend a follow-up appointment, with most women finding support from family and friends and/or through third sector agencies. The natural healing afforded by time passing would also reduce the number of women needing this additional appointment. It was thus felt that the number of women attending for follow-up would be fairly small and manageable within the existing resources allocated to providing care to women with pain and bleeding in early pregnancy.

Quality of evidence

The evidence for the review ranged from high to very low. The quality of the descriptive findings relating to women's experiences of care and preferences was moderate and low. Despite the limitations of these studies, the GDG members felt the evidence was valuable, brought an important perspective to the review findings and had high credibility in that it reflected their own experience.

Other considerations

The GDG emphasised that formal counselling and emotional support are not the same thing, and that there is some confusion of terms within the evidence reviewed. For the purposes of their discussion counselling was taken to mean formalised sessions provided by a person trained in counselling. Emotional or psychological support was taken to mean a more unstructured, informal type of support, including follow-up care and information giving provided by a healthcare professional.

The GDG noted that the location of the follow-up visit would be likely to have a bearing on how it is experienced by women. Returning to the place where the diagnosis of pregnancy loss was first made may be upsetting for some women, as would attendance at a location along with pregnant women such as at an antenatal clinic. Similarly some women might have a good relationship with their GP and prefer to see them for follow-up care. For this reason the GDG believed it important that women should be provided with a choice of where to attend for a follow-up appointment. It was also recognised that some women would choose not to accept the offer of a follow-up appointment but that they might need support or counselling at a later time. It was felt that the provision of information leaflets that included details of websites and contact numbers for support groups was important so that women would have easy access to this information for future reference.

It was noted from the evidence that sometimes women experienced a poor quality of care and support from their healthcare professional. The GDG highlighted the importance of healthcare professionals who provide care for women who experience complications in early pregnancy being trained in how to communicate sensitively and how to break bad news. They also recognised that as non-clinical staff, such as receptionists, will also be coming into contact with these women on a daily basis, they too should be trained in how to communicate sensitively.

The GDG were disappointed to note that there was very little evidence on emotional support for women following ectopic pregnancy, with the focus of the evidence base being on miscarriage. There was concern that, while for many women the experience may be similar between the two types of early pregnancy loss, any potential differences, for example relating to perceptions of future fertility, have not been explored in the literature. It was felt that an improved understanding of the differences between women's experiences of miscarriage and ectopic pregnancy would help carers provide more appropriate individualised support and a research recommendation was made to encourage work in

this area. It was also noted that none of the studies investigated the value of interventions for women with mental health problems following early pregnancy loss.

In every section of the guideline, when developing their recommendations, the GDG members identified the information with which women and their partners should be provided. Although some of this information was specific to each particular element of care (and is thus presented in the relevant chapter), the group noted that there were some key themes which were relevant to all women (such as what to do if their clinical symptoms worsen, and where to access support services including emergency care). As a result, the group felt that it was appropriate to write an overarching recommendation regarding the information that all women and their partners (where appropriate) should be provided with throughout their care. The resulting recommendation appears below but draws upon information reviewed in later chapters of the guideline, as well as that reviewed for the question on psychological and emotional support.

Recommendations

Number	Recommendation
1	Treat all women with early pregnancy complications with dignity and respect. Be aware that women will react to complications or the loss of a pregnancy in different ways. Provide all women with information and support in a sensitive manner, taking into account their individual circumstances and emotional response.*
2	Healthcare professionals providing care for women with early pregnancy complications in any setting should be aware that early pregnancy complications can cause significant distress for some women and their partners. Healthcare professionals providing care for these women should be given training in how to communicate sensitively and breaking bad news. Non-clinical staff such as receptionists working in settings where early pregnancy care is provided should also be given training on how to communicate sensitively with women who experience early pregnancy complications.
3	Throughout a woman's care, give her and (with agreement) her partner specific evidence-based information in a variety of formats. This should include (as appropriate): • When and how to seek help if existing symptoms worsen or new symptoms develop, including a 24-hour contact telephone number. • What to expect during the time she is waiting for an ultrasound scan. • What to expect during the course of her care (including expectant management), such as the potential length and extent of pain and/or bleeding, and possible side effects. This information should be tailored to the care she receives. • Information about post-operative care (for women undergoing surgery). • What to expect during the recovery period – for example, when it is possible to resume sexual activity and/or try to conceive again, and what to do if she becomes pregnant again. This information should be tailored to the care she receives. • Information about the likely impact of her treatment on future fertility. • Where to access support and counselling services, including leaflets, web addresses and helpline numbers for support organisations. Ensure that sufficient time is available to discuss these issues with women during the course of their care and arrange an additional appointment if more time is needed.
4	After an early pregnancy loss, offer the woman the option of a follow-up appointment with a healthcare professional of her choice.

* For further guidance about providing information, see Patient experience in adult NHS services (NICE clinical guidance 138)

Number	Research recommendations
RR 1	What interventions improve emotional and psychological outcomes for women following ectopic pregnancy?

5 Early pregnancy assessment units

5.1 Introduction

Management of early pregnancy complications is often undertaken in early pregnancy assessment units (EPAUs). EPAUs were established in the early 1990s and their locations, opening times and accessibility vary throughout England and Wales. Where there is not an EPAU, women with early pregnancy complications may be cared for within primary or secondary care. Comparisons of the different models of care were sought to establish the clinical and cost effectiveness of EPAUs. In addition, specific models of early pregnancy care were sought to determine if any particular model led to better outcomes for women.

5.2 Clinical and cost effectiveness of early pregnancy assessment units

Review question

What is the clinical and cost effectiveness of early pregnancy assessment units (EPAUs) compared with other models of service provision in improving women's clinical and psychological outcomes?

Description of included studies

Four studies were included in this review (Bignardi et al., 2010; Bigrigg et al., 1991; Brownlea et al., 2005; Tunde-Byass & Cheung, 2009).

One UK retrospective study (Bigrigg et al., 1991) assessed the impact of an EPAU on duration of stay in women with pain and bleeding in early pregnancy. Data were collected 6 months before the unit opened and compared with data collected during the first year of the unit's operation.

One Australian retrospective study (Brownlea et al., 2005) examined the hypothesis that the introduction of the early pregnancy problem service (EPPS) clinic reduced the length of stay in the emergency department for women with early pregnancy pain and bleeding that did not require hospital admission. The EPPS was established in June 1996. Data were collected from 2 months before the establishment of the EPPS and compared with 2 months in 2003, 7 years after the EPPS was established.

One Australian prospective study (Bignardi et al., 2010) evaluated the impact of an ultrasound-based unit (acute gynaecology unit [AGU]) in the management of women with acute gynaecology and early pregnancy complications. The AGU provided ultrasound investigation to women at the initial visit by the same person who took the history, and the ultrasound findings were interpreted in the context of the clinical picture.

One Canadian retrospective study (Tunde-Byass & Cheung, 2009) assessed the impact of an early pregnancy assessment clinic (EPAC) on the management of early pregnancy complications and its effect on the number of emergency room visits. The EPAC was established in August 2005. Data were collected from 1 year before the establishment of the EPAC and compared with 2 years after the EPAC was established.

Evidence profile

Table 5.1 GRADE summary of findings for comparison of before and after the opening of an EPAU/AGU

Number of studies	Number of women		Effect		Quality
	Before EPAU/AGU opened	After EPAU/AGU opened	Relative (95% CI)	Absolute (95% CI)	
Length of stay in emergency department (minutes)					
1 study (Brownlea et al. 2005)	Median 136	Median 107	Not calculable (NC)	Median 29 higher (CI NC) *P* < 0.001	Low
Re-presentation to emergency department					
1 study (Brownlea et al. 2005)	14/87 (16%)	6/85 (7%)	2.28 (0.92 to 5.65)	90 more per 1000 (from 6 fewer to 328 more)*	Very low
1 study (Tunde-Byass, & Cheung, 2009)	431/1514 (28.5%)	384/1603 (24%)	1.19 (1.06 to 1.34)	46 more per 1000 (from 14 more to 81 more)	Very low
Duration of stay for women requiring no treatment (hours)					
1 study (Bigrigg et al., 1991)	Mean 36 (range 12 to 72 days)	Mean 2	NC	MD 34 higher (CI NC)	Low
Duration of hospital stay for women requiring evacuation of the uterus (hours)					
1 study (Bigrigg et al., 1991)	Mean 72 (range 36 to 60)	Mean 24	NC	MD 48 higher (CI NC)	Low
Length of stay as inpatient (hours)					
1 study (Bignardi et al., 2010)	Mean 13.9	Mean 4.6	NC	MD 9.3 higher (CI NC) *P* = 0.011	Very low
Length of stay as outpatient (hours)					
1 study (Bignardi et al., 2010)	Mean 4.1	Mean 0.75	NC	MD 3.35 higher (CI NC) *P* = 0.0001	Very low
Proportion of women requiring hospital admission					
1 study (Brownlea et al., 2005)	37/88 (42%)	29/81 (36%)	1.17 (0.80 to 1.72)*	61 more per 1000 (from 72 fewer to 258 more)*	Very low

Number of studies	Number of women		Effect		Quality
	Before EPAU/AGU opened	After EPAU/AGU opened	Relative (95% CI)	Absolute (95% CI)	
1 study (Bignardi et al., 2010)	48/133 (36.1%)	11/157 (7%)	5.15 (2.79 to 9.51)	291 more per 1000 (from 125 more to 596 more)*	Very low
Proportion of women who re-presented to emergency department with further pain and bleeding					
1 study (Brownlea et al., 2005)	14/88 (16%)	6/81 (7%)	2.14 (0.90 to 5.21)*	84 more per 1000 (from 7 fewer to 312 more)* *P* = 0.6	Very low
Proportion of women discharged within 3 hours from emergency department					
1 study (Brownlea et al., 2005)	30/51 (60%)	44/52 (86%)	0.69 (0.25 to 0.88)*	262 fewer per 1000 (from 102 fewer to 635 fewer)* *P* < 0.0001	Very low

AGU acute gynaecology unit, CI confidence interval, EPAU early pregnancy assessment unit, MD mean difference, NC not calculable, *P* probability

* NCC calculation

Evidence statements

Length of stay in emergency department

One study found a longer median length of stay in the emergency department before the establishment of an EPAU compared with afterwards. This finding was statistically significant. The evidence for this outcome was of low quality.

Re-presentation to emergency department

One study found no statistically significant difference in the number of women returning to an emergency department before the establishment of an EPAU compared with afterwards. However, another study found a higher number of women returning to an emergency department before the establishment of an EPAU compared with afterwards. This finding was statistically significant. The evidence for this outcome was of very low quality.

Duration of stay for women requiring no treatment

One study found a longer mean duration of hospital stay before the establishment of an EPAU compared with afterwards for women presenting with pain and bleeding who required no treatment. The statistical significance of this finding was not calculable. The evidence for this outcome was low quality.

Duration of hospital stay for women requiring evacuation of the uterus

One study found a longer mean duration of hospital stay before the establishment of an EPAU compared with afterwards for women presenting with pain and bleeding who required evacuation of the uterus. The statistical significance of this finding was not calculable. The evidence for this outcome was of low quality.

Length of stay as inpatient

One study found a longer mean length of stay as an inpatient before the establishment of an AGU compared with afterwards for women presenting with pain and bleeding. This finding was statistically significant. The evidence for this outcome was of very low quality.

Length of stay as outpatient

One study found a longer mean length of stay as an outpatient before the establishment of an AGU compared with afterwards for women presenting with pain and bleeding. This finding was statistically significant. The evidence for this outcome was of very low quality.

Proportion of women requiring hospital admission

One study found no statistically significant difference in the number of women requiring hospital admission for treatment of pain and bleeding in early pregnancy before the establishment of an EPAU compared with afterwards. However, another study found more women requiring hospital admission for treatment of pain and bleeding in early pregnancy before the establishment of an AGU compared with afterwards. This finding was statistically significant. The evidence for this outcome was of very low quality.

Proportion of women who re-presented to emergency department with further pain and bleeding

One study found no statistically significant difference in the proportion of women who returned to an emergency department with further pain and bleeding following initial treatment for pain and bleeding in early pregnancy before the establishment of an EPAU compared with afterwards. The evidence for this outcome was of very low quality.

Proportion of women discharged within 3 hours from emergency department

One study found a lower proportion of women who were discharged within 3 hours of being seen by a doctor for pain and bleeding in early pregnancy before the establishment of an EPAU compared with afterwards. This finding was statistically significant. The evidence for this outcome was of very low quality.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG had hoped to find studies that compared women's experiences of care in EPAUs with those in other settings; unfortunately this evidence was not available. Similarly, there was no evidence on whether women attending an EPAU have better clinical or psychological outcomes than women cared for elsewhere. Therefore, the GDG based their decisions on the outcomes reported in studies that are likely to impact on the cost of providing services in early pregnancy, namely the need for hospital admission and the length of hospital stay.

Consideration of clinical benefits and harms

The guideline development group (GDG) noted that the introduction of an EPAU or AGU had resulted in a shorter length of stay in both emergency departments and outpatient clinics, a reduction in the proportion of women requiring hospital admission and a reduction in the number of women re-presenting to health services. The GDG felt that these would be important considerations for women, in addition to having potential cost implications as a result of a reduced inpatient stay. Despite the paucity of data, the GDG was aware of considerable anecdotal evidence that women have better experiences of care in EPAUs compared with other models of care, such as care based in antenatal wards. GDG members also felt that it was likely that access to a dedicated early pregnancy service, such as that provided in EPAUs, might lead to better clinical outcomes for women. However, they recognised that research was needed to confirm this hypothesis.

Consideration of health benefits and resource uses

In light of the lack of clinical outcomes reported in the evidence, a cost-effectiveness analysis could not be performed for this review question. A literature search performed for health economic evidence did not identify any relevant studies. Nevertheless, due to the potential cost savings from reduced admissions and length of stay, the GDG felt that it was likely that an EPAU would be more cost-effective than an inpatient service. However, it recognised that the cost of staffing a dedicated service

and the number of women attending the units would have implications for cost. Therefore, the GDG felt that it was important to recommend that health economics analysis be performed as soon as clinical outcome data becomes available.

Quality of evidence

The quality of evidence was low and there was a regrettable lack of evidence surrounding clinical outcomes, women's experiences of care and cost effectiveness. However, the GDG agreed that it was important that all women should have access to some sort of dedicated early pregnancy assessment service, which would provide ultrasound scanning and specialist clinical assessment for women in early pregnancy. The GDG did not anticipate that this early pregnancy assessment service would always be based in an EPAU, and did not feel able to recommend that this should be the case, due to the lack of evidence on their effectiveness. However, the EPAUs currently operating do offer this dedicated specialist service and it is generally thought that they improve women's experiences: the GDG therefore felt that it was vital to recommend that research be conducted to evaluate whether EPAUs improve outcomes, both clinical and psychological, for women experiencing early pregnancy complications.

Information giving and emotional support

The GDG believed that the availability of a dedicated service would minimise the risk of misdiagnosis and help to reduce the anxiety that women with an early pregnancy loss might experience, especially compared with attending services based in settings like antenatal units. In comparison with other models of care, the group felt that staff in a dedicated service, who specialise in early pregnancy issues, would be able to provide women with appropriate information and psychological support, which might help to mitigate some of their anxieties and concerns. They agreed that staff providing care in these settings should be appropriately trained in sensitive communication and in breaking bad news. They also felt that recommending that women could access this service promptly, where clinically indicated, would help to ensure that women spent as little time as possible in a state of uncertainty about their prognosis, and therefore would feel more informed and supported.

Other considerations

The GDG was aware that an EPAU may not be an appropriate model of care in every setting, for example in very rural areas with low pregnancy rates. In light of this, and the lack of evidence on their clinical and cost effectiveness, the GDG did not feel able to recommend that EPAUs should be established in areas currently lacking one.

5.3 Model for service organisation and delivery of EPAUs

Review question

What is the appropriate model for service organisation and delivery of EPAUs?

Description of included studies

Fourteen studies were included in this review (Akhter et al., 2007; Bignardi et al., 2010; Bigrigg & Read, 1991; Brownlea et al., 2005; Davies & Geoghegan, 1994; Edey et al., 2007; Fox et al., 1999; Harper 2003; Hill, 2009; Poddar et al., 2011; Sellapan et al., 2009; Shillito & Walker, 1997; Tunde-Byass & Cheung, 2009; Twigg et al., 2002).

The majority of the included studies were conducted in the UK, with the exception of one from Ireland (Akhter et al., 2007), one from Canada (Tunde-Byass & Cheung, 2009) and two from Australia (Bignardi et al., 2010; Brownlea et al., 2005).

Of the included studies, four are observational studies that compared outcomes before and after establishment of an early pregnancy assessment unit or clinic (EPAU or EPAC) or acute gynaecology unit (AGU) (Bignardi et al., 2010; Bigrigg & Read, 1991; Brownlea et al., 2005; Tunde-Byass & Cheung, 2009). Two of studies are cross-sectional studies, conducted using a postal survey of EPAUs (Poddar et al., 2011; Twigg et al., 2002). The remaining studies are descriptive, non-comparative papers, detailing the experiences and model of care in a single unit.

Evidence profile

This review aimed to establish how different models of care within EPAUs might impact on service outcomes, clinical outcomes and women's experiences of care. Due to the nature of the evidence that was available for this review question, the findings are presented in a modified evidence profile, split by study design. All of the evidence is of very low quality.

Table 5.2 Findings for service organisation and delivery of EPAUs

Study	Characteristics of model of care			Outcomes	
	Staffing	**Referral systems**	**Availability of out-of-hours care**	**Service outcomes**	**Women's views and experiences of care**
Cross-sectional data from surveys of early pregnancy assessment units (EPAUs)					
Poddar et al., 2011	**Practitioner performing ultrasound (n/total [%])** Sonographers: 67/140 (47.9%) EPAU nurse specialist: 12/140 (8.6%) Trained midwife: 7/140 (5%) Medical staff: 2/140 (1.4%) Combination: 52/140 (37.1%)	**Direct referral system for women (n/total [%])** With previous EP: 125/140 (89%) With recurrent mis-carriage: 113/140 (81%)	**Availability of service in clinics (n/total [%])** *Weekday:* 3-5 hours each weekday: 47/135 (34.8%) 6-11 hours each weekday: 74/135 (54.8%) 3 days a week: 1/135 (0.7%) 2 hours a day: 1/135 (0.7%) *Mean opening time/hours:* 7.3 ± 3.6 *Median (range) opening time/hours:* 8 (2–24) *Weekend:* Full or partial weekend service: 42/140 (30%) • Open Saturday and Sunday: 21/140 (15%) • Open Saturday: 11/140 (7.9%) • Open Sunday: 8/140 (5.7%) Inconsistent weekend service: 2/140 (1.4%)	None reported	None reported

Study	Characteristics of model of care			Outcomes	
	Staffing	**Referral systems**	**Availability of out-of-hours care**	**Service outcomes**	**Women's views and experiences of care**
			Availability of 24 hour contact telephone (n/total [%]) • For women receiving conservative/medical miscarriage management: 103/140 (74%) • For women receiving methotrexate for ectopic pregnancy: 99/125 (79%)		
Twigg et al., 2002	**Practitioner performing ultrasound (%)** Ultrasonographer: (52.0) Radiologist: (2.0) Gynaecologist: (11.8) Gynaecology nurse: (4.9) Other: (2.9) Midwife: (2.9) Combination: (23.5) 54.9% of units said that their scanning practi-tioners had formal training in breaking bad news. 51.5% of clinics said that all patients were seen by a gynaecologist. 95.8% said that they received adequate gynaecological back-up.	**Proportion of clinics accepting women by each referral method (%)** Referral from other clinicians and general practitioners (GPs): 100 Direct from patients: 51 Other (e.g. midwives, Accident and Emergency [A&E], gynaecology): 21	**Availability of service in clinics (%)** Weekday only: 77.4 Seven-day: 13.7 Once per week: 1 24-hour: 7	None reported	None reported

Study	Characteristics of model of care			Outcomes	
	Staffing	**Referral systems**	**Availability of out-of-hours care**	**Service outcomes**	**Women's views and experiences of care**
Descriptive data from individual EPAUs					
Akhter et al., 2007	Senior sonographer, junior doctor and dedicated counselling midwife. (Consultant input is available for complicated cases)	502/603 (83%) of women were self-referred. The remainder were referred by their GP or the A&E department of other hospitals	No. The clinic is open Monday to Friday 7.30 am to 10 am.	**Number of patients seen** 650 women attended during the study period of approximately 6 months **Waiting time/hours (range):** 1 – 3 **Need for a repeat scan (n [%]):** 121 (20%)	None reported
Bignardi et al., 2010	A gynaecological consultant is in charge of the unit on a day-to-day basis. History-taking, clinical examination and transvaginal ultrasound are all undertaken by the consultant.	Referrals must be made by another practitioner (walk-ins are not permitted). The majority are referred by their GP or the emergency department.	No. The clinic is open 9 am – 1 pm Monday to Friday.	**Waiting time/minutes (mean)** • To see trainee gynaecologist: 172 • For ultrasound exam: 199 **Length of stay/minutes (mean)** • as an outpatient: 45 • as an inpatient: 274 **Admission rate (n [%])** • Total: 11 (7) • For ultrasound: 4 (2.5)	None reported
Bigrigg & Read, 1991	Women are seen by the duty senior house officer (SHO), but a registrar and consultant are available on-site if needed.	GPs	Unclear. Open 7 days a week, with a limited on-call system. Out-of-hours operating is avoided.	**Number of women seen** In the first year, 771 women were referred to the unit. **Length of stay/days** • Maximum: 1.5 • For women with viable IUP	None reported

Study	Characteristics of model of care			Outcomes	
	Staffing	**Referral systems**	**Availability of out-of-hours care**	**Service outcomes**	**Women's views and experiences of care**
				or not pregnant: 0.08 (2 hours) • For women needing evacuation of uterus: 1 **Need for a repeat scan (%):** 11	
Brownlea et al., 2005	Women are reviewed by an obstetrics and gynaecology registrar who performs transvaginal ultrasound.	Referrals are received from both the emergency department (ED) and GPs. **Referrals from a non-ED source (%)** Year 1: 26 Year 7: 48	Unclear. The paper reports that referred patients are reviewed on a weekday morning.	**Number of patients seen in Jan-Feb of years following establishment of EPPS (n)** Year 1: 15 Year 7: 61 **Proportion of patients discharged from ED followed up in EPPS (n/total [%])** Year 1: 11/54 (20%) Year 7: 36/52 (69%) **Proportion of EPP patients re-presenting to ED with further pain and/or bleeding (n/total [%])** Year 1: 12/95 (13%) Year 4: 12/82 (15%) Year 7: 6/81 (7%) **Proportion of EPP patients requiring hospital admission (n/total [%])** Year 1: 41/95 (43%)	None reported

Study	Characteristics of model of care			Outcomes	
	Staffing	**Referral systems**	**Availability of out-of-hours care**	**Service outcomes**	**Women's views and experiences of care**
				Year 4: 28/82 (34%) Year 7: 29/81 (36%) (*P* = 0.6 for trend)	
Davies & Geogheg an, 1994	Nurse-led unit, with a team of ward clerks, doctors, scan stenographers and phlebotomists. Following the scan, a registrar compares the scan with the patient's history and makes a diagnosis.	GPs	No details given	None reported	None reported
Edey et al., 2007	An audit of the unit found that only 29% of the women needed to be seen by the junior doctor in the clinic, with the rest being managed by the sonographer and nurse practitioner.	**Source of referrals (%)** GPs: 40 A&E: 2 (No further details given)	Unclear. The clinic is open daily, but no further details are given. It is unclear whether this includes weekends or not.	None reported	None reported
Fox et al., 1999	Out of 198 women, 120 (61%) were managed by a nurse only. 78 (39%) required medical assessment.	Midwives or GPs	No. The clinic is open 5 days a week.	In 198 cases (100%), a nurse practitioner made the correct initial diagnosis in her assessment of the woman's condition.	None reported

Study	Characteristics of model of care			Outcomes	
	Staffing	**Referral systems**	**Availability of out-of-hours care**	**Service outcomes**	**Women's views and experiences of care**
Harper, 2003	Midwife provides care, with later referral to medical personnel if needed.	Self-referrals are accepted, as well as referrals from miscarriage assessment clinic, ante-natal clinic, GPs, A&E, team-based midwives.	Unclear. Women are provided with a 24-hour telephone advice number	None reported	None reported
Hill, 2009	Clinical nurse specialist (runs service), two ultrasonographers and an on-call registrar when required	**Source of referrals (n/total [%])** GP: 96/230 (42%) EPAC: 44/230 (19%) Consultant: 27/230 (12%) A&E: 24/230 (10%) Midwife: 14/230 (6%) SHO: 9/230 (4%) Antenatal: 8/230 (3%) Registrar: 3/230 (1%) Re-scan: 3/230 (1%) Jas: 2/230 (0.9%)	No. The clinic is open weekday mornings.	**Patients seen on time (n/total [%])** Yes: 217/237 (92%) No: 1/237 (0.4%) Not stated: 12/237 (5%) N/A: 2/237 (0.8%) Did not attend: 5/237 (2%) **Acceptable wait for appointment referral (n[(%])** Yes: 161 (68%) No: 1 (0%) Probable rescans or further treatment: 75 (32%) **Number of patients seen:** 82 over a two-month period	**Women reported being seen on time (n [%])** Yes: 79 (96%) No: 3 (4%) **Women felt wait for appointment was acceptable (n [%])** Yes: 76 (94%) No: 5 (6%) **Women felt care in scanning department was given in a sensitive manner (n [%])** Yes: 80 (99%) No: 1 (1%) **Sonographer explained results in a way that women could understand (n [%])** Yes: 81 (99%) No: 1 (1%)

Study	Characteristics of model of care			Outcomes	
	Staffing	**Referral systems**	**Availability of out-of-hours care**	**Service outcomes**	**Women's views and experiences of care**
					Women felt they were given a thorough explanation (n [%]) Yes: 81 (99%) No: 1 (1%) **Women felt questions were answered in a way they could understand (n [%])** Yes: 80 (98%) No: 2 (2%) **Women's satisfaction with interaction with different staff (n/total [%])** ***a.*** *Receptionist* Excellent: 27/63 (43%) Good: 30/63 (48%) Fair: 5/63 (8%) Poor: 1/63 (2%) *b. EPAC Nurse Specialist* Excellent: 76/82 (93%) Good: 6/82 (7%) Fair: 0/82 Poor: 0/82

Study	Characteristics of model of care			Outcomes	
	Staffing	Referral systems	Availability of out-of-hours care	Service outcomes	Women's views and experiences of care
					c. Sonographers Excellent: 66/81 (81%) Good: 14/81 (17%) Fair: 1/81 (1%) Poor: 0/81 *d. Doctors* Excellent: 13/22 (59%) Good: 9/22 (41%) Fair: 0/22 Poor: 0/22 **Women's satisfaction with privacy, dignity and care (n/total [%])** *a. Privacy* Excellent: 65/80 (81%) Good: 14/80 (18%) Fair: 1/80 (1%) Poor: 0/80 (0%) *b. Dignity* Excellent: 69/80 (86%) Good: 11/80 (14%) Fair: 0/80 (0%) Poor: 0/80 (0%)

Study	Characteristics of model of care			Outcomes	
	Staffing	**Referral systems**	**Availability of out-of-hours care**	**Service outcomes**	**Women's views and experiences of care**
					c. Care Excellent: 69/80 (86%) Good: 11/80 (14%) Fair: 0/80 (0%) Poor: 0/80 (0%)
Sellapan et al., 2009	Out of 198 women, 125 (66.5%) were managed by midwives only. 45 (23.9%) were managed by medical staff.	**Source of referrals (n/total [%])** GP: 90/188 (47.8%) Emergency department: 17/188 (9%) Self-referral: 31/188 (16.5%)	No details given	**Waiting time/minutes (n)** • Up to 30 minutes: 95 • Up to 60 minutes: 55 • More than 60 minutes: 18 **Average waiting time/minutes:** 11 **Need for a repeat scan:** 25/188 (13.3%)	None reported
Shillito & Walker, 1997	No details given	Most referrals come through GPs or A&E	No. The clinic is open Monday to Friday from 8 am to 12.30 pm; however staff deal with telephone enquiries until 8 pm.	**Workload per week (average):** 30 **Time of discharge (%)** Same day: 89 Immediately: 80 After same-day evacuation: 9	In a survey of 100 women, over half wanted to see a specialist nurse and less than 10% expected to see a doctor.
Tunde-Byass & Cheung, 2009	Team of dedicated gynaecologists and experienced obstetrical nurses. Gynaecologists perform the ultrasound scans.	**Source of referrals (n/total [%])** Emergency room (ER): 557/1448 (38.5%) Family physician: 445/1448 (30.7%)	No. The clinic is open three mornings per week from 9 am to 12 noon.	**Number of women requiring repeat ER assessment (n/total [%]):** 738/3062 (24.1%)	None reported

Study	Characteristics of model of care			Outcomes	
	Staffing	Referral systems	Availability of out-of-hours care	Service outcomes	Women's views and experiences of care
		Obstetrician-gynaecologist: 349/1448 (24.1%) Midwife: 30/1448 (2.1%) Other: 67/1448 (4.6%)			

A&E accident and emergency department, ED emergency department, EP ectopic pregnancy, EPAC early pregnancy assessment clinic, EPAU early pregnancy assessment unit, EPPS early pregnancy problem service, ER emergency room, IUP intrauterine pregnancy, *P* probability, SHO senior house officer

Evidence statements

Cross-sectional data from surveys of EPAUs

Staffing

Two surveys of EPAUs found that, in approximately half of units, scans were performed by ultrasonographers. Less than a quarter of the clinics reported the scanning was done by either a radiologist, gynaecologist, nurse, midwife or other practitioner.

Referral systems

One survey of EPAUs found that all units accepted referrals from other clinicians and general practitioners (GPs), whereas only 51% of units accepted self-referrals. Another survey found that over 80% of units had direct referrals systems in place for women with a history of ectopic pregnancy or recurrent miscarriage.

Availability of out-of-hours care

One survey of EPAUs (published in 2002) found that 77% of clinics provided a weekday service only, 14% provided a seven-day service, 1% of clinics only provided a weekly service and 7% provided 24-hour care. In a more recent survey (published in 2011), 30% of units reported offering a full or partial weekend service. The duration of opening hours during the week ranged from 2 to 24 hours.

Descriptive data from individual EPAUs

Staffing

Eleven studies reported details about the staffing structure of their unit and described a variety of models of care. Four studies reported that management, including ultrasound scanning, was performed primarily by clinicians, whereas the remainder described a team approach, with varying levels of input and onsite availability of clinicians. Three studies reported the proportion of women seen by each type of practitioner: these found that 24% to 39% of women required assessment by a doctor, with the remainder being successfully managed by nurses, midwives and ultrasonographers. In one nurse-led unit, it was reported that 100% of women were correctly diagnosed by the nurse practitioner in their initial assessment.

Referral systems

Twelve studies reported some details of their units' referral systems, of which only three reported accepting self-referrals. The majority of referrals were reported to be from GPs and emergency departments.

Availability of out-of-hours care

Ten studies reported some detail about the units' opening hours and availability of out-of-hours care. In six of these, it was clear that out-of-hours care was not available, whereas in the remaining papers the details provided were not sufficient to establish availability.

Service outcomes

Five studies reported the number of women seen in the unit, which ranged from about 30 per month to over 100.

Four studies reported waiting times, of which one reported that 92% of women were seen 'on time' (no criteria were reported). The average waiting time reported by the remaining units was between 11 minutes and 3 hours.

Two studies reported the length of stay, which ranged from 45 minutes for an outpatient, to a maximum of over a day. The admission rate ranged from 7% in one study to over 30% in another. One further study reported that 89% of women were discharged on the same day as presentation, 80% immediately and 9% after a same-day evacuation.

Three studies reported the number of women requiring a repeat ultrasound, which ranged from 11% to 20%. Two studies reported the proportion of women re-presenting at the emergency department, which ranged from 7% to 24%.

Women's views and experiences of care

One study found that, of women attending an EPAU, over half wanted to see a specialist nurse and less than 10% expected to see a doctor. A second study assessed women's satisfaction in their interaction with different staff, and found that women ranked their interaction with the nurse specialist as excellent in 93% of cases, compared to 81% for the sonographer, 59% for the doctor and 43% for the receptionist.

The same study found that over 80% of women rated their satisfaction with privacy, dignity and care as excellent. The study reported that 99% of women felt that scanning was done in a sensitive manner and the results were explained in a way that they could understand. Similarly, 99% of women felt that they were given a thorough explanation and 98% felt that their questions were answered in a way that they could understand.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG members wanted to evaluate whether the model of service organisation within an EPAU affected women's clinical outcomes and experiences, and service outcomes. In particular, they felt that the staffing structure, the ability of women to self-refer and the accessibility of the service might affect outcomes such as the length of hospital stay and need for admission, which are important considerations for resource use.

Consideration of clinical benefits and harms

There was a severe paucity of data linking aspects of the service organisation within the EPAU to outcomes; the GDG therefore felt that a research recommendation was warranted to audit models of service delivery within EPAUs and link it to outcomes, both for women and for the service.

The evidence showed that EPAUs currently operate a number of different staffing models, ranging from those led by a medical consultant to a team-based approach with varying levels of input by clinicians. However, there was insufficient evidence to associate staffing structures with outcomes, and it was recognised that any recommendations on personnel would have significant cost implications. Therefore, the GDG did not feel able to recommend that units adopt a specific staffing model without further evidence.

In reviewing the evidence, the GDG recognised that not all early pregnancy assessment services are run from a dedicated building. In some instances they will be run from within a gynaecology ward. Given this, the group agreed that, rather than referring specifically to EPAUs, the guideline should cover early pregnancy assessment services (EPASs) more generally. The group agreed this term would encompass any service dedicated to early pregnancy assessment run by staff with specific experience of caring for women with complications in early pregnancy, where scanning can be carried out, serum β-human chorionic gonadotrophin (hCG) levels measured and decisions about management made. As noted in the section above, the group was also keen to stress that the professionals working in these services should have specific training in how to communicate sensitively and how to break bad news.

From their clinical experience working in EPASs, the GDG members decided that allowing all women to self-refer to the service was not conducive to maximising quality of care. While they understood that some women may wish to attend for reassurance and/or for a scan early in a pregnancy that is progressing normally, they felt that this was not an appropriate use of EPAS resources, which are intended for women experiencing a miscarriage, ectopic pregnancy or other early pregnancy complications. They felt that an excess of self-referrals was likely to result in reduced quality of care within the EPAS for women with early pregnancy problems as a result of services becoming overstretched. Therefore, the group felt that it was appropriate to recommend that women go through a triaging process prior to being referred to an EPAS. It was anticipated that most referrals would come from GPs, with some coming through accident and emergency units (A&E) or midwives. The group agreed that most NHS treatment is accessed through primary care and felt that this model was appropriate in this context as well. They agreed that a benefit of early GP involvement is that it facilitates continuity of care, as it is likely that the GP will also provide any longer term follow-up care that the women requires.

The GDG recognised that women with a history of ectopic or molar pregnancy are at greater risk of a subsequent ectopic pregnancy. Given the raised safety concerns for this group of women the GDG recommended that they be advised that they can present at an EPAU without being referred.

In addition, although additional care for women with recurrent miscarriage was outside of the scope of the guideline, it was recognised that it is current practice for this group of women to be able to self-refer. The group did not wish to imply that these women could no longer do so, and so included this group of women in the recommendation.

The GDG recognised that it is important for women who are referred to an EPAS to be seen promptly. They felt that if a woman's symptoms and clinical situation suggested the need for further investigation or management, it was reasonable to recommend that they be able to access an EPAS within 24 hours. The group agreed that while it was not appropriate to recommend that the service be available 24 hours a day, it would be appropriate to recommend that regional services be organised so that an EPAS would be available 7 days a week. The group noted that this could mean two or more different services within a region working together to ensure that between them a clinic was available every day. The group also noted that this would not entail services opening all day. For example at weekends it might be appropriate to only run a morning clinic.

The group recognised that in some cases women will require immediate investigation. In these instances, if an EPAS service is not available, the group felt it was appropriate to refer women to the nearest facility offering specialist clinical assessment and ultrasound scanning, such as a gynaecology ward. The GDG noted that this was only the case for haemodynamically stable women and that haemodynamically unstable women should be referred directly to A&E.

Consideration of health benefits and resource uses

The GDG members felt that limiting the number of women able to self-refer to early pregnancy assessment units would reduce the cost of running such services, by minimising the number of appointments given to women for whom the service was not intended. They hoped that this would allow resources to be focused on women with the greatest need; that is, those with a threatened or actual miscarriage or ectopic pregnancy. Similarly, they agreed that, without evidence of any association with improved clinical outcomes, it was not appropriate to recommend that units expend resources on providing a 24-hour service or adopting a specific staffing model.

The group did not feel that requiring a 7-day service to be available within regions would have a large impact on resources. They felt that many EPASs currently provide care every day and so this would not be a major change to practice, particularly as the recommendation is only at a regional level, rather than an individual service level. While they accepted that there might be additional costs in some areas, when combined with the likely savings as a result of fewer self-referrals, overall the recommendations in this section were unlikely to have a large cost impact in either direction.

Quality of evidence

The quality of evidence for this review was universally very low: therefore, the GDG members only felt able to make limited recommendations, based on their own experiences, about how early pregnancy assessment services should be organised. The group thought that it was vital that research be conducted to elucidate the most appropriate model of service organisation and delivery, in order to maximise the benefit to women and cost effectiveness of the service.

Information giving and emotional support

As discussed above, the GDG felt that recommending that the majority of women be triaged before referral to a dedicated early pregnancy service would improve care for women attending the service. In particular, reducing the number of women attending the units unnecessarily should help to ensure that healthcare professionals have more time and resources to counsel and support women undergoing the potentially traumatic experience of early pregnancy loss. However, the group also noted that for women with a previous ectopic or molar pregnancy or history of recurrent miscarriage, the prospect of having another serious complication of pregnancy might cause significant fear and psychological problems. Therefore, they felt that it was appropriate that these women be able to self-refer to early pregnancy services.

Other considerations

The group felt that women who have difficulty accessing health care, for example travellers or those with difficulty reading or speaking English, merited extra consideration. Ultimately, the GDG felt that for these different groups of women, the difficulty is with them not accessing healthcare at all. As a result, the GDG felt that allowing these women to self-refer was unlikely to increase the number of them accessing care in a timely manner. Thus it was agreed that there should not be a separate recommendation for this group and that they should be encouraged to access care in the usual way.

Recommendations

Number	Recommendation
5	Regional services should be organised so that an early pregnancy assessment service is available 7 days a week for women with early pregnancy complications, where scanning can be carried out and decisions about management made.
6	An early pregnancy assessment service should: • be a dedicated service provided by healthcare professionals competent to diagnose and care for women with pain and/or bleeding in early pregnancy **and** • offer ultrasound and assessment of serum human chorionic gonadotrophin (hCG) levels **and** • be staffed by healthcare professionals with training in sensitive communication and breaking bad news.
7	Early pregnancy assessment services should accept self-referrals from women who have had recurrent miscarriage* or a previous ectopic or molar pregnancy. All other women with pain and/or bleeding should be assessed by a healthcare professional (such as a GP, accident and emergency [A&E] doctor, midwife or nurse) before referral to an early pregnancy assessment service.
8	Ensure that a system is in place to enable women referred to their local early pregnancy assessment service to attend within 24 hours if the clinical situation warrants this. If the service is not available, and the clinical symptoms warrant further assessment, refer women to the nearest accessible facility that offers specialist clinical assessment and ultrasound scanning (such as a gynaecology ward or A&E service with access to specialist gynaecology support).

Number	Research recommendation
RR 2	A national evaluation of early pregnancy assessment unit service provision should be carried out to identify factors affecting outcomes. Factors should include whether care is provided in a dedicated unit, staffing configuration and opening hours of dedicated services. Outcomes should include both process (service) outcomes and pregnancy-related outcomes. Data collected should be used to analyse the cost effectiveness of early pregnancy assessment units compared with other models of care. **Why this is important** The first report of an early pregnancy assessment unit in England was published over 20 years ago, and prompted the rapid development of centres for the management of problems in early pregnancy. Today there are an estimated 150 early pregnancy

* Although additional care for women with recurrent miscarriage is not included in the scope of the guideline, the Guideline Development Group recognised that it is common clinical practice to allow these women to self-refer to an early pregnancy assessment service and wished this to remain the case.

assessment units in England and Wales (Association of Early Pregnancy Units, 2012). However, there is considerable variation between centres in access to services and levels of care provided. In addition, there has been very little good quality research on the effectiveness of early pregnancy assessment units in improving physical and emotional health compared with services provided outside of a dedicated unit.

A national audit of early pregnancy assessment services would help to make up for this lack of information. Such an audit should be along the lines of the National Caesarean Section Sentinel Audit, a cross-sectional national survey of service configuration and outcomes. Data recorded would include service location, opening hours and the healthcare professionals involved. Outcomes would include time of attendance, length of stay, admission rates, time to treatment and women's experience. Obtaining some of this information would involve early pregnancy services carrying out more formal follow-up of women than they may do currently, for the duration of the audit. The evaluation should be structured to allow for comparisons between different models of care.

Comparative outcome data collected would be used to conduct an analysis of the cost effectiveness of early pregnancy assessment units compared with other models of care.

6 Diagnosis of ectopic pregnancy and miscarriage

6.1 Signs and symptoms of ectopic pregnancy

Review question

What are the signs and symptoms associated with ectopic pregnancy?

Introduction

Ectopic pregnancy is a relatively common and potentially life-threatening complication of pregnancy. Despite this, morbidity and mortality attributable to failure to consider the diagnosis, and therefore missed or delayed diagnosis, continues to be problematic. This is often due to misconceptions and ignorance of symptoms and signs of an ectopic pregnancy. This review seeks to clarify the relative importance of these individual factors in diagnosing an ectopic pregnancy.

Description of included studies

Twenty-nine studies were included in this review (Aboud & Chaliha, 1998; Al-Suleiman & Khwaja, 1992; Banerjee et al., 1999; Barnhart et al., 2003; Barnhart et al., 2006; Bouyer et al., 2002; Buckley et al., 1998; Choi et al., 2011; Clancy & Illingworth, 1989; Condous et al., 2007; Diamond et al., 1994; Dimitry, 1989; Downey & Zun, 2011; Easley et al., 1987; Goksedef et al., 2011; Gonzalez & Waxman, 1981; Hutton & Narayan, 1986; Jabbar & Al-Wakeel, 1980; Jiao et al., 2008; Kazandi & Turan, 2011; Larrain et al., 2011; Makinen et al., 1984; Menon et al., 2007; Michelas et al., 1980; Powers, 1980; Raziel et al., 2004; Shaunik et al., 2011; Tsai et al., 1995; Wong & Suat, 2000).

The included studies consist of one case–control study (Barnhart et al., 2006) and four prospective observational studies (Banerjee et al., 1999; Buckley et al., 1998; Condous et al., 2007; Shaunik et al., 2011), while the remainder were retrospective case series.

The studies were conducted in the UK (Aboud & Chaliha, 1998; Banerjee et al., 1999; Clancy & Illingworth, 1989; Condous et al., 2007; Dimitry, 1989), the USA (Barnhart et al., 2003; Barnhart et al., 2006; Buckley et al., 1998; Diamond et al., 1994; Downey & Zun, 2011; Easley et al., 1987; Gonzalez & Waxman, 1981; Menon et al., 2007; Powers, 1980; Shaunik et al., 2011), France (Bouyer et al., 2002; Larrain et al., 2011;), Finland (Makinen et al., 1984), Greece (Michelas et al., 1980), Turkey (Goksedef et al., 2011; Kazandi & Turan, 2011), New Zealand (Hutton & Narayan, 1986), China (Jiao et al., 2008; Tsai et al., 1995), Singapore (Wong & Suat, 2000), South Korea (Choi et al., 2011), Israel (Raziel et al., 2004), and Saudi Arabia (Al-Suleiman & Khwaja, 1992; Jabbar & Al-Wakeel, 1980).

All studies evaluated the presenting signs and symptoms of women diagnosed with an ectopic pregnancy (EP), or reported the frequency of risk factors among the participants. Two studies included only cases of ovarian pregnancy (Choi et al., 2011; Raziel et al., 2004), one study only included cases of proximal ectopic pregnancy (Larrain et al., 2011) and one study included only cases of caesarean scar pregnancy (Jiao et al., 2008). Three studies evaluated the signs and symptoms of women initially classified as having pregnancies of unknown location (PUL) who were later diagnosed with an ectopic pregnancy (Banerjee et al., 1999; Condous et al., 2007; Shaunik et al., 2011). The GDG recognised that the key clinical question centred on recognition of signs and symptoms of ectopic pregnancy; however it felt it might also be helpful to report the risk factors for ectopic

pregnancy if these were available from included studies as it wanted to highlight the limitations inherent in using risk factors to help make a diagnosis.

Evidence profile

When more than one study reported a risk factor, symptom or sign, the reported percentage is the median frequency derived from the reported frequency in each study. The range of frequencies given is simply the minimum and maximum frequency as reported in the studies that included that particular risk factor, symptom or sign. These have been presented in order to provide some guidance as to which risk factors, signs and symptoms are most frequently associated with ectopic pregnancy and to illustrate the wide range of possible presenting symptoms and signs.

Evidence quality has been downgraded if the studies were retrospective, had a small sample size (N of 50 or fewer), or if five or fewer studies reported the finding and there was a serious issue of indirectness with at least one of the study populations. Unusual study populations are detailed in the table.

Risk factors and symptoms are presented in order of decreasing frequency; signs are presented in the order in which they might be elicited.

Table 6.1 GRADE summary of findings for the risk factors, symptoms, and signs of ectopic pregnancy

Risk factor, symptom, or sign	Number of studies	Number of study participants	Observed frequency (median % [minimum – maximum])	Other considerations (such as study population)	Quality
Risk factors for ectopic pregnancy					
Smoking	3	1990	48.1 (19–59.5)	Maximum reported in a study of proximal ectopic pregnancies	Low
No risk factors	6	691	37.2 (23.8–76.9)	Maximum reported in a study whose inclusion criterion was presentation with pain and/or bleeding	Moderate
Prior pelvic or abdominal surgery	15	2963	22.5 (9.5–100)	Maximum reported in a study of 28 caesarean scar pregnancies (maximum is otherwise 48.8%)	Moderate
History of a sexually transmitted infection	3	2498	19.7 (4.9–21.3)	Maximum reported in a study whose inclusion criterion was presentation with pain and/or bleeding	Moderate
History of elective abortion	7	1594	18.6 (14.9–47)	None	Moderate
History of infertility	10	1367	16.9 (5.5–46.7)	Maximum reported in a study with 53% ruptured EP (maximum is otherwise 37.9%)	Moderate

Risk factor, symptom, or sign	Number of studies	Number of study participants	Observed frequency (median % [minimum – maximum])	Other considerations (such as study population)	Quality
History of miscarriage	7	3069	16.4 (11.3–33)	None	Moderate
History of pelvic inflammatory disease	18	3446	15.5 (4–44.4)	Maximum reported in a study with 53% ruptured EP (maximum is otherwise 33%)	Moderate
History of ectopic pregnancy	16	4498	10.5 (2.2–27.9)	Minimum reported in a study with 53% ruptured EP (minimum is otherwise 6%) Maximum reported in a study of proximal ectopic pregnancies (maximum is otherwise 16.6%)	Moderate
History of IUCD use	18	5025	10.1 (2.2–68.4)	Minimum reported in a study with 53% ruptured EP (minimum is otherwise 4.1%) Maximum reported in a study of 19 ovarian pregnancies (maximum is otherwise 33.3%)	Moderate
Use of the oral contraceptive pill	7	1302	6.7 (0.6–64.6)	Maximum reported in a population of 65 proximal ectopic pregnancies (maximum is otherwise 15.0%)	Moderate
Prior tubal surgery	11	3353	6 (3.9–18.7)	Minimum reported in a study with 74% ruptured EP (minimum is otherwise 4.8%)	Moderate
Endometriosis	5	671	4.7 (3.6–32.7)	Maximum reported in a study of 49 ovarian pregnancies (maximum is otherwise 5%)	Low
Symptoms reported					
Abdominal or pelvic pain	21	3356	93.3 (42.9–100)	Minimum reported in a study of 49 ovarian pregnancies (minimum is otherwise 54.2%)	Moderate

Risk factor, symptom, or sign	Number of studies	Number of study participants	Observed frequency (median % [minimum – maximum])	Other considerations (such as study population)	Quality
Amenorrhea	11	2228	73 (8.2–98)	Minimum reported in a study of 49 ovarian pregnancies (minimum is otherwise 64.3%) Maximum reported in a study with 68% ruptured EP (maximum is otherwise 96.4%)	Moderate
Vaginal bleeding with/without clots	25	3942	64.0 (14–82)	None	Moderate
Breast tenderness	3	666	25.6 (8.9–31.7)	Minimum reported in a study with 68% ruptured EP (minimum is otherwise 25.6%)	Low
Gastro-intestinal symptoms	10	1623	21.3 (2.0–48.3)	Minimum reported in a study of 49 ovarian pregnancies (minimum is otherwise 15.5%)	Moderate
Dizziness/fainting/ syncope	12	2334	21.1 (4.7–84.2)	Maximum reported in a study where the denominator for this finding was n = 19 (maximum is otherwise 49%)	Moderate
Shoulder tip pain	7	818	19 (5–35.1)	None	Moderate
Urinary symptoms	3	588	8.7 (5.9–23.3)	Minimum reported in a study with 68% ruptured EP (minimum is otherwise 8.7%)	Low
Asymptomatic	3	247	8.3 (2.9–18.4)	Maximum reported in a study of 49 ovarian pregnancies	Low
Passage of tissue	2	143	7.6 (2.6–12.5)	Minimum reported in a study whose inclusion criterion was presentation with pain and/or bleeding	Moderate
Rectal pressure or pain on defecation	3	753	7 (6.7–9)	Median reported in a study with 68% ruptured EP	Low

Risk factor, symptom, or sign	Number of studies	Number of study participants	Observed frequency (median % [minimum – maximum])	Other considerations (such as study population)	Quality
Signs identified on examination					
Shock or collapse	8	906	14.7 (2–23)	Minimum reported in a study of 49 ovarian pregnancies (minimum is otherwise 10%)	Moderate
Pallor	1	97	44.3 (N/A)	None	Moderate
Tachycardia or hypotension	5	1077	21 (13.6–75.6)	Minimum reported in a study with 68% ruptured EP (minimum is otherwise 15%) Maximum reported in a study with 53% ruptured EP (maximum is otherwise 23%)	Low
Orthostatic hypotension	3	580	4.6 (3.3–17.6)	None	Moderate
Abdominal distension	2	259	36.8 (17.2–56.4)	Minimum reported in a study with 74% ruptured EP	Low
Abdominal tenderness	11	1659	77.9 (7.4–91.2)	Minimum reported in a population of 27 EP initially diagnosed as PUL (minimum is otherwise 58.8%) Maximum reported in a study with 74% ruptured EP (maximum is otherwise 91%)	Moderate
Rebound tenderness/peritoneal signs	9	1469	45.1 (23.1–86)	Minimum reported in a study whose inclusion criterion was presentation with pain and/or bleeding	Moderate
Adnexal tenderness	7	821	82 (53.3–94.6)	Maximum reported in a study with 74% ruptured EP (maximum is otherwise 85.5%)	Moderate
Cervical motion tenderness	8	1334	50.3 (33.3–86.5)	Minimum reported in a study whose inclusion criterion was presentation with pain and/or bleeding	Moderate

Risk factor, symptom, or sign	Number of studies	Number of study participants	Observed frequency (median % [minimum – maximum])	Other considerations (such as study population)	Quality
Pelvic tenderness	1	177	91 (N/A)	None	Moderate
Enlarged uterus	6	952	28.4 (15.4–36.7)	Minimum reported in a study with 68% ruptured EP (minimum is otherwise 17.6%)	Moderate
Adnexal mass	9	855	26.9 (5.1–55.7)	Minimum reported in a study whose inclusion criterion was presentation with pain and/or bleeding (minimum is otherwise 6.1%) Maximum reported in a study with 68% ruptured EP (maximum is otherwise 49.5%)	Moderate
Palpable pelvic mass	2	242	15.7 (12.3–19)	None	Moderate

EP ectopic pregnancy, IUCD intrauterine contraceptive device, N/A not available, PUL pregnancy of unknown location,

Evidence statements

Unless otherwise stated, all the evidence is of moderate quality.

Risk factors for ectopic pregnancy

Evidence from six studies showed that, on average, 37% of women with ectopic pregnancy had no risk factors for ectopic pregnancy.

Evidence from three studies showed that, on average, 48% of women with ectopic pregnancy smoked cigarettes (low quality).

Evidence from 15 studies showed that, on average, 23% of women with ectopic pregnancy had a prior pelvic or abdominal surgery.

The evidence showed that 10–20% of women with ectopic pregnancy had a history of a sexually transmitted infection (three studies), a previous elective abortion (seven studies), a history of infertility (10 studies), a previous miscarriage (seven studies), a history of pelvic inflammatory disease (18 studies), a previous ectopic pregnancy (16 studies) or a history of intrauterine contraceptive device (IUCD) use (13 studies).

The evidence showed that less than 10% of women with ectopic pregnancy had a history of oral contraceptive pill use (seven studies), prior tubal surgery (11 studies) or endometriosis (two studies, low quality).

Symptoms reported

The evidence showed that the majority of women with ectopic pregnancy presented with abdominal or pelvic pain (93%, 21 studies), amenorrhea (73%, 11 studies) or vaginal bleeding (64%, 25 studies).

The evidence showed that 20–30% of women with ectopic pregnancy presented with breast tenderness (three studies, low quality), gastro-intestinal symptoms (10 studies) or dizziness, fainting or syncope (12 studies).

The evidence showed that 10–20% of women with ectopic pregnancy presented with shoulder tip pain (seven studies).

The evidence showed that less than 10% of women with ectopic pregnancy presented with urinary symptoms (three studies, low quality), passage of tissue (two studies), rectal pressure or pain on defecation (three studies, low quality) or no symptoms (three studies, low quality).

Signs identified on examination

The evidence showed that the majority of women with ectopic pregnancy had pelvic tenderness (91%, one study), adnexal tenderness (82%, seven studies) or abdominal tenderness (78%, 11 studies).

The evidence showed that 40–75% of women with ectopic pregnancy had cervical motion tenderness (eight studies), pallor (one study) or rebound tenderness or peritoneal signs (nine studies).

The evidence showed that 20–40% of women with ectopic pregnancy had abdominal distension (two studies, low quality), an enlarged uterus (six studies), an adnexal mass (nine studies) or tachycardia or hypotension (five studies, low quality).

The evidence showed that less than 20% of women with ectopic pregnancy had a palpable pelvic mass (two studies), were collapsed or in shock (eight studies) or had orthostatic hypotension (three studies).

Evidence to recommendations

Relative value placed on the outcomes considered

In conducting this review, the GDG was keen to identify uncommon signs and symptoms associated with ectopic pregnancy.

Consideration of clinical benefits and harms

The group recognised that there was a wide range of symptoms associated with ectopic pregnancy, including some non-specific symptoms such as gastro-intestinal symptoms. Given this, it felt that there is value in healthcare professionals always considering pregnancy in women of childbearing age presenting with these symptoms, and thus they should consider conducting a pregnancy test. If a woman is found to be pregnant, the GDG agreed that ectopic pregnancy should be considered, as many of the symptoms of ectopic pregnancy are the same as those of pregnancy in general. The group felt strongly that all healthcare professionals who provide care to women of reproductive age should have access to pregnancy tests, so that women with a suspected ectopic pregnancy can be identified and referred promptly and appropriately.

The evidence showed that cervical motion tenderness, pelvic tenderness and pain or tenderness in the abdominal region were associated with ectopic pregnancy. As a result, the group recommended that women with tenderness or pain in these areas and a positive pregnancy test should be immediately referred for further assessment. ‘Immediately’ here means the further assessment should take place as soon as possible, and at least within a few hours of the initial assessment. Where possible the woman should go directly from the place of the initial assessment to the early pregnancy assessment service (EPAS) – or alternative out of hours gynaecology service if the EPAS is not open – so as not to incur further delay.

The GDG recognised that risk factors were not a helpful method for identifying women with an ectopic pregnancy, as about a third of women with an ectopic pregnancy had no identifiable risk factors. The group agreed that even in the absence of risk factors, it would still be necessary for a healthcare professional to rule out the possibility of ectopic pregnancy, and thus agreed that risk factors should not be used as a diagnostic aid.

Consideration of health benefits and resource use

The group recognised that lowering the index of suspicion for ectopic pregnancy was likely to lead to an increase in the number of women being offered a pregnancy test and thus an increase in the number of women referred to an EPAS. However, the group felt that this approach was very likely to be cost effective given the potential large loss of quality adjusted life years (QALYs) associated with missing a diagnosis of ectopic pregnancy.

Quality of evidence

The majority of evidence was of moderate quality and, as such, the GDG felt that it was sufficient to make recommendations.

Information giving and emotional support

From their clinical experience, the GDG members thought that uncertainty about what was happening would increase women's anxiety. Therefore, they felt that it was important that women who required referral were given information about why the referral was necessary, and what they might expect when they arrived at the EPAS.

Other considerations

The GDG was keen to emphasise that ectopic pregnancy can present with a variety of symptoms and agreed that it would be helpful for healthcare professionals to be able to refer to a list of potential signs and symptoms. Although reported in the evidence, the GDG members felt that it was not appropriate to include 'adnexal mass' or 'palpable pelvic mass' in the list of signs and symptoms. From their clinical experience, they noted that palpation can increase the risk of an ectopic pregnancy rupturing. They also felt that, while palpation to detect an internal mass might once have been used in the diagnosis of ectopic pregnancy, the development of new diagnostic modalities (such as transvaginal ultrasound and biochemical tests) has meant that it is no longer appropriate.

The GDG felt that a decision tool, incorporating risk factors, signs and symptoms, could be very valuable in decreasing the likelihood of women with ectopic pregnancies being misdiagnosed and therefore mismanaged. The group noted, however, that the evidence from this review was not sufficient to develop and validate such a tool, and therefore decided that a research recommendation was warranted. The group felt that such a tool would be extremely valuable in allowing healthcare professionals, particularly non-specialists, to evaluate a woman's likelihood of having an ectopic pregnancy and to determine the level of urgency of any resulting referral.

The GDG felt it important to note that not all women presenting to a healthcare professional with bleeding in early pregnancy need to be referred for a transvaginal ultrasound scan. For women who are reporting to be less than 6 weeks pregnant with bleeding but no pain, expectant management could be undertaken. The GDG felt that this was justified, because at gestations of earlier than 6 weeks, the pregnancy is likely to be too small to yield any information about viability. In addition, from their clinical experience, the GDG members agreed that many women experience spotting in early pregnancy which resolves without need for further intervention. They agreed that these women should be advised to take a pregnancy test 7–10 days later and that they should return in the interim if their symptoms continue or worsen.

The group agreed that in all other cases, that is where women are more than 6 weeks pregnant with blood loss or are in pain, or where there is uncertainty about the pregnancy's gestation, referral to a dedicated early pregnancy service should be made in order that an ultrasound scan can be carried out.

Recommendations

Number	Recommendation
9	Refer women who are haemodynamically unstable, or in whom there is significant concern about the degree of pain or bleeding, directly to A&E.
10	Be aware that atypical presentation for ectopic pregnancy is common.
11	Be aware that ectopic pregnancy can present with a variety of symptoms. Even if a symptom is less common, it may still be significant. Symptoms of ectopic pregnancy include: • common symptoms: o abdominal or pelvic pain o amenorrhoea or missed period o vaginal bleeding with or without clots

- other reported symptoms:
  - breast tenderness
  - gastrointestinal symptoms
  - dizziness, fainting or syncope
  - shoulder tip pain
  - urinary symptoms
  - passage of tissue
  - rectal pressure or pain on defecation.

12 Be aware that ectopic pregnancy can present with a variety of signs on examination by a healthcare professional. Signs of ectopic pregnancy include:

- more common signs:
  - pelvic tenderness
  - adnexal tenderness
  - abdominal tenderness
- other reported signs:
  - cervical motion tenderness
  - rebound tenderness or peritoneal signs
  - pallor
  - abdominal distension
  - enlarged uterus
  - tachycardia (more than 100 beats per minute) or hypotension (less than 100/60 mmHg)
  - shock or collapse
  - orthostatic hypotension.

13 During clinical assessment of women of reproductive age, be aware that:

- they may be pregnant, and think about offering a pregnancy test even when symptoms are non-specific **and**
- the symptoms and signs of ectopic pregnancy can resemble the common symptoms and signs of other conditions – for example, gastrointestinal conditions or urinary tract infection.

14 All healthcare professionals involved in the care of women of reproductive age should have access to pregnancy tests.

15 Refer immediately to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) for further assessment women with a positive pregnancy test and the following on examination:

- pain and abdominal tenderness **or**
- pelvic tenderness **or**
- cervical motion tenderness.

16 Exclude the possibility of ectopic pregnancy, even in the absence of risk factors (such as previous ectopic pregnancy), because about a third of women with an ectopic pregnancy will have no known risk factors.

17 Refer to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) women with bleeding or other symptoms and signs of early pregnancy complications who have:

- pain **or**
- a pregnancy of 6 weeks gestation or more **or**
- a pregnancy of uncertain gestation.

The urgency of this referral depends on the clinical situation.

18	Use expectant management for women with a pregnancy of less than 6 weeks gestation who are bleeding but not in pain. Advise these women: • to repeat a urine pregnancy test after 7–10 days and to return if it is positive • a negative pregnancy test means that the pregnancy has miscarried • to return if their symptoms continue or worsen.
19	Refer women who return with worsening symptoms and signs that could suggest an ectopic pregnancy to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) for further assessment. The decision about whether she should be seen immediately or within 24 hours will depend on the clinical situation.
20	If a woman is referred to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available), explain the reasons for the referral and what she can expect when she arrives there.

Number	Research recommendation
RR 3	Research should be undertaken to design and validate a decision tool for evaluating signs, symptoms and risk factors for correctly identifying ectopic pregnancy

6.2 Ultrasound for determining a viable intrauterine pregnancy

Review question

What is the diagnostic value of ultrasound for determining a viable intrauterine pregnancy?

Introduction

The application of ultrasound is well established and important in the assessment and evaluation of early pregnancy events and complications. Its use in early pregnancy assessment may be routine but practices vary considerably. Although high resolution transvaginal ultrasound has been widely adopted, the limitations of accuracy in defining ultra-small structures, such as a fetal heart at early gestations, are generally acknowledged. The aim of this review was to identify the point at which the viability of a pregnancy can be definitively confirmed using ultrasound. This threshold also represents the point at which miscarriage can be definitively diagnosed.

Description of included studies

Fifteen studies were included in this review (Abaid et al., 2007; Abdallah et al., 2011; Bree et al., 1989; Brown et al., 1990; Cacciatore et al., 1990; de Crespigny, 1988; Ferrazzi et al., 1993; Goldstein, 1992; Hassan et al., 2009; Levi et al., 1988; Levi et al., 1990; Pennell et al., 1991; Rempen, 1990; Rowling et al., 1999; Steinkampf et al., 1997).

The included studies consist of nine prospective observational studies (Abdallah et al., 2011; Bree et al., 1989; Cacciatore et al., 1990; de Crespigny, 1988; Goldstein, 1992; Hassan et al., 2009; Pennell et al., 1991; Rempen, 1990; Rowling et al., 1999), five retrospective observational studies (Abaid et al., 2007; Ferrazzi et al., 1993; Levi et al., 1988; Levi et al., 1990; Steinkampf et al., 1997) and one partially retrospective observational study (Brown et al., 1990).

The studies were conducted in the UK (Abdallah et al., 2011; Hassan et al., 2009), Germany (Rempen, 1990), Italy (Ferrazzi et al., 1993), Finland (Cacciatore et al., 1990), the USA (Abaid et al.,

2007; Bree et al., 1989; Brown et al., 1990; Goldstein, 1992; Pennell et al., 1991; Rowling et al., 1999; Steinkampf et al., 1997), Canada (Levi et al., 1988; Levi et al., 1990) and Australia (de Crespigny, 1988).

All included studies evaluated the use of transvaginal ultrasound for visualising fetal cardiac activity in intrauterine pregnancies, and stratified their findings by gestational age, crown–rump length (CRL) or gestation sac size. Two studies additionally compared the performance of transabdominal ultrasound in visualising cardiac activity (Ferrazzi et al., 1993; Pennell et al., 1991).

Evidence profile

Table 6.2 GRADE summary of findings for evaluation of ultrasound for determining a viable intrauterine pregnancy

Number of studies	Type of ultrasound scan (transvaginal [TVU] or transabdominal [TAU])	Number of women scanned for fetal cardiac activity, and stratified by fetal size/age (total study participants)	Threshold at which 100% of fetuses that later proved to be viable can be identified	Quality
Visualisation of cardiac activity by crown–rump length (mm)				
1 study (Rempen, 1990)	5 MHz TVU	292 (363)	3	High
1 study (Pennell et al., 1991)	5 MHz / 3.5 MHz TAU 5 MHz / 7.5 MHz TVU	175 (175)	TAU: 9 TVU: 5	High
1 study (Hassan et al., 2009)	TVU	1174 (1174)	6.0	Moderate
1 study (Abaid et al., 2007)	8 MHz TVU	179 (179)	3.5	Moderate
1 study (Brown et al., 1990)	5 MHz TVU	375 (375)	5	Moderate
1 study (Abdallah et al., 2011)	6–12 MHz TVU	179 (1060)	5.3	Low
1 study (Levi et al., 1990)	6.5 MHz TVU	71 (71)	4.0	Low
1 study (Goldstein, 1992)	5 MHz / 7.5 MHz TVU	96 (96)	4	Low
Visualisation of cardiac activity by gestation sac diameter (mm)				
1 study (Rempen, 1990)	5 MHz TVU	354 (363)	18.3 *	High

Number of studies	Type of ultrasound scan (transvaginal [TVU] or transabdominal [TAU])	Number of women scanned for fetal cardiac activity, and stratified by fetal size/age (total study participants)	Threshold at which 100% of fetuses that later proved to be viable can be identified	Quality
1 study (Abdallah et al., 2011)	6–12 MHz TVU	462[§] (1060)	21	Moderate
		419[§] (1060)	21	
1 study (Bree et al., 1989)	7 MHz TVU	53 (53)	> 9	Moderate
1 study (Rowling et al., 1999)	9-5 MHz TVU	39 (39)	13	Low
1 study (Levi et al., 1988)	6.5 MHz TVU	35 (62)	16	Very low
1 study (de Crespigny, 1988)	5 MHz TVU	353 (353)	> 12	Low
1 study (Steinkampf et al., 1997)	5 MHz TVU	82 (82)	19[†]	Very low
1 study (Cacciatore et al., 1990)	5 MHz / 6.5 MHz TVU	20 (22)	> 18[‡]	Very low
Visualisation of cardiac activity by gestational or menstrual age (days)				
1 study (Rempen, 1990)	5 MHz TVU	252 (363)	46 (menstrual age)	High
1 study (Bree et al., 1989)	7 MHz TVU	53 (53)	> 40 (gestational age)	Moderate
1 study (Steinkampf et al., 1997)	5 MHz TVU	82 (82)	45.5[†] (gestational age)	Very low
1 study (Ferrazzi et al., 1993)	5 MHz TAU / 5 MHz TVU	76 (598)	TAU: 37 TVU: 35 (menstrual age)	Very low
1 study (Cacciatore et al., 1990)	5 MHz / 6.5 MHz TVU	20 (22)	> 43[‡] (gestational age)	Very low

TAU transabdominal ultrasound, TVU transvaginal ultrasound

* Chorionic cavity diameter

† Point of 99% probability of visualisation

‡ Point of 'reliable detection'

§ 462 scans showed a gestation sac without a visible embryo or yolk sac. 419 scans showed a gestation sac with a yolk sac, but without a visible embryo.

Evidence statements

All evidence statements relate to the use of transvaginal ultrasound (TVU) unless otherwise stated.

Visualisation of cardiac activity by crown–rump length

One study provided high quality evidence that cardiac activity can be visualised in all viable fetuses with a CRL of at least 3 mm. One further study provided high quality evidence that cardiac activity can be visualised in all viable fetuses with a CRL of at least 5 mm using transvaginal ultrasound, and at least 9 mm using transabdominal ultrasound. Three studies provided moderate quality evidence that cardiac activity can be visualised in all viable fetuses with a CRL of at least 6.0 mm, at least 5 mm and at least 3.5 mm respectively. One study provided low quality evidence that viability can be correctly determined in all fetuses with a CRL of 5.3 mm. Two further studies provided low quality evidence that cardiac activity can be visualised in all viable fetuses with a CRL of at least 4 mm.

Visualisation of cardiac activity by gestation sac

One study provided high quality evidence that cardiac activity can be visualised in all viable fetuses with a chorionic cavity diameter of at least 18.3 mm. One study provided moderate quality evidence that viability can be correctly determined in all fetuses with a gestation sac of 21 mm, in the absence of an embryo, with or without a yolk sac. One study provided moderate quality evidence that cardiac activity can be visualised in all viable fetuses with a gestation sac diameter exceeding 9 mm. Two studies provided low quality evidence that cardiac activity can be visualised in all viable fetuses with a gestation sac diameter of at least 13 mm or exceeding 12 mm. One study provided very low quality evidence that cardiac activity can be visualised in all viable fetuses with a gestation sac diameter of at least 16 mm while another study provided very low quality evidence that cardiac activity can be visualised in 99% of viable fetuses with a gestation sac diameter of at least 19 mm. One study provided very low quality evidence that cardiac activity can be reliably detected when the gestation sac diameter exceeds 18 mm.

Visualisation of cardiac activity by gestational age

One study provided high quality evidence that cardiac activity can be visualised in all viable fetuses with a gestational age of at least 46 days. One study provided moderate quality evidence that cardiac activity can be visualised in all viable fetuses with a gestational age exceeding 40 days. One study provided very low quality evidence that cardiac activity can be visualised in 99% of viable fetuses with a gestational age of at least 45.5 days. One study provided very low quality evidence that cardiac activity can be visualised in all viable fetuses with a gestational age of at least 35 days using transvaginal ultrasound, and at least 37 days using transabdominal ultrasound. One further study provided very low quality evidence that cardiac activity can be reliably detected in all viable fetuses with a gestational age exceeding 43 days.

Evidence to recommendations

Relative value placed on the outcomes considered

The outcomes for this review were the thresholds of gestational age, CRL or gestation sac diameter at which 100% of fetuses that later proved to be viable had cardiac activity visible on ultrasound. The GDG noted that, even when women could be completely certain about the date of intercourse or last menstrual period, variation in the menstrual cycle and rate of fetal growth might result in inaccurate estimates of gestational age. Therefore, the GDG felt that the use of a gestational age threshold alone was not appropriate for the determination of viability. From their own clinical experience the GDG members felt that, where it was possible to measure the crown–rump length, this would provide the most accurate estimate of development. They were also aware of recent work by Pexsters et al. (2011) which found that measurement of mean gestational sac diameter was associated with higher inter-observer variability than measurement of crown–rump length. Therefore, measurement of mean gestational sac diameter was only recommended in cases where a fetal pole could not be identified.

Consideration of clinical benefits and harms

The evidence suggested that transvaginal ultrasound scans are more effective than transabdominal ultrasound scans for visualising structures and this was borne out by the GDG's clinical experience. The group agreed that the majority of scans are now conducted transvaginally and felt that it was appropriate to recommend that a transvaginal scan be recommended in the first instance. It accepted that some women may opt for a transabdominal scan, and that this could be offered as an alternative. However, GDG members felt that it was important that women be given information about the potential limitations of transabdominal scanning so that they could make a fully informed choice.

The GDG felt that it was appropriate to set thresholds for the determination of a viable intrauterine pregnancy; however, considering the consequences of misdiagnosing a viable intrauterine pregnancy as a miscarriage, the group felt that the thresholds should be conservative. The group noted that in the studies there was a 100% success rate in diagnosing viable intrauterine pregnancies using a CRL threshold of 6 mm or more. However, GDG members also noted that Pexsters et al. (2011) documented the potential for considerable intra- and inter-observer variation in measurements of CRL and mean gestational sac diameter. They also felt that there was additional potential for variation in measurements linked to the quality of scanning equipment and the skill level of the sonographer. In light of all of these considerations, the GDG determined that fetal non-viability should not be diagnosed based on the absence of a heartbeat in fetuses with a CRL of less than 7.0 mm or a mean gestational sac diameter of less than 25.0 mm, as measured on a single transvaginal ultrasound. They felt that, at such small sizes, it would not be possible to determine whether a miscarriage had truly occurred or whether the embryo was simply too small for there to be a visible heartbeat. Therefore, up to and including these thresholds, all women should have a repeat scan to confirm the findings of the initial scan. The GDG discussed what would be an appropriate interval between scans, balancing the fact that sufficient time would need to pass to be able to confirm the diagnosis with the fact that women might understandably want an answer as soon as possible. They agreed that when using a transvaginal ultrasound, it would be appropriate to wait for a minimum of 7 days before repeating the scan when measuring either the CRL or the mean gestational sac diameter.

Due to the significant consequences of misclassifying a viable pregnancy as a miscarriage, the GDG felt that it was reasonable to recommend that, in the absence of a visible heartbeat above these thresholds (that is, a CRL greater than or equal to 7 mm and/or a mean gestational sac diameter greater than or equal to 25 mm), all sonographers should seek a second opinion before definitively diagnosing a non-viable pregnancy. However, they also realised that some women might instead wish to wait and have a second confirmatory scan at a later date, and felt that this was a reasonable alternative.

Based on their clinical experience, and evidence from another review comparing transvaginal and transabdominal ultrasound for diagnosing ectopic pregnancy (see Section 6.3 below), the GDG members decided that transvaginal ultrasound would generally be the optimal mode of scanning. However, they recognised that, in some circumstances, a transvaginal ultrasound might not be appropriate or acceptable to women, and therefore a transabdominal scan could be offered as an alternative. Given the poorer quality of imaging when using a transabdominal scan, the group agreed that there should be an interval of at least 14 days between repeat transabdominal scans before providing a diagnosis, in order to ensure that any change in the size of the CRL or mean gestational sac diameter was identifiable. The group felt that while there were thresholds where a definitive diagnosis was possible following second opinion when using transvaginal scans, this was not possible with a transabdominal scan. Since there is a greater potential for key features not to be visible on a transabdominal scan, it was felt a second opinion would not be helpful.

Consideration of health benefits and resource uses

The GDG did not feel that recommending a repeat ultrasound scan would add significantly to the case load and resource use, because in practice this often happens anyway. However, it did feel that cost effectiveness should be a component of any research conducted in this area, and therefore incorporated it into a research recommendation. Given the number of women requesting scans in early pregnancy and the associated service and cost implications, the group felt that it was important that research be done in this area, to determine the timing and frequency of ultrasound examinations that would maximise improvements in diagnosis, outcomes and women's experience.

Quality of evidence

The quality of evidence ranged from high to very low quality and the GDG members felt that, in conjunction with their clinical experience, it was appropriate to make recommendations based on the findings.

Information giving and emotional support

The GDG recognised that throughout all episodes of care it is important that women be given evidence-based information about the risks, benefits and limitations of investigations being offered as well as determining what the woman expects from the investigation in order to ensure any misunderstandings can be clarified. They cross-referred here to NICE clinical guidance 138 Patient experience in adult NHS services.

From their own experience, and data about the risks of expectant management reported in another review question (see Section 6.3), the GDG members felt that there would be minimal risk in recommending that some women wait a week for a repeat scan, particularly when balanced against the consequences of accidentally terminating a viable pregnancy after misdiagnosis. However, they felt that it was important that women were informed about what to expect in the intervening week and what symptoms should prompt them to seek medical attention. Given this, they also recommended that women should be provided with a 24-hour contact telephone number. The GDG was of the opinion that, due to the fact that miscarriage is a potentially traumatic experience, it was important that women be able to contact someone who would be able to give them accurate information and appropriate support. Therefore, it recommended that this telephone number should allow women to speak directly with someone with experience of dealing with early pregnancy complications and should not simply be a non-specific service like an emergency department.

6.3 Accuracy of imaging techniques for diagnosis of an ectopic pregnancy

Review question

What is the accuracy of transvaginal ultrasound compared with transabdominal ultrasound for diagnosing ectopic pregnancy?

Introduction

The estimated prevalence of ectopic pregnancy is 1–2% worldwide, with nearly 12,000 ectopic pregnancies diagnosed each year in the UK. Associated costs are high due to repeated diagnostic tests, delayed diagnosis and its treatment (Jurkovic & Wilkinson, 2011). Critical evaluation of patient symptoms and signs remains important for the detection of ectopic pregnancy; however, ultrasound scanning remains the cornerstone of clinical diagnosis. Transabdominal ultrasound has, in recent years been largely replaced by transvaginal ultrasound imaging. It is important to note that the diagnostic accuracy of both ultrasound methods is experience-based and allied to constant vigilance for the potential presence of ectopic pregnancy. The GDG therefore considered the evidence for application of the two different methods in order to determine which should be used.

Description of included studies

Five studies were included in this review. Three studies were conducted in the USA (Kivikoski et al., 1990; Shapiro et al., 1988; Thorsen et al., 1990), one in Austria (Schurz et al., 1990) and one in Finland (Cacciatore, 1989). Four prospective studies (Cacciatore, 1989; Kivikoski et al., 1990; Shapiro et al., 1988; Thorsen et al., 1990) compared the diagnostic accuracy of transvaginal and transabdominal ultrasound in women with suspected ectopic pregnancy. One prospective study (Schurz et al., 1990) evaluated reliability and advantages of transabdominal and transvaginal ultrasound compared with clinical signs for detection of ectopic pregnancy.

The reference standard for diagnosis of ectopic pregnancy was reported as laparoscopy in one study (Schurz et al., 1990), surgery (the type of which was not specified) in three studies (Cacciatore, 1989; Shapiro et al., 1988; Thorsen et al., 1990) and either laparoscopy or surgery in one study (Kivikoski et al., 1990).

In one prospective study (Kivikoski et al., 1990) women were first seen at 4–12 weeks amenorrhea at the time of evaluation. Four prospective studies (Cacciatore, 1989; Schurz et al., 1990; Shapiro et al., 1988; Thorsen et al., 1990) did not report women's gestation at the time of ultrasound evaluation.

Evidence profile

The evidence is presented below in one profile. Diagnostic accuracy for ectopic pregnancy was measured using transvaginal and transabdominal ultrasound.

Table 6.3 GRADE summary of findings for accuracy of diagnosing ectopic pregnancy using transvaginal or transabdominal ultrasound

Number of studies	Number of women	Measure of diagnostic accuracy						Quality
		Sensit-ivity	Specif-icity	Positive predict-ive value	Negative predict-ive value	Positive likelihood ratio	Negative likelihood ratio	
Transvaginal ultrasound								
1 study (Shapiro et al., 1988)	25	90 (78 to 100)*	33 (20 to 86)*	90 (78 to 100)*	33 (20 to 86)*	1.36 (0.60 to 3.06)*	0.27 (0.05 to 2.17)*	Very low
1 study (Thorsen et al., 1990)	193	38 (26 to 50)*	100 (100 to 100)*	100 (100 to 100)*	78 (72 to 84)*	infinity*	0.6 (0.50 to 0.75)*	Moder-ate
1 study (Kiviko-ski et al., 1990)	34	72 (56 to 90)*	100 (100 to 100)*	100 (100 to 100)*	53 (28 to 78)*	infinity*	0.26 (0.14 to 0.50)	Low
Transabdominal ultrasound								
1 study (Shapiro et al., 1988)	25	50 (29 to 70)*	Not calcul-able (NC)	NC	NC	NC	NC	Very low
1 study (Thorsen et al., 1990)	193	21 (11 to 32)*	100 (100 to 100)*	100 (100 to 100) *	73 (67 to 80)*	infinity*	0.7* (0.67 to 0.89)	Moder-ate
1 study (Kiviko-ski et al., 1990)	34	44 (25 to 63)*	100 (100 to 100)*	100 (100 to 100)*	31 (12 to 51)*	infinity*	0.55 (0.39 to 77)*	Low

NC not calculable

* NCC calculation

Two very low quality studies also evaluated the diagnostic accuracy of transvaginal and transabdominal ultrasound for ectopic pregnancy in women with clinical suspicion of ectopic pregnancy. However, there was not adequate information reported in the studies to calculate diagnostic accuracy measures.

Table 6.4 Additional diagnostic accuracy findings for transvaginal and transabdominal ultrasound from two observational studies

Additional data	
1 study (Cacciatore, 1989)	In one very low quality study (Cacciatore, 1989) there was no statistically significant difference between the transvaginal and transabdominal ultrasounds in detection of an adnexal mass (90% vs. 80%), gestational sac (92% vs. 89%). More ectopic fetuses (21% vs. 0.0%), ectopic sacs (69% vs. 44%), un-ruptured ectopic pregnancies (82% vs. 50%) and yolk sacs or viable fetuses (49% vs. 0.0%) were detected by transvaginal ultrasound when compared with transabdominal ultrasound.
1 study (Schurz et al., 1990)	In the other very low quality study (Schurz et al., 1990) reliability and advantages of transabdominal and transvaginal ultrasound were compared with clinical signs for detection of ectopic pregnancy. Clinical findings were more likely to lead to a correct diagnosis of ectopic pregnancy than the findings obtained from transabdominal ultrasound (58% vs. 25%; $P < 0.05$). However, clinical findings were less likely to lead to a correct diagnosis of ectopic pregnancy than the findings obtained by transvaginal ultrasound (26% vs. 95%; $P < 0.05$). This sample was examined at an earlier gestational age than the sample used to compare abdominal ultrasound (hence the difference in detection of ectopic pregnancy based on clinical findings).

Evidence statements

In the evidence statements the following definitions have been used when summarising the levels of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV):

- High – 90% and above
- Moderate – 75% to 89%
- Low – below 75%

The following terms have been used when summarising likelihood ratios:

- Positive likelihood ratio:
  - Very useful – more than 10
  - Moderately useful – 5 to 10
  - Not useful – less than 5
- Negative likelihood ratio:
  - Very useful – 0 to 0.1
  - Moderately useful – more than 0.1 up to 0.5
  - Not useful – more than 0.5

Evidence was identified for transvaginal and transabdominal ultrasounds to determine diagnostic accuracy for ectopic pregnancy in women with clinical suspicion of ectopic pregnancy. The quality of the evidence was moderate, low and very low for the included studies.

Transvaginal ultrasound

Three studies evaluated the diagnostic accuracy of transvaginal ultrasound for ectopic pregnancy in women with suspected ectopic pregnancy. One very low quality study reported a high sensitivity, a low specificity, a high PPV, a low NPV, a not useful positive likelihood ratio and a moderately useful negative likelihood ratio. One moderate quality study reported low sensitivity, high specificity, a high PPV, a moderate NPV, a very useful positive likelihood ratio and a not useful negative likelihood ratio. One low quality study reported low sensitivity, high specificity, a high PPV, a low NPV, a very useful positive likelihood ratio and a moderately useful negative likelihood ratio.

Transabdominal ultrasound

The same three studies evaluated the diagnostic accuracy of transabdominal ultrasound for ectopic pregnancy in women with suspected ectopic pregnancy. One study of very low quality reported a low sensitivity with no information provided about other diagnostic accuracy measures. One moderate quality study reported low sensitivity, high specificity, a high PPV, a low NPV, a very useful positive likelihood ratio and a not useful negative likelihood ratio. One low quality study reported a low sensitivity, a high specificity, a high PPV, a low NPV, a very useful positive likelihood ratio and a not useful negative likelihood ratio.

Diagnosis of ectopic pregnancy

Two very low quality studies evaluated the diagnostic accuracy of transvaginal and transabdominal ultrasound for ectopic pregnancy in women with clinical suspicion of ectopic pregnancy. In one low quality study (Cacciatore, 1989) there was no statistically significant difference between the transvaginal and transabdominal ultrasounds in detection of an adnexal mass and gestational sac. More ectopic fetuses, ectopic sacs, un-ruptured ectopic pregnancies and yolk sacs or viable fetuses were detected by transvaginal ultrasound when compared with transabdominal ultrasound.

In the other very low quality study (Schurz et al., 1990) reliability and advantages of transabdominal and transvaginal ultrasound were compared with clinical signs for detection of ectopic pregnancy in two populations. Clinical findings were more likely to lead to a correct diagnosis of ectopic pregnancy than the findings obtained from transabdominal ultrasound. However; clinical findings were less likely to lead to a correct diagnosis of ectopic pregnancy than the findings obtained by transvaginal ultrasound.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG recognised the importance of both sensitivity and specificity when diagnosing ectopic pregnancies. Given the risks of failing to identify women with an ectopic pregnancy, it is important that the test be sensitive. However, the group also recognised that there is a danger with a false positive diagnosis, as this could potentially lead to women receiving treatment when they actually have a viable intrauterine pregnancy.

Consideration of clinical benefits and harms

The evidence showed mixed results for both ultrasound methods. Both methods of ultrasound displayed a high specificity (most studies reported findings of 100%). However, each study that looked at transvaginal and transabdominal ultrasound showed that the transvaginal method had a higher sensitivity. As a result, the GDG agreed that transvaginal ultrasound should be the preferred approach but that women's views should be taken into account and accommodated where possible. The GDG members also identified from their clinical experience that there might be occasions when transabdominal ultrasound would be the better option, such as when women have an enlarged uterus or other pelvic pathology.

Consideration of health benefits and resource uses

The group did not feel that there was a difference in cost between the two different methods as the time taken to perform them both would be the same. It was also recognised that some personnel performing ultrasound scans tend to perform an abdominal ultrasound prior to a transvaginal ultrasound. It was the view of the group that unless there were particular indications for performing two scans in this way this practice was not necessary, given the additional resource implications and the superior accuracy of transvaginal scans.

Quality of evidence

The evidence varied in quality from very low to moderate. The GDG was disappointed that there was no recent evidence to address this review question. The members agreed that although scanning technology had improved from the time the studies were conducted, it was likely that both technologies would have improved similarly, and thus that comparisons of the two techniques were still valid. Overall, they felt that taking into account the evidence reviewed and the group's clinical experience, along with the experience of two expert advisers, it was possible to make recommendations.

Information giving and emotional support

The GDG recognised that, while the method of performing an ultrasound scan can make a difference, it is also extremely important that the scanning is undertaken by someone with specific training and experience in identifying ectopic pregnancy. Not only can this can make a large difference to the validity of the diagnosis, it can also impact the experience of the woman undergoing the scan. From their clinical experience, the GDG members felt that having a scan performed by a practitioner without appropriate experience would be likely to make a woman feel anxious and uncertain about her prognosis. In contrast, having a scan performed by a healthcare professional with experience in diagnosing ectopic pregnancies would help to ensure that women felt informed and supported.

Recommendations

Number	Recommendation
21	Offer women who attend an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) a transvaginal ultrasound scan to identify the location of the pregnancy and whether there is a fetal pole and heartbeat.
22	Consider a transabdominal ultrasound scan for women with an enlarged uterus or other pelvic pathology, such as fibroids or an ovarian cyst.
23	If a transvaginal ultrasound scan is unacceptable to the woman, offer a transabdominal ultrasound scan and explain the limitations of this method of scanning.
24	Inform women that the diagnosis of miscarriage using 1 ultrasound scan cannot be guaranteed to be 100% accurate and there is a small chance that the diagnosis may be incorrect, particularly at very early gestational ages.
25	When performing an ultrasound scan to determine the viability of an intrauterine pregnancy, first look to identify a fetal heartbeat. If there is no visible heartbeat but there is a visible fetal pole, measure the crown–rump length. Only measure the mean gestational sac diameter if the fetal pole is not visible.
26	If the crown–rump length is less than 7.0 mm with a transvaginal ultrasound scan and there is no visible heartbeat, perform a second scan a minimum of 7 days after the first before making a diagnosis. Further scans may be needed before a diagnosis can be made.
27	If the crown–rump length is 7.0 mm or more with a transvaginal ultrasound scan and there is no visible heartbeat: • seek a second opinion on the viability of the pregnancy **and/or** • perform a second scan a minimum of 7 days after the first before making a diagnosis.
28	If there is no visible heartbeat when the crown–rump length is measured using a transabdominal ultrasound scan: • record the size of the crown–rump length **and** • perform a second scan a minimum of 14 days after the first before making a diagnosis.
29	If the mean gestational sac diameter is less than 25.0 mm with a transvaginal ultrasound scan and there is no visible fetal pole, perform a second scan a minimum of 7 days after the first before making a diagnosis. Further scans may be needed before a diagnosis can be made.

30 If the mean gestational sac diameter is 25.0 mm or more using a transvaginal ultrasound scan and there is no visible fetal pole:

- seek a second opinion on the viability of the pregnancy **and/or**
- perform a second scan a minimum of 7 days after the first before making a diagnosis.

31 If there is no visible fetal pole and the mean gestational sac diameter is measured using a transabdominal ultrasound scan:

- record the size of the mean gestational sac diameter **and**
- perform a second scan a minimum of 14 days after the first before making a diagnosis.

32 Do not use gestational age from the last menstrual period alone to determine whether a fetal heartbeat should be visible.

33 Inform women that the date of their last menstrual period may not give an accurate representation of gestational age because of variability in the menstrual cycle.

34 Inform women what to expect while waiting for a repeat scan and that waiting for a repeat scan has no detrimental effects on the outcome of the pregnancy.

35 Give women a 24-hour contact telephone number so that they can speak to someone with experience of caring for women with early pregnancy complications who understands their needs and can advise on appropriate care.*

36 When diagnosing complete miscarriage on an ultrasound scan, in the absence of a previous scan confirming an intrauterine pregnancy, always be aware of the possibility of ectopic pregnancy. Advise these women to return for further review if their symptoms persist.

37 All ultrasound scans should be performed and reviewed by someone with training in, and experience of, diagnosing ectopic pregnancies.

Number — Research recommendation

RR 4 How does the timing and frequency of ultrasound examination affect diagnosis and outcomes of early pregnancy complications, including women's experience and cost effectiveness?

Why this is important

The rationale behind the frequency of ultrasound to improve diagnosis and outcomes of early pregnancy complications addresses the problems associated with pregnancy of unknown location and intrauterine pregnancy of uncertain viability. The evidence base for the timing and frequency of scanning in early pregnancy is limited, and the number of scans is organised by individual units according to capacity and demand. Some healthcare professionals choose to wait 5 days between scans whereas others will wait 10 to 14 days. These decisions are driven by resource availability as well as clinical considerations, but in particular the effect of different strategies on cost and women's experience is not clear. The literature suggests that there is no clear consensus, but there is general agreement that by 14 days a diagnosis will be clear. To establish the most appropriate time for scans, the efficacy of scans taken after 14 days could be compared with scans taken after 7 days for diagnosis of ectopic pregnancy or viability.

* See also recommendation 3 for details of further information that should be provided.

6.4 Diagnostic accuracy of two or more human chorionic gonadotrophin (hCG) measurements for ectopic pregnancy

Review question

What is the diagnostic accuracy of two or more hCG measurements for determining an ectopic pregnancy in women with pain and bleeding and pregnancy of unknown location?

Introduction

The diagnosis of ectopic pregnancy remains problematic in a significant number of cases. Women may present with a positive urine or blood pregnancy test but no visible evidence of the location of the pregnancy on an ultrasound scan (pregnancy of unknown location [PUL]). In these circumstances there is often a tension between not missing an ectopic pregnancy and not subjecting women with an early intrauterine pregnancy to a battery of expensive and potentially unnecessary tests or interventions. One possible alternative is to use serial measurements of human chorionic gonadotrophin (hCG) as a diagnostic tool to try to identify women who might have an ectopic pregnancy and those who are likely to have an early viable intrauterine pregnancy. The following reviews evaluate the diagnostic accuracy of this approach, and consider whether there is added value in the use of a single progesterone measurement.

Description of included studies

Ten studies were included in this review (Barnhart et al., 2010; Condous et al., 2004; Condous et al., 2007; Dart et al., 1999; Daus et al., 1989; Hahlin et al., 1991; Mol et al., 1998; Morse et al., 2012; Stewart et al., 1995; Thorburn et al., 1992).

The included papers consist of five prospective cohort studies (Condous et al., 2004; Condous et al., 2007; Hahlin et al., 1991; Mol et al., 1998; Thorburn et al., 1992) and five retrospective cohort studies (Barnhart et al., 2010; Dart et al., 1999; Daus et al., 1989; Morse et al., 2012; Stewart et al., 1995). One study (Barnhart et al., 2010) was conducted in both the UK and USA; the other studies were conducted in the UK (Condous et al., 2004; Condous et al., 2007), the USA (Dart et al., 1999; Daus et al., 1989; Morse et al., 2012; Stewart et al., 1995), the Netherlands (Mol et al., 1998) and Sweden (Hahlin et al., 1991; Thorburn et al., 1992).

The study participants were women with pain and bleeding in the first trimester of pregnancy who had been classified as having a pregnancy of unknown location on ultrasound. All the studies used two or more serum hCG measurements for diagnosis, and either reported measures of diagnostic accuracy or presented data that allowed calculations to be performed by the technical team. Four studies evaluated the percentage change in hCG over 48 hours (Dart et al., 1999; Daus et al., 1989; Mol et al., 1998; Morse et al., 2012), one study evaluated the rate of change of log hCG using two different thresholds (Stewart et al., 1995) and two studies evaluated the diagnostic accuracy of an abnormal hCG score (Hahlin et al., 1991; Thorburn et al., 1992). A further two papers (Condous et al., 2004; Condous et al., 2007) evaluated the diagnostic accuracy of two different predictive models: M1 and M4. Model M1 incorporated the hCG ratio (ratio of concentration at 48 hours to concentration at 0 hours) and its performance was evaluated using three different sets of parameters. Firstly, the model was evaluated using a probability threshold to distinguish between ectopic pregnancies and non-ectopic pregnancies. Then, the authors incorporated different statistical costs for misclassifying outcomes, using costs of 1 for misclassifying failing pregnancies of unknown location and intrauterine pregnancies, and a cost of either 4 or 5 for misclassifying an ectopic pregnancy. The different costs represent the relative importance of making different types of prediction errors, in this case reflecting that misclassifying an ectopic pregnancy may have more serious consequences than misclassifying other conditions. Model M4 incorporated the average hCG concentration (from measurements at 0 and 48 hours), the ratio of the two hCG measurements and the quadratic effect of the hCG ratio. M4 was only evaluated using the optimal costs of 1, 1 and 4 for misclassifying a failing pregnancy of unknown location, an intrauterine pregnancy and an ectopic pregnancy, respectively.

The reference standards used for the confirmation of the diagnosis of ectopic pregnancy varied between the studies. Laparoscopy was used as the reference standard in four studies (Condous et al., 2004; Hahlin et al., 1991; Mol et al., 1998; Thorburn et al., 1992) and two further studies reported that the diagnosis was confirmed using tissue diagnosis after surgery, the type of which was not specified (Daus et al., 1989; Stewart et al., 1995). Three studies used different reference standards (laparoscopy, ultrasound visualisation or serial serum hCG measurements combined with no evidence of chorionic villi after dilation and evacuation) according to how the ectopic pregnancy was managed (Barnhart et al., 2010; Condous et al., 2007; Dart et al., 1999). In one study it is reported that the ectopic pregnancies included visualised and non-visualised pregnancies but no further details are given (Morse et al., 2012). Further details of how diagnoses were confirmed, including ultrasound criteria, can be found in the evidence tables (see Appendix H).

Evidence profile

Table 6.5 GRADE summary of findings for the diagnosis of ectopic pregnancy using two or more hCG measurements

Number of studies	Number of women	Measure of diagnostic accuracy						Quality
		Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predict-ive value % (95% CI)	Negative predict-ive value % (95% CI)	Positive likeli-hood ratio (95% CI)	Negative likeli-hood ratio (95% CI)	
% change in serum hCG in 48 hours: decline, or rise of < 50 %								
1 study (Mol et al., 1998)	195	68.4 (53.6 to 83.2)*	11.5 (6.5 to 16.5)*	15.8 (10.2 to 21.3)*	60.0 (42.5 to 77.5)*	0.77 (0.62 to 0.97)*	2.75 (1.45 to 5.22)*	Low
% change in serum hCG in 48 hours: decline, or rise of < 63 %								
1 study (Daus et al., 1989)	357	93.6 (86.6 to 100)*	18.4 (14.1 to 22.7)*	14.8 (10.8 to 18.9)*	95.0 (89.5 to 100)*	1.15 (1.05 to 1.26)*	0.35 (0.11 to 1.06)*	Very low
% change in serum hCG in 48 hours: decline, or rise of < 66 %								
1 study (Dart et al., 1999)	307	81.8 (68.7 to 95.0)*	16.8 (12.4 to 21.2)*	10.6 (6.8 to 14.4)*	88.5 (79.8 to 97.2)*	0.98 (0.83 to 1.16)*	1.08 (0.50 to 2.34)*	Low
% change in serum hCG in 48 hours: between a decline of 36-47% and a rise of 35%								
1 study (Morse et al., 2012)	1005	83.2 (77.7 to 88.8)	70.8 (67.7 to 73.9)	38.2 (33.4 to 43.0)	95.1 (93.4 to 96.8)	not reported (NR)	NR	Very low
% change in serum hCG in 48 hours: between a decline of 36-47% and a rise of 53%								
1 study (Morse et al., 2012)	1005	91.1 (86.8 to 95.3)	66.6 (63.4 to 69.8)	37.1 (32.6 to 41.7)	97.2 (95.8 to 98.5)	NR	NR	Very low

Number of studies	Number of women	Measure of diagnostic accuracy						Quality
		Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predict-ive value % (95% CI)	Negative predict-ive value % (95% CI)	Positive likeli-hood ratio (95% CI)	Negative likeli-hood ratio (95% CI)	
% change in serum hCG in 48 hours: between a decline of 36-47% and a rise of 71%								
1 study (Morse et al., 2012)	1005	92.2 (88.2 to 96.2)	62.8 (59.5 to 66.1)	35.0 (30.6 to 39.3)	97.4 (96.0 to 98.7)	NR	NR	Very low
Rate of change of log hCG: < 0.11								
1 study (Stewart et al., 1995)	36[†]	89.7 (81.8 to 97.5)*	37.3 (25.0 to 49.6)*	58.4 (48.2 to 68.7)*	78.6 (63.4 to 93.8)*	1.43 (1.15 to 1.77)*	0.28 (0.12 to 0.63)*	Very low
Rate of change of log hCG: < 0.14								
1 study (Stewart et al., 1995)	36[†]	98.3 (94.9 to 100)*	22.0 (11.5 to 32.6)*	55.3 (45.7 to 64.9)*	92.9 (79.4 to 100)*	1.26 (1.10 to 1.45)*	0.08 (0.01 to 0.58)*	Very Low
Abnormal hCG score								
1 study (Hahlin et al., 1991)	307	88.7 (83.8 to 93.6)*	47.3 (39.3 to 55.3)*	64.4 (58.0 to 70.7)*	79.6 (71.1 to 88.0)*	1.68 (1.43 to 1.98)*	0.24 (0.15 to 0.38)*	Low
1 study (Thorburn et al., 1992)	261	81.1 (73.0 to 89.2)*	43.9 (36.4 to 51.3)*	43.2 (35.7 to 50.7)*	81.5 (73.6 to 89.5)*	1.44 (1.22 to 1.71)*	0.43 (0.27 to 0.68)*	Low
Model M1: using probability thresholds								
1 study (Condous et al., 2004)	196	83.3 (62.3 to 100)[‡]	88.0 (83.4 to 92.7)[‡]	31.3 (15.2 to 47.3)[‡]	98.8 (97.1 to 100)[‡]	6.97 (4.37 to 11.11)*	0.19 (0.05 to 0.67)*	Low
Model M1: using costs 1, 1 and 4								
1 study (Condous et al., 2004)	196	83.3 (62.3 to 100)[‡]	86.4 (81.5 to 91.4)[‡]	28.6 (13.6 to 43.5)[‡]	98.8 (97.1 to 100)[‡]	6.13 (3.94 to 9.56)*	0.19 (0.05 to 0.68)*	Low
1 study (Condous et al., 2007)	173	73.3 (51.0 to 95.7)[‡]	87.3 (82.2 to 92.5)[‡]	35.5 (18.6 to 52.3)[‡]	97.2 (94.5 to 99.9)[‡]	5.79 (3.48 to 9.66)[‡]	0.31 (0.13 to 0.71)[‡]	Low

Number of studies	Number of women	Measure of diagnostic accuracy						Quality
		Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predict-ive value % (95% CI)	Negative predict-ive value % (95% CI)	Positive likeli-hood ratio (95% CI)	Negative likeli-hood ratio (95% CI)	
Model M1: using costs 1, 1 and 5								
1 study (Condous et al., 2004)	196	91.7 (76.0 to 100)‡	84.2 (79.0 to 89.5)‡	27.5 (13.7 to 41.3)‡	99.4 (98.1 to 100)‡	5.82 (4.00 to 8.46)*	0.10 (0.02 to 0.65)*	Low
Model M4								
1 study (Condous et al., 2007)	173	80.0 (59.8 to 100)‡	88.6 (83.7 to 93.6)‡	40.0 (22.5 to 57.5)‡	97.9 (95.6 to 100)‡	7.02 (4.25 to 11.61)‡	0.23 (0.08 to 0.62)‡	Low
1 study (Barnhart et al., 2010) (2 included cohorts: UK and adjusted USA)	431	80.8 (65.6 to 95.9)‡	88.9 (85.8 to 92.0)‡	31.8 (20.6 to 43.1)‡	98.6 (97.4 to 99.8)‡	7.27 (5.21 to 10.14)*	0.22 (0.10 to 0.48)*	Very low
	544	54.8 (45.2 to 64.4)‡	87.7 (84.7 to 90.8)‡	51.4 (42.1 to 60.7)‡	89.2 (86.2 to 92.1)‡	4.47 (3.29 to 6.06)*	0.52 (0.46 to 0.64)*	Very low

CI confidence interval, hCG β-human chorionic gonadotrophin, NR not reported

* Calculated by NCC-WCH technical team

† There were 36 women who received multiple hCG measurements, leading to a total of 117 pairs of hCG measurement used for the diagnostic accuracy calculations

‡ Confidence intervals calculated by NCC-WCH technical team

Evidence statements

The following definitions have been used when summarising the levels of sensitivity, specificity, PPV and NPV:

- High – 90% and above
- Moderate – 75% to 89.9%
- Low – 75% and below

The following terms have been used when summarising the likelihood ratios:

- Positive likelihood ratio:
  - Very useful – more than 10
  - Moderately useful – 5 to 10
  - Not useful – less than 5
- Negative likelihood ratio:
  - Very useful – 0 to 0.1

- Moderately useful – more than 0.1 up to 0.5
- Not useful – more than 0.5

Percentage change in serum hCG concentration in 48 hours

One study evaluated the use of a decline or a rise to less than 50% in serum hCG over 48 hours for the diagnosis of ectopic pregnancy. The study reported a low sensitivity, low specificity, low PPV, low NPV, not useful positive likelihood ratio and not useful negative likelihood ratio. The evidence for this finding was of low quality.

One study evaluated the diagnostic accuracy of a decline or a rise to less than 63% in serum hCG over 48 hours for the diagnosis of ectopic pregnancy. The study reported a high sensitivity, low specificity, low PPV, high NPV, not useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for this finding was of very low quality.

One study evaluated the diagnostic accuracy of a decline or a rise to less than 66% in serum hCG over 48 hours for the diagnosis of ectopic pregnancy. The study reported a moderate sensitivity, low specificity, low PPV, moderate NPV, not useful positive likelihood ratio and not useful negative likelihood ratio. The evidence for this finding was of low quality.

One study evaluated the diagnostic accuracy of a change in serum hCG between a decline of 36–47% and a rise of 35%. The study reported a moderate sensitivity, low specificity, low PPV and high NPV. The study did not report likelihood ratios. The evidence for this finding was of very low quality.

One study evaluated the diagnostic accuracy of a change in serum hCG between a decline of 36–47% and a rise of 53%. The study reported a high sensitivity, low specificity, low PPV and high NPV. The study did not report likelihood ratios. The evidence for this finding was of very low quality.

One study evaluated the diagnostic accuracy of a change in serum hCG between a decline of 36–47% and a rise of 71%. The study reported a high sensitivity, low specificity, low PPV and high NPV. The study did not report likelihood ratios. The evidence for this finding was of very low quality.

Rate of change of log hCG concentration

One study evaluated the diagnostic accuracy of a rate of change of log hCG of less than 0.11 for the diagnosis of ectopic pregnancy. The study reported a moderate sensitivity, low specificity, low PPV, moderate NPV, not useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for this finding was of very low quality.

One study evaluated the diagnostic accuracy of a rate of change of log hCG of less than 0.14 for the diagnosis of ectopic pregnancy. The study reported a high sensitivity, low specificity, low PPV, high NPV, not useful positive likelihood ratio and useful negative likelihood ratio. The evidence for this finding was of very low quality.

hCG score

Two studies evaluated the diagnostic accuracy of an abnormal hCG score for the diagnosis of ectopic pregnancy. They both reported a moderate sensitivity, low specificity, low PPV, moderate NPV, not useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for these findings was of low quality.

Models

One study evaluated the diagnostic accuracy of model M1, using a probability threshold, for the diagnosis of ectopic pregnancy. The study reported a moderate sensitivity, moderate specificity, low PPV, high NPV, moderately useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for this finding was of low quality.

Two studies evaluated the diagnostic accuracy of model M1, incorporating costs of 1, 1 and 4, for the diagnosis of ectopic pregnancy. One study reported a moderate sensitivity, moderate specificity, low PPV, high NPV, moderately useful positive likelihood ratio and moderately useful negative likelihood ratio. The other study reported a low sensitivity, moderate specificity, low PPV, high NPV, moderately useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for both sets of findings was of low quality.

One study evaluated the diagnostic accuracy of model M1, incorporating costs of 1, 1 and 5, for the diagnosis of ectopic pregnancy. The study reported a high sensitivity, moderate specificity, low PPV, high NPV, moderately useful positive likelihood ratio and very useful negative likelihood ratio. The evidence for this finding was of low quality.

Two studies evaluated the diagnostic accuracy of model M4 for the diagnosis of ectopic pregnancy. One study reported a moderate sensitivity, moderate specificity, low PPV, high NPV, moderately useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for this finding was of low quality. One further study incorporated two populations. In the UK population, the study reported a moderate sensitivity, moderate specificity, low PPV, high NPV, moderately useful positive likelihood ratio and moderately useful negative likelihood ratio. In the adjusted USA population, the study reported a low sensitivity, moderate specificity, low PPV, moderate NPV, not useful PPV and not useful NPV. The evidence for this finding was of very low quality

Evidence to recommendations

Please see Section 6.7 where the evidence from all of the reviews which assess the use of hCG for diagnosis has been considered.

6.5 Diagnostic accuracy of two or more hCG measurements plus progesterone for ectopic pregnancy

Review question

What is the diagnostic accuracy of two or more hCG measurements plus progesterone for determining an ectopic pregnancy in women with pain and bleeding and pregnancy of unknown location?

Description of included studies

Three studies were included in this review (Condous et al., 2004; Gevaert et al., 2006; Hahlin et al., 1991). These were two prospective cohort studies (Condous et al., 2004; Hahlin et al., 1991) and one retrospective study (Gevaert et al., 2006). The studies were conducted in the UK (Condous et al., 2004; Gevaert et al., 2006) and Sweden (Hahlin et al., 1991).

The study participants were women with pain and bleeding in the first trimester of pregnancy who had been classified as having a pregnancy of unknown location on ultrasound. All of the studies used the combination of two or more serum hCG measurements and progesterone for diagnosis, and either reported measures of diagnostic accuracy or presented data that allowed calculations to be performed by the NCC-WCH technical team. One study evaluated the diagnostic accuracy of an abnormal hCG score in conjunction with a progesterone concentration of less than 30 nmol/l (Hahlin et al., 1991), and two studies evaluated the diagnostic accuracy of predictive models (Condous et al., 2004; Gevaert et al., 2006). The Bayesian model (parameter prior model [PPM]) incorporated the hCG ratio (ratio of concentration at 48 hours to concentration at 0 hours), progesterone concentration at 48 hours and the number of gestation days. The model M3 incorporated the hCG ratio, the average progesterone concentration (from measurements at 0 and 48 hours) and maternal age in years.

The reference standard used for the confirmation of the diagnosis of ectopic pregnancy was laparoscopy in two studies (Condous et al., 2004; Hahlin et al., 1991). In the third study, diagnosis was based on ultrasound visualisation and was then confirmed at laparoscopy in women who underwent surgery (Gevaert et al., 2006). Further details, including ultrasound criteria, can be found in the evidence tables (see Appendix H).

Table 6.6 GRADE summary of findings for the diagnosis of ectopic pregnancy using two or more hCG measurements plus progesterone

Number of studies	Number of women	Measure of diagnostic accuracy						Quality
		Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predict-ive value % (95% CI)	Negative predict-ive value % (95% CI)	Positive likeli-hood ratio (95% CI)	Negative likeli-hood ratio (95% CI)	
Abnormal hCG score and progesterone concentration < 30 nmol/l								
1 study (Hahlin, et al., 1991)	307	71.7 (64.7 to 78.7)*	58.8 (50.9 to 66.7)*	65.1 (58.1 to 72.2)*	65.9 (57.8 to 74.0)*	1.74 (1.40 to 2.16)*	0.48 (0.36 to 0.64)*	Low
Bayesian model (parameter prior model)								
1 study (Gevaert et al., 2006)	257	77 (Not calculable [NC])	83 (NC)	NC	NC	4.5 (NC)	0.28 (NC)	Very low

CI confidence interval, hCG β-human chorionic gonadotrophin NC not calculable

* Calculated by NCC-WCH technical team

Table 6.7 GRADE summary of findings for the diagnosis of ectopic pregnancy using two or more hCG measurements plus progesterone (Model M3)

Number of studies	Number of women	Area under the ROC curve (95% CI)	Quality
Model M3			
1 study (Condous et al., 2004)	195	Test set: 0.836 (0.693 to 0.979) (Other diagnostic accuracy measures not reported and not calculable)	Low

CI confidence interval, hCG β-human chorionic gonadotrophin, ROC receiver operating characteristic

Evidence statements

hCG score and progesterone concentration

One study evaluated the diagnostic accuracy of an abnormal hCG score in combination with a progesterone concentration of less than 30 nmol/l for the diagnosis of ectopic pregnancy. The study reported a low sensitivity, low specificity, low PPV, low NPV, not useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for this finding was of low quality.

Models

One study evaluated the diagnostic accuracy of Bayesian model PPM for the diagnosis of ectopic pregnancy. The study reported a moderate sensitivity, moderate specificity, not useful positive likelihood ratio and moderate useful negative likelihood ratio; PPV and NPV were not reported. The evidence for this finding was of very low quality.

One study evaluated the diagnostic accuracy of model M3 for the diagnosis of ectopic pregnancy. Only the area under the ROC curve was reported, therefore other diagnostic accuracy measures could not be assessed. The evidence for this finding was of low quality.

Evidence to recommendations

Please see Section 6.7 where the evidence from all of the reviews which assess the use of hCG for diagnosis has been considered.

6.6 Diagnostic accuracy of two or more hCG measurements for viable intrauterine pregnancy

Review question

What is the diagnostic accuracy of two or more hCG measurements for determining a viable intrauterine pregnancy in women with pain and bleeding and pregnancy of unknown location?

Description of included studies

Six studies were included in this review (Dart et al., 1999; Daus et al., 1989; Hahlin et al., 1991; Mol et al., 1998; Morse et al., 2012; Stewart et al., 1995).

The included papers consist of two prospective cohort studies (Hahlin et al., 1991; Mol et al., 1998) and four retrospective cohort studies (Dart et al., 1999; Daus et al., 1989; Morse et al., 2012; Stewart et al., 1995). The studies were conducted in the USA (Dart et al., 1999; Daus et al., 1989; Morse et al., 2012; Stewart et al., 1995), the Netherlands (Mol et al., 1998) and Sweden (Hahlin et al., 1991).

The study participants were women with pain and bleeding in the first trimester of pregnancy who had been classified as having a pregnancy of unknown location on ultrasound. All the studies used two or more serum hCG measurements for diagnosis and either reported measures of diagnostic accuracy or presented data that allowed calculations to be performed by the NCC-WCH technical team. Four studies evaluated the percentage change in hCG over 48 hours (Dart et al., 1999; Daus et al., 1989; Mol et al., 1998; Morse et al., 2012), one study evaluated the rate of change of log hCG (Stewart et al., 1995) and one study evaluated the diagnostic accuracy of a normal hCG score, calculated by plotting the initial hCG value against the rate of change of the serum level of hCG (Hahlin et al., 1991).

The reference standard was a repeat ultrasound scan in three studies (Hahlin et al., 1991; Mol et al., 1998; Morse et al., 2012) and either a repeat ultrasound scan or the birth of the baby in two studies (Dart et al., 1999; Stewart et al., 1995). Further details, including the time of the repeat ultrasound scan, can be found in the evidence tables (see appendix H). In one study details of how the viable intrauterine pregnancies were confirmed are not reported (Daus et al., 1989).

Evidence profile

Table 6.8 GRADE summary of findings for the diagnosis of viable intrauterine pregnancy using two or more hCG measurements

Number of studies	Number of women	Measure of diagnostic accuracy						Quality
		Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predict-ive value % (95% CI)	Negative predict-ive value % (95% CI)	Positive likeli-hood ratio (95% CI)	Negative likeli-hood ratio (95% CI)	
% change in serum hCG in 48 hours: rise > 35 %								
1 study (Morse et al., 2012)	1005	92.3 (89.0 to 95.6)	94.0 (92.3 to 95.7)	84.2 (79.9 to 88.4)	97.2 (96.0 to 98.4)	NC	NC	Very low
% change in serum human chorionic gonadotrophin (hCG) in 48 hours: rise > 50 %								
1 study (Mol et al., 1998)	195	93.3 (80.7 to 100)*	91.1 (87.0 to 95.3)*	46.7 (28.8 to 64.5)*	99.4 (98.2 to 100)*	10.50 (6.45 to 17.09)*	0.07 (0.01 to 0.49)*	Low
% change in serum hCG in 48 hours: rise > 53 %								
1 study (Morse et al., 2012)	1005	82.6 (78.0 to 87.3)	97.2 (96.0 to 98.4)	91.1 (87.4 to 94.7)	94.2 (92.5 to 95.8)	NC	NC	Very low
% change in serum hCG in 48 hours: rise > 63 %								
1 study (Daus et al., 1989)	357	87.1 (78.8 to 95.4)*	98.0 (96.4 to 99.6)*	90.0 (82.4 to 97.6)*	97.3 (95.5 to 99.2)*	42.82 (19.28 to 95.09)*	0.13 (0.07 to 0.25)*	Very low
% change in serum hCG in 48 hours: rise > 66 %								
1 study (Dart et al., 1999)	307	75.5 (63.9 to 87.1)*	95.3 (92.7 to 97.9)*	76.9 (65.5 to 88.4)*	94.9 (92.2 to 97.6)*	15.97 (9.01 to 28.34)*	0.26 (0.16 to 0.41)*	Low
% change in serum hCG in 48 hours: rise > 71 %								
1 study (Morse et al., 2012)	1005	72.6 (67.1 to 78.1)	98.1 (97.1 to 99.1)	93.1 (89.5 to 96.6)	91.2 (89.2 to 93.1)	NC	NC	Very low
Rate of change of log hCG: > 0.11								
1 study (Stewart et al., 1995)	36[†]	80.0 (62.5 to 97.5)[‡]	87.6 (81.1 to 94.2)[‡]	57.1 (38.8 to 75.5)*	95.5 (91.2 to 99.8)*	6.47 (3.65 to 11.47)*	0.23 (0.09 to 0.55)*	Very low

Number of studies	Number of women	Measure of diagnostic accuracy						Quality
		Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predict-ive value % (95% CI)	Negative predict-ive value % (95% CI)	Positive likeli-hood ratio (95% CI)	Negative likeli-hood ratio (95% CI)	
Rate of change of log hCG: > 0.14								
1 study (Stewart et al., 1995)	36†	65.0 (44.1 to 85.9)‡	99.0 (97.0 to 100)‡	92.9 (79.4 to 100)*	93.2 (88.3 to 98.1)*	63.05 (8.74 to 454.93)*	0.35 (0.19 to 0.64)*	Very low
Normal hCG score								
1 study (Hahlin et al., 1991)	307	94.5 (89.3 to 99.7)*	91.9 (88.4 to 95.4)*	78.4 (69.8 to 87.0)*	98.2 (96.4 to 100)*	11.64 (7.54 to 17.98)*	0.06 (0.02 to 0.15)*	Low

CI confidence interval, hCG β-human chorionic gonadotrophin, NC not calculable

* Calculated by NCC-WCH technical team

† There were 36 women who received multiple hCG measurements, leading to a total of 117 pairs of hCG measurement used for the diagnostic accuracy calculations

‡ Confidence intervals calculated by NCC-WCH technical team

Evidence statements

Percentage change in serum hCG concentration in 48 hours

One study evaluated the diagnostic accuracy of a rise of more than 35% in serum hCG over 48 hours for the diagnosis of viable intrauterine pregnancy. The study reported a high sensitivity, high specificity, moderate PPV and high NPV. The study did not report likelihood ratios. The evidence for this finding was of very low quality.

One study evaluated the diagnostic accuracy of a rise of more than 50% in serum hCG over 48 hours for the diagnosis of viable intrauterine pregnancy. The study reported a high sensitivity, high specificity, low PPV, high NPV, very useful positive likelihood ratio and very useful negative likelihood ratio. The evidence for this finding was of low quality.

One study evaluated the diagnostic accuracy of a rise of more than 53% in serum hCG over 48 hours for the diagnosis of viable intrauterine pregnancy. The study reported a moderate sensitivity, high specificity, high PPV and high NPV. The study did not report likelihood ratios. The evidence for this finding was of very low quality.

One study evaluated the diagnostic accuracy of a rise of more than 63% in serum hCG over 48 hours for the diagnosis of viable intrauterine pregnancy. The study reported a moderate sensitivity, high specificity, high PPV, low NPV, very useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for this finding was of very low quality.

One study evaluated the diagnostic accuracy of a rise of more than 66% in serum hCG over 48 hours for the diagnosis of viable intrauterine pregnancy. The study reported a moderate sensitivity, high specificity, moderate PPV, high NPV, very useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for this finding was of low quality.

One study evaluated the diagnostic accuracy of a rise of more than 71% in serum hCG over 48 hours for the diagnosis of viable intrauterine pregnancy. The study reported a low sensitivity, high specificity, high PPV and high NPV. The study did not report likelihood ratios. The evidence for this finding was of very low quality.

Rate of change of log hCG concentration

One study evaluated the diagnostic accuracy of a rate of change of log hCG of more than 0.11 for the diagnosis of viable intrauterine pregnancy. The study reported a moderate sensitivity, moderate specificity, low PPV, high NPV, moderately useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for this finding was of very low quality

One study evaluated the diagnostic accuracy of a rate of change of log hCG of more than 0.14 for the diagnosis of viable intrauterine pregnancy. The study reported a low sensitivity, high specificity, high PPV, high NPV, very useful positive likelihood ratio and moderately useful negative likelihood ratio. The evidence for this finding was of very low quality.

hCG score

One study evaluated the diagnostic accuracy of a normal hCG score for the diagnosis of viable intrauterine pregnancy. The study reported a high sensitivity, high specificity, moderate PPV, high NPV, very useful positive likelihood ratio and very useful negative likelihood ratio. The evidence for this finding was of low quality.

Evidence to recommendations

Please see Section 6.7 where the evidence from all of the reviews which assess the use of hCG for diagnosis has been considered.

6.7 Diagnostic accuracy of two or more hCG measurements plus progesterone for viable intrauterine pregnancy

Review question

What is the diagnostic accuracy of two or more hCG measurements plus progesterone for determining a viable intrauterine pregnancy in women with pain and bleeding and pregnancy of unknown location?

Description of included studies

One study was included in this review (Hahlin et al., 1991). The included paper is a prospective cohort study, conducted in Sweden. The study used the combination of a normal hCG score and progesterone concentration of more than 30 nmol/l for diagnosis, and included women with pain and bleeding in the first trimester of pregnancy who had been classified as having a pregnancy of unknown location on ultrasound. The reference standard used to confirm a viable intrauterine pregnancy was a transvaginal ultrasound scan in the 8th–10th week of gestation showing normal fetal development, including heart activity.

Evidence profile

Table 6.9 GRADE summary of findings for the diagnosis of viable intrauterine pregnancy using two or more hCG measurements plus progesterone

Number of studies	Number of women	Measure of diagnostic accuracy						Quality
		Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predict-ive value % (95% CI)	Negative predict-ive value % (95% CI)	Positive likeli-hood ratio (95% CI)	Negative likeli-hood ratio (95% CI)	
Normal hCG score and progesterone > 30 nmol/l								
1 study (Hahlin et al., 1991)	307	93.2 (87.4 to 99.0)*	94.4 (91.5 to 97.4)*	84.0 (76.0 to 91.9)*	97.8 (95.9 to 99.7)*	16.77 (9.85 to 28.54)*	0.07 (0.03 to 0.17)*	Low

CI confidence interval, hCG β-human chorionic gonadotrophin

* Calculated by NCC-WCH technical team

Evidence statements

One study evaluated the diagnostic accuracy of a normal hCG score in combination with a progesterone concentration of more than 30 nmol/l for diagnosing viable intrauterine pregnancy. The study reported a high sensitivity, high specificity, moderate positive predictive value, high negative predictive value, very useful positive likelihood ratio and very useful negative likelihood ratio. The evidence for this finding was of low quality.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG had hoped to identify in these reviews whether the use of two or more hCG measurements (with or without progesterone) was appropriate for diagnosing both an ectopic pregnancy and a viable intrauterine pregnancy. The group was therefore looking for a test which provided both high sensitivity and high specificity. However, while the evidence indicated a number of different ways of documenting the change in hCG levels (measuring percentage change, measuring log change or applying various mathematical models), none of these methods showed the use of hCG to be useful as a test for comprehensively and definitively diagnosing either an ectopic pregnancy or a viable intrauterine pregnancy.

When developing the protocol for this question, the GDG agreed that it was best to focus the search on serial hCG measurements. It was aware that a small number of units use a single hCG plus progesterone measurement but did not think that this was common practice. The GDG felt that it was unlikely that a single measurement would provide sufficient accuracy to be helpful to clinicians. As the primary focus of clinicians at this stage would be to identify those women who are likely to have an ectopic pregnancy, the group agreed that most would not be comfortable making this judgement based on one measurement alone.

Consideration of clinical benefits and harms

The GDG recognised that some of the papers considered mathematical models. While they understood the intrinsic potential value that such models could have, the models considered in the review had not been widely validated nor did they lend themselves to ease of use. Thus it was not felt appropriate to recommend their use.

The evidence showed that the use of the rate of log change hCG or a change in hCG levels of greater than 63% both provided a high negative predictive value but a low positive predictive value. In other words, these measures were effective as tests to rule out the presence of an ectopic pregnancy but not effective as tests to specifically identify the presence of an ectopic pregnancy. Thus the group felt

that the value of the tests would be as a risk stratification tool to determine the urgency and type of care that each woman requires, with the most urgent care being focused on those women in whom an ectopic pregnancy was more likely.

The group recognised that both measuring the rate of log change hCG and measuring the rate of change of hCG gave similar diagnostic findings. It was felt that measuring an increase of greater than 63% would be easier to calculate and a more useful measure in clinical practice than calculating the rate of log change. In addition, the findings regarding the greater than 63% change were likely to be more valid as the sample size of the study was much larger. As a result, the group agreed to recommend the use of an hCG increase of greater than 63%. The evidence suggested that approximately 17% women with a PUL would fall into this category and would have a high chance of having a viable intrauterine pregnancy. Daus et al. (1989) reported that 60/357 women with a PUL had an hCG rise of greater than 63%. Of these 54/60 were ultimately diagnosed with a viable intrauterine pregnancy (IUP). Similar findings were reported by Dart et al. (1999) who found that 52/307 of women with a PUL had an hCG rise of greater than 66% and 40/52 of these were ultimately diagnosed with a viable IUP.

The GDG discussed whether clinicians should also take into account absolute hCG levels. While there wasn't specific evidence about this available from the studies, the group agreed that for women with an hCG level under 1500 international units per litre (IU/l), they would feel comfortable waiting 7 to 14 days for a second scan. However, for women with an hCG level over 1500 IU/l it would be prudent for clinicians to consider the possibility of an earlier scan given the increased risk if the pregnancy was ectopic. In the studies, the two hCG measurements were taken at different times, but generally with an interval of around 48 hours. The group agreed that this was a reasonable interval to use and for early pregnancy assessment services (EPASs) to aim to achieve.

The GDG interrogated the evidence to determine an appropriate lower threshold to identify those women likely to have a failing pregnancy and for whom a different management strategy could be used. Of the four papers which evaluated a decline of hCG, one (Daus et al., 1999) used 'any decline', one used a decline of 36–47% (Morse et al., 2012) and the other two (Mol et al., 1998; Dart et al., 1999) evaluated a decline of 'greater than 50%'. These last two studies suggested that 32–36% (63/195 and 109/307 respectively) of women with a PUL would fall into the latter category (that is, a decline of hCG of greater than 50%) and were therefore likely to have a failing pregnancy. In these studies none of these women had a viable intrauterine pregnancy and the risk of an ectopic pregnancy was low (about 1% when both studies were combined). In Morse et al. (2012), which used a threshold for decline of 36–47%, a higher proportion of women (over 3%) were misclassified as having a miscarriage when they were eventually diagnosed with an ectopic pregnancy. From these data and their own clinical experience, the GDG members felt that a decline in hCG levels of greater than 50% was highly likely to indicate a failing pregnancy and that this was an appropriately conservative threshold to use.

The group agreed that for women with a decline in hCG levels of greater than 50% it would not be necessary to conduct a repeat ultrasound scan, but instead that they should be asked to do a urine pregnancy test in two weeks' time. If this was negative and the woman was asymptomatic no further action would be necessary. However, if it were positive then the woman should return to the dedicated early pregnancy service within 24 hours for a further clinical review and individualised management.

For the remaining group of women (those with an hCG level change between a decline of less than or equal to 50% and a rise of less than or equal to 63%) it was agreed that a review in the early pregnancy assessment service within 24 hours would be warranted.

The group discussed the relative urgency of referral which should be associated with each threshold. They agreed that women who have an hCG increase of more than 63% and no confirmed ultrasound diagnosis of an intrauterine pregnancy on a subsequent scan should be referred immediately, given the risk of a rupturing ectopic pregnancy. Women with an hCG decrease of more than 50% and a positive pregnancy test after 14 days and women with an hCG level between the two thresholds should be reviewed within 24 hours. The GDG felt it was important that both of these groups of women be seen promptly, given the chance of there being an ectopic pregnancy. However, the GDG agreed that in these instances, the chance of rupture was reduced and thus an immediate referral was not required.

The group wished to highlight that hCG levels are a measurement of trophoblastic proliferation only and should not be used for a confirmatory diagnosis. Final confirmation can only be provided by either an ultrasound scan or a negative pregnancy test (to identify a failed pregnancy).

The GDG considered the evidence that was available for the use of progesterone levels in conjunction with hCG. It noted that for both diagnosis of ectopic pregnancy and diagnosis of viable intrauterine pregnancy, there was little or no improvement in the negative predictive value of the tests compared with using hCG alone.

The group felt it important to stress the importance of symptoms over hCG. The group agreed that all women, regardless of their hCG level, should be given written information about what to do if they experience any new or worsening symptoms, including details about how to access emergency care.

Consideration of health benefits and resource uses

The GDG felt that the use of large numbers of serum hCG measurements was not an effective use of resources, both in terms of women's care and the cost of the tests. It wanted to avoid large numbers of tests being performed without a diagnosis being made, and agreed that the use of more than two serum hCG measurements should only be undertaken following review by a senior healthcare professional. Considering that there was no evidence of any added value of progesterone in making a diagnosis when combined with hCG measurements, and that performing the test has associated costs, the GDG agreed that progesterone should not be used with serial hCG measurements in the assessment of women with pain and bleeding and a PUL.

Quality of evidence

The quality of the evidence was either low or very low. The GDG was aware of the limitations of the studies but ultimately agreed that there was sufficient evidence to make recommendations.

Information giving and emotional support

The GDG felt that it was important that women be given a realistic likely prognosis for their pregnancy based on their hCG levels, and also that they be informed that further confirmation would be needed. For women whose pregnancies might be unlikely to continue, they thought that this would avoid giving women false hope and ensure that they felt informed about the likely outcome. The group also felt that it was very important that these women be given information about where and how to access support and counselling services.

Other considerations

The GDG discussed the reference standards used for the diagnosis of ectopic pregnancy. Most of the included studies used confirmation of the diagnosis at surgery (generally laparoscopy) as the reference standard. While the GDG members noted that there might be a small risk of misdiagnosis using laparoscopy, their opinion was that this was a very rare event and therefore its use as a reference standard was reasonable. They noted that in some of the studies other reference standards were used if women had their ectopic pregnancy managed expectantly or with methotrexate. They agreed that this might undermine the validity of those studies; however, they concluded that overall the body of evidence remained robust and the findings of the review valid.

Recommendations

Number	Recommendation
38	Be aware that women with a pregnancy of unknown location could have an ectopic pregnancy until the location is determined.
39	Do not use serum hCG measurements to determine the location of the pregnancy.
40	In a woman with a pregnancy of unknown location, place more importance on clinical symptoms than on serum hCG results, and review the woman's condition if any of her symptoms change, regardless of previous results and assessments.
41	Use serum hCG measurements only for assessing trophoblastic proliferation to help to determine subsequent management.

42 Take 2 serum hCG measurements as near as possible to 48 hours apart (but no earlier) to determine subsequent management of a pregnancy of unknown location. Take further measurements only after review by a senior healthcare professional.

43 Regardless of serum hCG levels, give women with a pregnancy of unknown location written information about what to do if they experience any new or worsening symptoms, including details about how to access emergency care 24 hours a day. Advise women to return if there are new symptoms or if existing symptoms worsen.

44 For a woman with an increase in serum hCG concentration greater than 63% after 48 hours:

- Inform her that she is likely to have a developing intrauterine pregnancy (although the possibility of an ectopic pregnancy cannot be excluded).
- Offer her a transvaginal ultrasound scan to determine the location of the pregnancy between 7 and 14 days later. Consider an earlier scan for women with a serum hCG level greater than or equal to 1500 IU/litre.
    - If a viable intrauterine pregnancy is confirmed, offer her routine antenatal care*
    - If a viable intrauterine pregnancy is not confirmed, refer her for immediate clinical review by a senior gynaecologist.

45 For a woman with a decrease in serum hCG concentration greater than 50% after 48 hours:

- inform her that the pregnancy is unlikely to continue but that this is not confirmed **and**
- provide her with oral and written information about where she can access support and counselling services† **and**
- ask her to take a urine pregnancy test 14 days after the second serum hCG test, and explain that:
    - if the test is negative, no further action is necessary
    - if the test is positive, she should return to the early pregnancy assessment service for clinical review within 24 hours.

46 For a woman with a change in serum hCG concentration between a 50% decline and 63% rise inclusive, refer her for clinical review in the early pregnancy assessment service within 24 hours.

47 For women with a pregnancy of unknown location, when using serial serum hCG measurements, do not use serum progesterone measurements as an adjunct to diagnose either viable intrauterine pregnancy or ectopic pregnancy.

* See Antenatal care (NICE clinical guideline 62)
† See recommendation 3 for details of further information that should be provided

7 Management of threatened miscarriage and miscarriage

7.1 Introduction

Threatened miscarriage is the most common complication of early pregnancy, occurring in approximately 20% of pregnant women before 20 weeks of gestation (Sotiriadis et al, 2004). Although many women who have threatened miscarriage go on to have a successful pregnancy, there is an increase in risk of miscarriage in the same pregnancy of 2.6 times and 17% of women with threatened miscarriage go on to have further complications in the same pregnancy. In the UK, it is estimated that around a quarter of a million pregnancies each year end in a miscarriage (The Miscarriage Association, 2011). This loss is associated with a significant amount of physical and psychological morbidity. This chapter presents evidence and guidance for clinically effective and cost-effective care for women with miscarriage considering both clinical and psychological outcomes.

7.2 Progesterone for threatened miscarriage

Review question

What is the effectiveness of progesterone in improving outcomes in women with threatened miscarriage?

Introduction

Progesterone is an essential hormone secreted by the corpus luteum that provides early pregnancy support until placental production takes over at 10 to 12 weeks of gestation. Historically, low levels of circulating progesterone have been linked to impending miscarriage and the presence of associated vaginal bleeding. It has been postulated, therefore, that a lack of progesterone is a cause of miscarriage rather than a secondary signal of failing pregnancy.

This review analyses the evidence from published studies where progesterone/progestogen supplementation has been introduced in pregnancies complicated by threatened miscarriage in the first trimester (presence of vaginal bleeding before 12^{+6} weeks of gestation). Various outcomes were examined to determine any detrimental effect or proven efficacy.

Description of included studies

Six studies were included in this review (Duan et al., 2010; El-Zibdeh et al., 2009; Pandian, 2009; Gerhard et al., 1987; Omar et al., 2005; Palagiano, et al. 2004).

Four studies are randomised trials (El-Zibdeh et al., 2009; Pandian, 2009; Gerhard et al., 1987; Palagiano, et al. 2004) and two are observational studies (Duan et al., 2010; Omar et al., 2005). One study was conducted in Jordan (El-Zibdeh et al., 2009), two in Malaysia (Pandian, 2009; Omar et al., 2005), one in Germany (Gerhard et al., 1987), one in China (Duan et al., 2010) and one in Italy (Palagiano et al., 2004).

Three included studies (Duan et al., 2010; Gerhard et al., 1987; Palagiano, et al. 2004) assessed the efficiency of progesterone administration in women with bleeding in early pregnancy and three other

studies (El-Zibdeh et al., 2009; Pandian, 2009; Omar et al., 2005) evaluated the effect of progestogen (dydrogesterone) on pregnancy outcomes for threatened miscarriages. Route of administration varied, consisting of intramuscular administration in one study (Duan et al., 2010), oral in three studies (El-Zibdeh et al., 2009; Pandian, 2009; Omar et al., 2005) and vaginal pessary in two studies (Gerhard et al., 1987; Palagiano et al., 2004).

Evidence profile

Table 7.1 GRADE summary of findings for comparison of progesterone with no treatment or placebo

Number of studies	Number of women or mean ± SD		Effect		Quality
	Progesterone / progestogen	No treatment / placebo	Relative (95% CI)	Absolute (95% CI)	
Term birth					
1 meta-analysis of 2 studies (El-Zibdeh et al., 2009; Gerhard et al., 1987)	88/112 (78.6%)	61/86 (70.9%)	RR 1.12 (0.95 to 1.32)	85 more per 1000 (from 35 fewer to 227 more)	Low
Preterm birth					
1 meta-analysis of 2 studies (El-Zibdeh et al., 2009 Pandian, 2009)	12/182 (6.6%)	9/155 (5.8%)	RR 1.10 (0.48 to 2.52)	6 more per 1000 (from 30 fewer to 88 more)	Low
1 study (Duan et al., 2010)	66/532 (12.4%)	2257/21,054 (10.7%)	RR 1.16 (0.92 to 1.46)	17 more per 1000 (from 9 fewer to 49 more)	Very low
Miscarriage (any route)					
1 meta-analysis of 4 studies (El-Zibdeh et al., 2009; Gerhard et al., 1987; Palagiano et al., 2004; Pandian, 2009)	31/224 (13.8%)	51/197 (25.9%)	RR 0.53 (0.35 to 0.79)	122 fewer per 1000 (from 54 fewer to168 fewer)	Low
1 study (Omar et al., 2005)	3/74 (4.1%)	11/80 (13.8%)	RR 0.29 (0.09 to 1.02) *P* = 0.05*	98 fewer per 1000 (from 125 fewer to 3 more)	Very low

Number of studies	Number of women or mean ± SD		Effect		Quality
	Progesterone / progestogen	No treatment / placebo	Relative (95% CI)	Absolute (95% CI)	
Miscarriage in women with vaginal bleeding (stratified analysis)					
1 study (Omar et al., 2005)	2/29 (6.9%)	6/37 (16.2%)	RR 0.43 (0.09 to 1.95)	92 fewer per 1000 (from 148 fewer to 154 more)	Very low
Miscarriage in women with vaginal spotting (stratified analysis)					
1 study (Omar et al., 2005)	1/45 (2.2%)	5/43 (11.6%)	RR 0.19 (0.02 to 1.57)	94 fewer per 1000 (from 114 fewer to 66 more)	Very low
Miscarriage in women with fetal heart activity (stratified analysis)					
1 study (Omar et al., 2005)	1/31 (3.2%)	3/34 (8.8%)	RR 0.37 (0.04 to 3.33)	56 fewer per 1000 (from 85 fewer to 206 more)	Very low
Miscarriage in women with presence of yolk sac (stratified analysis)					
1 study (Omar et al., 2005)	0/23 (0%)	1/25 (4%)	RR 0.36 (0.02 to 8.45)	26 fewer per 1000 (from 39 fewer to 298 more)	Very low
Miscarriage in women with regular intrauterine gestational sac (stratified analysis)					
1 study (Omar et al., 2005)	2/7 (28.6%)	3/5 (60%)	RR 0.48 (0.12 to 1.88)	312 fewer per 1000 (from 528 fewer to 528 more)	Very low
Miscarriage (oral progesterone)					
1 meta-analysis of 2 studies (El-Zibdeh et al., 2009; Pandian, 2009)	27/182 (14.8%)	42/155 (27.1%)	RR 0.54 (0.35 to 0.84)	125 fewer per 1000 (from 43 fewer to 176 fewer)	Low
Miscarriage (vaginal progesterone)					
1 meta-analysis of 2 studies (Gerhard et al., 1987; Palagiano et al., 2004)	4/42 (9.5%)	9/42 (21.4%)	RR 0.47 (0.17 to 1.30)	114 fewer per 1000 (from 178 fewer to 64 more)	Low

Number of studies	Number of women or mean ± SD		Effect		Quality
	Progesterone / progestogen	No treatment / placebo	Relative (95% CI)	Absolute (95% CI)	
Pregnancy rate at 20 weeks					
1 study (Pandian, 2009)	84/96 (87.5%)	68/95 (71.6%)	RR 1.22 (1.05 to 1.42)	157 more per 1000 (from 36 more to 301 more)	Low
1 study (Omar et al., 2005)	71/74 (95.9%)	69/80 (86.3%)	RR 1.11 (1.01 to 1.23)	95 more per 1000 (from 9 more to 198 more)	Very low
Pregnancy rate at 20 weeks in women with vaginal bleeding (stratified analysis)					
1 study (Omar et al., 2005)	27/29 (93.1%)	31/37 (83.8%)	RR 1.11 (0.93 to 1.32)	92 more per 1000 (from 59 fewer to 268 more)	Very low
Pregnancy rate at 20 weeks in women with vaginal spotting (stratified analysis)					
1 study (Omar et al., 2005)	44/45 (97.8%)	38/43 (88.4%)	RR 1.11 (0.98 to 1.24)	97 more per 1000 (from 18 fewer to 212 more)	Very low
Pregnancy rate at 20 weeks in women with fetal heart activity (stratified analysis)					
1 study (Omar et al., 2005)	30/31 (96.8%)	31/34 (91.2%)	RR 1.06 (0.94 to 1.2)	55 more per 1000 (from 55 fewer to 182 more)	Very low
Pregnancy rate at 20 weeks in women with presence of yolk sac (stratified analysis)					
1 study (Omar et al., 2005)	23/23 (100%)	24/25 (96%)	RR 1.04 (0.93 to 1.16)	38 more per 1000 (from 67 fewer to 154 more)	Very low
Placental abruption					
1 study (Duan et al., 2010)	5/532 (0.94%)	153/21054 (0.73%)	RR 1.29 (0.53 to 3.14)	2 more per 1000 (from 3 fewer to 16 more)	Very low
Hypertensive disorders in pregnancy					
1 meta-analysis of 2 studies (El-Zibdeh et al., 2009; Pandian, 2009)	19/182 (10.4%)	17/155 (11%)	RR 1.00 (0.54 to 1.88)	0 fewer per 1000 (from 50 fewer to 97 more)	Low

Number of studies	Number of women or mean ± SD		Effect		Quality
	Progesterone / progestogen	No treatment / placebo	Relative (95% CI)	Absolute (95% CI)	
1 study (Duan et al., 2010)	16/532 (3%)	974/21054 (4.6%)	RR 0.66 (0.41 to 1.08)	16 fewer per 1000 (from 27 fewer to 4 more)*	Very low
Gestational diabetes					
1 study (Duan et al., 2010)	37/532 (7%)	1141/21054 (5.4%)	RR 1.28 (0.94 to 1.76)	15 more per 1000 (from 3 fewer to 41 more)	Very low
Intrahepatic cholestasis of pregnancy					
1 study (Duan et al., 2010)	51/532 (9.6%)	1712/21054 (8.1%)	RR 1.18 (0.9 to 1.54)	15 more per 1000 (from 8 fewer to 44 more)	Very low
Pain score at the end of 5 day treatment (mean ± SD)					
1 study (Palagiano et al., 2004)	0.4 ± 0.7 n = 25	2.4 ± 0.8 n = 25	not calculable	MD 2.0 lower (2.42 lower to 1.58 lower) *P* < 0.001	Moderate

CI confidence interval, MD mean difference, *P* probability, RR relative risk, SD standard deviation

* *P* = 0.05 calculated by RevMan and *P* = 0.03 reported in the paper

Evidence statements

Term birth

One meta-analysis of two studies found no statistically significant difference in term birth in women who received progesterone/progestogen treatment compared with women who had no treatment. The evidence for this finding was of low quality.

Preterm birth

One meta-analysis of two studies and one further study found no statistically significant difference in preterm birth in women who received progesterone/progestogen treatment compared with women who had no treatment. The evidence for these findings was of low and very low quality.

Miscarriage

One meta-analysis of four studies found a reduced incidence of miscarriage in women who received progesterone/progestogen treatment compared with women who had no treatment. This finding was statistically significant and the evidence for this finding was of low quality. One further study found that incidence of miscarriage was lower in women who received progestogen treatment compared with women who had no treatment. This finding was statistically significant. When stratified sub-group analyses were conducted for women with vaginal bleeding, women with vaginal spotting, women with fetal heart activity, women with presence of yolk sac and women with regular intrauterine gestational sac the findings favoured the progesterone group but the difference was no longer statistically significant. The evidence for these findings was of very low quality.

Miscarriage (oral progesterone)

One meta-analysis of two studies found a reduced incidence of miscarriage in women who received oral progestogen treatment compared with women who had no treatment. This finding was statistically significance and the evidence for this finding was of low quality.

Miscarriage (vaginal progesterone)

One meta-analysis of two studies found no statistically significant difference in incidence of miscarriage in women who received vaginal progesterone treatment compared with women who had no treatment. The evidence for this finding was of low quality.

Pregnancy rate at 20 weeks

Two studies found that the rate of pregnancy at 20 weeks was higher in women who received progestogen treatment compared with women who had no treatment. This finding was statistically significant in both studies. The evidence for this finding was of low quality in one study and very low in the other. When stratified sub-group analyses were conducted for women with vaginal bleeding, women with vaginal spotting, women with fetal heart activity and women with presence of yolk sac the findings favoured progesterone treatment but the difference was no longer statistically significant. The evidence for these findings was of very low quality.

Placental abruption

One study found no statistically significant difference in incidence of placental abruption in women who received progesterone treatment compared with women who had no treatment. The evidence for this finding was of very low quality.

Hypertensive disorders in pregnancy

One meta-analysis of two studies and one further study found no statistically significant difference in incidence of hypertensive disorders of pregnancy in women who received progesterone/progestogen treatment compared with women who had no treatment. The evidence for this finding was of very low quality.

Gestational diabetes

One study found no statistically significant difference in incidence of gestational diabetes in women who received progesterone treatment compared with women who had no treatment. The evidence for this finding was of very low quality.

Intrahepatic cholestasis of pregnancy

One study found no statistically significant difference in intrahepatic cholestasis of pregnancy in women who received progesterone treatment compared with women who had no treatment. The evidence for this finding was of very low quality.

Pain score at the end of 5 day treatment

One study found that the mean pain score at the end of the 5 days of treatment was lower in women who received progesterone treatment compared with women who had placebo treatment. This finding was statistically significant. The evidence for this finding was of moderate quality.

Health economics

The cost-effectiveness analysis undertaken for this guideline suggested that progesterone for threatened miscarriage was cost effective when compared with no treatment. In the base case analysis progesterone dominated no treatment, producing an incremental quality adjusted life year (QALY) gain and a cost saving of £49. Progesterone saved costs because the savings from averted miscarriage more than offset treatment costs. Probabilistic sensitivity analysis found progesterone to be cost effective in 99.93% of Monte Carlo simulations. In sensitivity analysis when a much higher treatment cost of £200 was assumed, progesterone still had an 83% probability of being cost effective at a willingness to pay threshold of £20,000 per QALY. The model is described in more detail in Section 10.2.

Evidence to recommendations

Relative value placed on the outcomes considered

The guideline development group (GDG) agreed that the most important outcomes were the rate of term pregnancy, miscarriage and pregnancy rate beyond 20 weeks of gestation. It also recognised that the side effects associated with progesterone treatment is an important outcome. The group had hoped that there would be evidence regarding long-term outcomes of progesterone use, but none was reported in the included studies.

Consideration of clinical benefits and harms

The evidence from randomised controlled trials (RCT) showed that progesterone or dydrogesterone treatment and placebo or no treatment of miscarriage had a similar effect on both term and preterm birth. Progesterone or dydrogesterone treatment was significantly associated with fewer miscarriages, less severe pain and higher rate of pregnancy at 20 weeks of gestation in women with threatened miscarriages. A significant difference in favour of dydrogesterone for the pregnancy rate at 20 weeks was also shown in a small and underpowered observational study. However, when a pre-specified stratified analysis was performed based on vaginal bleeding, vaginal spotting and presence of yolk sac, the result was no longer statistically significant, though this could be due to the very small sample size.

The GDG acknowledged the importance of the chosen end point for each of the included studies. The studies chose different end points (some at 20 weeks of gestation, others at birth), but none adopted an end point beyond the birth and none included neonatal congenital abnormalities as an outcome. The GDG was concerned that routine administration of progesterone or dydrogesterone might interfere with 'natural' miscarriages that were associated with genetic abnormalities in the fetus. This, in turn, could result in an increase in the rate of neonatal abnormalities or later miscarriages.

The evidence showed that women receiving progesterone treatment and women receiving placebo or no treatment of threatened miscarriage had similar rates of pregnancy complications (gestational diabetes, hypertension in pregnancy and intrahepatic cholestasis of pregnancy).

The group noted that there was no evidence available for longer term outcomes such as developmental delay and incidence of congenital abnormalities. While they recognised that there was no evidence suggesting short-term harm, the GDG members felt that without evidence about the longer term effects of progesterone or dydrogesterone, they would be concerned about recommending its use. In particular, the group was concerned about the use of synthetic progestogens as they believed that these were more likely to be associated with poor long-term outcomes.

Separately from the issue of whether or not progesterone or dydrogesterone should be offered, the GDG agreed that there should be a follow-up procedure in place for women with a threatened miscarriage. The GDG members agreed that if the bleeding gets worse, women should be advised to return in order to receive further assessment. They also agreed that there should be a follow-up scan if the bleeding persists in order to determine whether or not the pregnancy is still viable. The group wished to strike a balance between offering women reassurance and ensuring that not all women would need to return for a scan. Ultimately, it was agreed that 14 days would be an appropriate time to wait before offering a follow-up scan.

Information giving and emotional support

The GDG recognised that for many women threatened miscarriage will be a stressful and difficult time. Healthcare professionals providing care for these women will need to provide accurate information and communicate this in a way that balances optimism with a degree of caution. As well as providing information about what to expect, women should be given details of support organisations and advice about what to do in an emergency. The GDG also recognised that the offer of a follow-up ultrasound scan for women in whom bleeding persists was an important source of support.

Consideration of health benefits and resource uses

The economic evaluation undertaken for this guideline demonstrated that progesterone or dydrogesterone treatment was likely to be a cost-effective treatment for women with threatened miscarriage as it not only reduces the threat of miscarriage but also produces net savings as a result

of averted miscarriage. However, the GDG had reservations about some of the studies which informed the treatment effect size in the health economic model. Furthermore, in the UK it is not usual practice to offer progesterone or dydrogesterone for threatened miscarriage, and the group had concerns about recommending a significant change in practice based on such poor quality evidence.

Quality of evidence

The evidence available for this question was generally of low or very low quality. The few studies that were included generally had a low numbers of participants, and the GDG was concerned that even the randomised trials that were included were potentially subject to bias. Two of the trials were funded by manufacturers of progesterone, including one trial with a single author and which had a high loss to follow-up.

Overall, the GDG felt that the evidence was insufficient to recommend the use of progesterone or dydrogesterone. This was partly because there was no demonstrated significant difference in the rate of term birth, but mainly because of the GDG's concern about the lack of long-term safety data. The group felt strongly that further, high quality studies investigating both the efficacy and safety of progesterone and progestogens were needed, and decided that this was a priority area for research, particularly considering outcomes of term birth, late miscarriage and incidence of congenital abnormalities.

Recommendations

Number	Recommendation
48	Advise a woman with vaginal bleeding and a confirmed intrauterine pregnancy with a fetal heartbeat that: • if her bleeding gets worse, or persists beyond 14 days, she should return for further assessment • if the bleeding stops, she should start or continue routine antenatal care.

Number	Research recommendation
RR 5	Are progesterone or progestogens effective in treating threatened miscarriage? **Why this is important** Approximately 20% of pregnancies miscarry in the first trimester and many women will experience some bleeding and/or pain in early pregnancy that does not cause miscarriage. In many countries, women with bleeding and/or pain will be treated with progesterone or progestogens to try and decrease the risk of miscarriage. The evidence for the effectiveness of this treatment has been inconclusive, but data from a meta-analysis of several small studies suggest that progestogens are better than placebo. However, there are theoretical risks to prescribing any treatment in pregnancy and for many practitioners this will be a major change in practice. The lack of strong evidence makes this a priority area for research. A very large multicentre randomised controlled trial of women treated with either progesterone/progestogen or placebo should be conducted. The trial should be large enough so that it is sufficiently powered to detect differences in long-term outcomes. The population would be women with pain and bleeding and a spontaneous, confirmed, viable, singleton, intrauterine pregnancy between 6 and 12 weeks gestation. Progesterone/progestogen or placebo would be administered from when bleeding starts until the end of the 13th week. Pregnancy proceeding beyond the end of the first trimester might be the primary outcome. Live birth should also be measured, as well as pregnancy outcome, gestation at birth and presence of congenital abnormalities.

7.3 Expectant management compared with active treatment of miscarriage

Review question

How effective is expectant management of miscarriage compared with active treatment for improving women's clinical and psychological outcomes?

Introduction

Although historically miscarriages were often treated with a surgical procedure, there are now other less invasive options available, in the forms of medical treatment and expectant management. However, the ability of women to access each mode of management varies across England and Wales, a fact which could be attributed to uncertainty about their relative efficacy and risk of complications. Therefore, these reviews aimed to establish which treatment option is the most clinically effective and cost effective, recognising the importance of women's psychological outcomes. This includes establishing whether simply allowing the natural process of miscarriage to complete its course leads to any worse outcomes than if medical or surgical treatment are used.

Description of included studies

Twelve studies were included in this review of which one was a qualitative paper (Smith et al., 2006) and the other 11 were reports of seven RCTs (Blohm et al., 1997; Chipchase & James, 1997; Ngai et al., 2001; Nielsen & Hahlin, 1995; Nielsen et al., 1996; Nielsen et al., 1999; Shelley et al., 2005; Smith et al., 2009; Trinder et al., 2006; Wieringa-de Waard et al., 2002a; Wieringa-de Waard et al., 2002b).

The RCT papers report the outcomes and follow-up data of seven trials conducted in the UK (one trial reported on by Chipchase & James, 1997 and a second trial reported on by Smith et al., 2009 and Trinder et al., 2006), Australia (Shelley et al., 2005), Sweden (one trial reported on by Nielsen & Hahlin, 1995, Nielsen et al., 1996 and Blohm et al., 1997 and a second trial reported on by Nielsen et al., 1999), The Netherlands (one trial reported on by both Wieringa-de Waard et al., 2002a and Wieringa-de Waard et al., 2002b) and Hong Kong (Ngai et al., 2001). The qualitative study is the follow-up to an RCT conducted in the UK, including both participants and non-participants of the trial (Smith et al., 2006).

All studies compared expectant management with medical and/or surgical management of miscarriage (both of which in isolation or in combination were defined as 'active' by the GDG) and reported at least one priority outcome. The GDG felt that the experience of being in the placebo arm of a randomised controlled trial was not comparable to expectant management because women receiving a placebo are blinded to whether they are receiving an active mode of management, which may have an effect on outcomes. Therefore placebo controlled trials were not included for this comparison and were instead included for the review question on the appropriate dose of misoprostol and mifepristone (see Section 7.5).

The trials were all conducted in developed countries and their populations include women with missed miscarriages and/or women with ongoing miscarriages. One RCT (Wieringa-de Waard et al., 2002b) also included a group of women who did not accept randomisation but instead chose to be managed according to their preferences. They were followed up in exactly the same way as the randomised group and their outcomes were analysed separately and compared to the randomised group.

Evidence profile

Thirteen outcomes (grouped in seven broad categories) were chosen by the GDG as being of priority to inform recommendations.

Heterogeneity was low (under 60%) for all outcomes except for bleeding duration (two trials) where it was 86%; therefore for this outcome, the NCC-WCH technical team used a random effects model in the meta-analysis. The high heterogeneity could be the result of the fact that one of the trials compared expectant with medical management whereas the other compared expectant with surgical management.

Table 7.2 GRADE summary of findings for comparison of expectant management with active treatment

Number of studies	Number of women or average		Effect		Quality
	Expectant	**Active**	**Relative (95% CI)**	**Absolute (95% CI)**	
Need for unplanned intervention*					
1 meta-analysis of 6 studies (Ngai et al., 2001; Nielsen & Hahlin, 1995; Nielsen et al., 1999; Shelley et al., 2005; Trinder et al., 2006; Wieringa-de Waard et al., 2002a)	238/672 (35.4%)	181/1020 (17.7%)	RR 2.28 (1.93 to 2.7)	227 more per 1000 (from 165 more to 302 more)	High
Infection (incidence up to 15 days)					
1 meta-analysis of 7 studies (Chipchase & James, 1997; Ngai et al., 2001; Nielsen & Hahlin, 1995; Nielsen et al., 1999; Shelley et al., 2005; Trinder et al., 2006; Wieringa-de Waard et al., 2002a)	17/691 (2.5%)	30/1038 (2.9%)	RR 0.82 (0.46 to 1.44)	5 fewer per 1000 (from 16 fewer to 13 more)	High
Gastrointestinal side effects (number of events)					
1 study (Ngai et al., 2001	12/87 (13.8%)	25/90 (27.8%)	RR 0.5 (0.27 to 0.92)	139 fewer per 1000 (from 22 fewer to 203 fewer)	High

Number of studies	Number of women or average		Effect		Quality
	Expectant	**Active**	**Relative (95% CI)**	**Absolute (95% CI)**	
Need for a blood transfusion					
1 meta-analysis of 4 studies (Ngai et al., 2001; Shelley et al., 2005; Trinder et al., 2006; Wieringa-de Waard et al., 2002a)	8/507 (1.6%)	4/911 (0.4%)	RR 3.39 (1.08 to 10.61)	10 more per 1000 (from 0 more to 42 more)	High
Duration of bleeding (days)					
1 study (Trinder et al., 2006)	Median 12 (IQR 7 to 15) n = 398	**Medical:** Median 11 (IQR 7 to 15) n = 398 **Surgical:** Median 8 (IQR 4 to 14) n = 402	not calculable (NC)	**Expectant vs. medical** Median 1 higher (confidence interval NC) *P* (NC) **Expectant vs. surgical** Median 4 higher (confidence interval NC) *P* < 0.0001	High
1 meta-analysis of 2 studies (Nielsen & Hahlin, 1995; Nielsen et al., 1999)	n = 179	n = 134	NC	MD 0.28 higher (1.64 lower to 2.20 higher)	Moderate
1 study (Ngai et al., 2001)	Mean 15 (SD not reported [NR]) n = 29	Mean 14.6 (SD NR) n = 30	NC	MD 0.4 higher (confidence intervals NC) *P* value NR	Moderate
1 study (Wieringa-de Waard et al., 2002a)	Median 17 (IQR 10 to 26 n = 64	Median 13 (IQR 9 to 17) n = 58	NC	Median 4 higher (confidence interval NC) *P* = 0.04	Moderate

Number of studies	Number of women or average		Effect		Quality
	Expectant	**Active**	**Relative (95% CI)**	**Absolute (95% CI)**	
1 study (Chipchase & James, 1997)	Median 4 (range 0 to 7) n = 19	Median 2 (range 0 to 7) n = 16	NC	Median 2 higher (confidence interval NC) NS (*P* value NR)	Moderate
Pain: duration (days)					
1 study (Nielsen & Hahlin, 1995)	Mean 1.92 (SD 1.47) n = 103	Mean 1.69 (SD 1.46) n = 52	NC	MD 0.230 higher (0.263 lower to 0.723 higher) NS (*P* > 0.03)	Moderate
1 study (Wieringa-de Waard et al., 2002a)	Median 14 (IQR 7 to 24) n = 64	Median 11 (IQR 6 to 26) n = 58	NC	Median 3 higher (confidence interval NC) NS (*P* value not reported)	Moderate
1 study (Chipchase & James, 1997)	Median 0 (range 0 to 5) n = 19	Median 0 (range 0 to 2) n = 16	NC	Median 0 higher (confidence interval NC) NS (*P* value NR)	Moderate
1 study (Shelley et al., 2005)	Median 3.0 (range 0.0 to 11.0) n = 15	**Medical:** Median 3.0 (range 0.2 to 16.0) n = 11 **Surgical:** Median 2.0 (range 0.2 to 12.0) n = 12	NC	**Expectant vs. medical** Median 0 higher (confidence interval NC) **Expectant vs. surgical** Median 1 higher (confidence interval NC) *P* values NR	Moderate
Pain severity					
1 study (Nielsen et al., 1999)	Mean 62.0 (SD 30.1) n = 62	Mean 66.1 (SD 26.3) n = 60	NC	MD 4.10 lower (12.97 lower to 4.77 higher) NS (*P* value NR)	Moderate

Number of studies	Number of women or average		Effect		Quality
	Expectant	Active	Relative (95% CI)	Absolute (95% CI)	
1 study (Shelley et al., 2005)	Median 3 (range 1 to 7) n = 15	**Medical:** Median 3 (range 1 to 8) n = 11 **Surgical:** Median 3 (range 1 to 10) n = 12	NC	Median difference NC (confidence interval NC) NS between 3 groups but *P* values NR	Moderate
Unplanned admissions[†]					
1 study (Trinder et al., 2006)	196/398 (49.2%)	104/800 (13%)	RR 3.79 (3.09 to 4.65)	363 more per 1000 (from 272 more to 475 more)	High
Women's satisfaction					
1 study (Nielsen et al., 1999)	Mean 25.2 (SD 25.6) n = 62	Mean 28.6 (SD 24.8) n = 60	NC	MD 3.40 lower (11.32 lower to 4.52 higher) *P* = 0.174	Moderate
1 study (Chipchase & James, 1997)	19/19 (100%)	14/16 (87.5%)	RR 1.14 (0.95 to 1.38)	125 more per 1000 (44 fewer to 388 more)	Low
Anxiety					
1 study (Nielsen et al., 1996)	Mean 57.5 (SD 12.4) n = 58	Mean 57.5 (SD 14.0) n = 28	NC	MD 0.00 higher (5.92 lower to 5.92 higher) *P* > 0.30	Moderate
1 study (Wieringa-de Waard et al., 2002b)	Mean/SD NR n = 46	Mean/SD NR n = 36	NC	MD NC (confidence interval NC) *P* = 0.09	Low
1 study (Shelley et al., 2005)	3/15 (20%)	5/22 (22.7%)	RR 0.88 (0.25 to 3.14)	27 fewer per 1000 (171 fewer to 486 more)	Low

Number of studies	Number of women or average		Effect		Quality
	Expectant	Active	Relative (95% CI)	Absolute (95% CI)	
Mental health					
1 study (Wieringa-de Waard et al., 2002b)	Mean/SD NR n = 46	Mean/SD NR n = 36	NC	MD 7.4 in favour of expectant (confidence interval NC) *P* = 0.004	Low
1 study (Shelley et al., 2005)	Mean 37.1 (SD 13.0) n = 15	Mean 39.3 (SD 14.2) n = 22	NC	MD 2.2 lower (11.54 lower to 7.14 higher)	Low
Live birth rate in a subsequent pregnancy					
1 study (Smith et al., 2009)	177/224 (79.0%)	373/465 (80.2%)	RR 0.99 (0.91 to 1.07)	12 fewer per 1000 (from 74 fewer to 55 more)	Moderate
Subsequent conception rate					
1 study (Chipchase & James, 1997)	9/12 (75%)	6/9 (66.7%)	RR 1.13 (0.64 to 1.98)	83 more per 1000 (from 241 fewer to 654 more)	Low
1 study (Blohm et al., 1997)	Cumulative conception rate: 0.7	Cumulative conception rate: 0.6	NC	NS (*P* value NR)	Low

CI confidence interval, IQR interquartile range, MD mean difference, NC not calculable, NR not reported, NS not significant, *P* probability, RR relative risk, SD standard deviation

* Unplanned interventions include: surgery (including repeat surgery) due to first-line treatment failure, emergency surgery prior to allocated treatment, surgical completion on maternal request, or treatment to deal with a complication of the initial treatment

† Unplanned admission is an admission to hospital during the trial that was not pre-specified in the methodology as part of the management protocol

Two studies undertook additional data collection and analysis as a follow-up to an RCT. One of these is a UK study that includes qualitative data collection and analysis (Smith et al, 2006); the other was conducted in the Netherlands and compares quality of life and anxiety scores for both randomised and not randomised women taking part in a trial (Wieringa-de Waard et al, 2002b). Findings from these studies are summarised in Table 7.3 with quotations used to illustrate key themes identified from the qualitative research.

Table 7.3 Additional findings evaluating expectant and active miscarriage management strategies

Qualitative data on emotional/psychological outcomes and women's satisfaction with management	
1 study (Smith et al., 2006) (High*)	**Areas with general consensus:** *Fear* There was near uniform fear of intervention, especially anaesthetic, and a perception of hospitalisation and surgery as traumatic events. *'... I didn't really want to have anything done. I thought it was bad enough having lost it, without having to have any more fiddling around.'* *Predictability* Women wanted a predictable end, so they could get on with their lives, and they wanted their management and symptoms to have a predictable course. *'And it was like: I wanted it done, I wanted it done now. I wanted to get home for tea, sort of thing, that was how I was: can't we just do it.'* *Need for more information* Women felt they did not know what to expect in terms of bleeding and pain, and wanted more details on the timing, duration and effects of interventions. *'I didn't want to sort of just go home and wait for a miscarriage, because I didn't know what to expect at all.'* **Areas with wider variation in responses** *Appropriateness* Some women queried whether intervention was necessary and wished to be allowed to miscarry naturally themselves, whereas others were in favour of something being done to help expedite completion. *'I didn't want a D & C, … I know it sounds silly, 'cos the baby was already dead, but I don't agree with abortion, and things like that, and to me it felt the same; I wanted to do it on my own, and I got the D & C.'* *'I remember thinking about the three options, and coming to the conclusion that, at least a D & C was quick … because at the time I'd been off work for 3 weeks already … and I just thought: I don't want to wait anymore, particularly as I don't know what's going to happen.'* *Awareness of the event* Some women felt benefit in experiencing the event, to allow them to say goodbye, whereas others preferred surgery to avoid consciousness of the miscarriage. *'… it's very clean, very quick, wonderful operation, but, in a way, I think probably letting it miscarry helps to grieve in a funny way, because you're going through your grief all of the time that you are waiting for it to go, and then it goes, and you do a sort of mental realignment or whatever, you know, you have time to sort of prepare yourself.'* *The 'baby'* A few women wanted to see it and say goodbye, whereas others were scared about what they might see and wanted to avoid it. Some women wanted to avoid intervention because in the case of a misdiagnosis they felt that they would have been responsible for the baby's death. *'… but you know, I just sort of thought: what's that there? You know and, then, sort of waited, and then when you pull the flush, it's like a real goodbye, you know.'* *Pain and bleeding* Pain and bleeding were mentioned mostly by medical and expectant groups. Experiences of pain varied considerably, whereas bleeding was generally described as being a lot. *'They said it would be like a contraction, but it wasn't like a contraction at all, really … it was like very strong period pain … I likened it to when I first started my periods, when I was 13.'*

	'… I mean, looking back on it, I bled for about 40 hours, and had 40 hours of pain and bleeding; but I think that the actual psychological support I had was so much better, that it didn't seem that bad.' *Care received* A minority of women in the medical and surgical groups described a lack of caring by staff. In contrast, several women in the expectant group commented that although the experience was upsetting for them they found it reassuring to be at home. *'... and I hated it! The whole thing was cold! It was so insensitive, it was horrible! I will never forget how insensitive and cold it felt.' (woman who had surgical treatment)* *'… so, you know, I thought: no, I'll be at home, I'll be safe, and if there's any real problems, I've got a phone number to ring, or my GP, or we'll just call...' (woman who chose expectant management)*
Emotional and psychological outcomes in non-randomised women	
1 study (Wieringa-de Waard et al., 2002b) (Very low*)	In addition to the randomised women (n = 82), this study reports the outcomes of women who chose to be managed according to their own preference (n = 147). Their outcomes are analysed separately, and in comparison with the randomised group. Within the preference group, there were no statistically significant differences between the mental health scores and anxiety scores of women who chose expectant management (n = 61) and women who chose active treatment (n = 86). **Comparing randomised and non-randomised women** When comparing women who were randomised to expectant management and women who chose expectant management, there were no significant differences in mental health score and anxiety. Women who were randomised to active treatment had significantly worse mental health scores than women who chose active treatment (*P* = 0.03). Within the randomised group, no differences were found between women who were randomly allocated to the mode of management for which they had expressed a slight preference and those who were randomised to the other mode of management. *Note* Other than expressing a strong preference for a specific management option, it is unclear whether randomised and non-randomised women were comparable. Mean values for all scores at different assessment times were not reported as figures in the text but only in graphs from which it is impossible to extract accurate values.

* Qualitative studies not ranked in GRADE but using NICE quality assessment for qualitative studies

Evidence statements

Need for unplanned intervention

One study found that the need for unplanned intervention was higher in women who received expectant management compared with women who received active treatment. This finding was statistically significant and the evidence for this outcome was of high quality.

Infection

One meta-analysis of seven studies did not find a statistically significant difference in infection for women who received expectant management compared with women who received active treatment. The evidence for this outcome was of high quality.

Gastrointestinal side effects

One study found that gastrointestinal side-effects were lower in women who received expectant management compared with women who received active treatment. This finding was statistically significant and the evidence for this outcome was of high quality.

Need for a blood transfusion

One study found that the need for a blood transfusion was higher in women who received expectant management compared with women who received active treatment. This finding was statistically significant and the evidence for this outcome was of high quality.

Duration of bleeding

One study found that the duration of bleeding was longer in women who received expectant management compared with women who received active treatment. This finding was statistically significant. The evidence for this finding was of moderate quality. One study found that the duration of bleeding was longer in women who received expectant management compared with women who received surgical management. This finding was statistically significant. However, the same study did not find a statistically significant difference in duration of bleeding in women who received expectant management compared with women who received medical management. The evidence for both of these findings was of high quality. One meta-analysis of two studies and one further study did not find a statistically significant difference in duration of bleeding in women who received expectant management compared with women who received active treatment. The evidence for this finding was of moderate quality. One study reported duration of bleeding in a manner that did not allow assessment of statistical significance.

Pain

Three studies did not find a statistically significant difference in the duration of pain for women who received expectant management compared with women who received active treatment. One further study reported this outcome in a manner that did not permit assessment of statistical significance. The evidence for this outcome was of moderate quality.

Two studies did not find a statistically significant difference in the severity of pain for women who received expectant management compared with women who received active treatment. The evidence for this outcome was of moderate quality.

Unplanned admissions

One study found that unplanned admissions were higher in women who received expectant management compared with women who received active treatment. This finding was statistically significant and the evidence for this outcome was of high quality.

Women's satisfaction

Two studies did not find a statistically significant difference in satisfaction for women who received expectant management compared with women who received active treatment. The evidence for this outcome was of moderate quality in one study and low quality in the other.

Anxiety

Three studies did not find a statistically significant difference in anxiety for women who received expectant management compared with women who received active treatment. The evidence for this outcome was of moderate quality in one study and low in the others.

Mental health

One study found that mental health scores were higher in women who received expectant management compared with women who received active treatment. This finding was statistically significant. One further study found no statistically significant difference in mental health scores between the two groups. The evidence for this outcome was of low quality.

Live birth rate in a subsequent pregnancy

One study did not find a statistically significant difference in the live birth rate in a subsequent pregnancy for women who received expectant management compared with women who received active treatment. The evidence for this outcome was of moderate quality.

Subsequent conception rate

Two studies did not find a statistically significant difference in subsequent conception rate for women who received expectant management compared with women who received active treatment. The evidence for this outcome was of low quality.

Emotional and psychological outcomes

One qualitative study found that when comparing expectant management and active treatment there was general consensus among women related to the following issues:

- fear of intervention, especially anaesthetic, hospitalisation and surgery
- desire to have a predictable course/end in terms of management and symptoms
- need for more information in terms of bleeding and pain, details on the timing, duration and effects of interventions.

In contrast there were areas with great variation in responses:

- appropriateness and need for intervention (to miscarry naturally compared with having something done to help expedite completion)
- awareness of the event (benefit in experiencing the event and saying goodbye compared with avoiding consciousness of the miscarriage)
- the 'baby' (seeing it and saying goodbye compared with being scared about what they might see and feeling responsible for the 'baby's' death in case of misdiagnosis)
- degree and experiences of pain and bleeding and care received (lack of caring by staff compared with it being reassuring to be at home).

The evidence for these findings was of high quality.

One study found that mental health scores were worse in women who were randomised to active treatment compared with women who had chosen active treatment. This difference was statistically significant and the evidence for this outcome was of very low quality.

The same study did not find a statistically significant difference between women randomised to expectant management and women who chose expectant management for mental health score or anxiety. In addition, the study did not find a statistically significant difference between women who chose expectant management and women who chose active treatment for either mental health score or anxiety. The evidence for these outcomes was of very low quality.

Health economics

One good quality economic evaluation of the miscarriage treatment (MIST) trial (Petrou et al., 2006) undertaken in an English setting found that the mean cost of surgical management was £200 more expensive than medical management (95% confidence interval [CI] £122–£278) and that the mean cost of medical management was £273 more expensive than expectant management (95% CI £160–£376). There was more than a 50% chance that expectant management was the most cost-effective treatment if the decision maker was not prepared to spend more than £70,000 to prevent a single gynaecological infection.

Five studies of lower quality (Hughes et al., 1996; Graziosi et al., 2005; Niinimaki et al., 2009; Rocconi et al., 2005; You & Chung, 2005) generally agreed with the economic evaluation of the MIST trial in that they all found surgical management to be more expensive than medical management. Where the studies also considered expectant management (Rocconi et al., 2005; You & Chung, 2005) this was found to be the least expensive alternative apart from a decision tree artefact where expectant management cost exceeded that of medical management because the expected management decision could be overridden by a patient preference for surgical treatment (You & Chung, 2005). For a full description of the literature review see Section 10.3.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG felt that the most important clinical outcomes were the need for an unplanned intervention, the incidence of infection, gastrointestinal side-effects and the need for a blood transfusion. While it recognised that live birth rate is an important outcome, it did not feel that it was likely the evidence would be of a sufficient size to show a statistically significant difference. Women's emotional and

psychological outcomes were also prioritised. The group also recognised that women's satisfaction with their care is an important outcome, but felt that this is a difficult outcome to capture in research as the women are not able to express their satisfaction with the care they received compared with care that they did not receive. Thus it is difficult to determine which management strategy women are likely to prefer.

Consideration of clinical benefits and harms

The evidence showed that expectant and active treatment of miscarriage were similar in terms of severity of pain experienced, anxiety, women's satisfaction with care, number of days in pain and the incidence of infection. Expectant treatment of miscarriage was associated with fewer gastro-intestinal side-effects, but women having expectant management of miscarriage had more days of bleeding and a significantly greater chance of needing a blood transfusion. Unplanned intervention was significantly greater in the expectant management group.

Consideration of health benefits and resource uses

The review of health economic literature clearly demonstrated that expectant management is the most cost-effective approach by a significant margin, even taking into account the additional care that some women may require as the result of emergency procedures and unplanned interventions. As a result, the GDG agreed that, for the majority of women, expectant management should be the first-line treatment that is offered. The GDG members felt that, for most women, expectant management would be an acceptable or even preferable alternative, as it negates the risk of intervening and accidentally terminating a viable pregnancy. In addition, they noted the almost universal fear of intervention that was reported in the qualitative study. However, the GDG also recognised that for some women, expectant management will be unacceptable. It recognised the importance of being able to offer a choice if this were the case and so agreed that medical management could be offered as an alternative as this was the next most cost-effective treatment.

The group also recognised that there may be some clinical reasons why expectant management would not be appropriate. In particular, it noted the increased rate of blood transfusion following expectant management. Based on their clinical experience, the GDG members felt that this could be due to an increase in severe blood loss at later gestation. Using their clinical judgement, they agreed that, for women at increased risk of haemorrhage, such as those late in the first trimester or women at increased risk of the effects of haemorrhage (such as women with coagulopathies), other management options (both medical and surgical) should be considered. They were aware that this might have cost implications in terms of treatment, but felt that this should be weighed against the increased likelihood of a blood transfusion and need for emergency care in this subset of women, and the risk of poor outcomes following haemorrhage. The group also recognised that for women with evidence of infection, expectant management would be inappropriate and so other management options (both medical and surgical) should be considered. Finally, the group agreed that women who have had a previous traumatic experience associated with pregnancy (such as previous miscarriage or antepartum haemorrhage) should be offered their choice of treatment. The GDG felt that these women would likely be particularly anxious about having to wait for up to two weeks and more at risk of resultant psychological morbidities.

The GDG noted that there was a failure rate associated with expectant management of miscarriage, which is captured in a rate of further intervention of over 35%. It also recognised that for some women, a lengthy period of expectant management would not be acceptable; therefore the group felt that it was appropriate to designate an endpoint, after which women in whom expectant management had thus far been unsuccessful could choose to undergo an intervention to expedite the process. From their clinical experience, the GDG members felt that the natural course of a miscarriage might generally be expected to occur over a period of 7 to 14 days from the start of bleeding, and therefore that women should be reviewed after this time. The decision about the precise timing of the appointment for review should be made by the woman and healthcare professional together based on individual circumstances. Women should be rescanned after 7 to 14 days unless the symptoms are improving or have resolved, in which case a pregnancy test after 3 weeks would be sufficient.

Quality of evidence

The evidence available for this question was generally of high or moderate quality. In addition, it was felt that the health economic literature was of sufficient quality that it would be used to inform the

review, rather than needing to develop a bespoke model for the question. While the quality of evidence was not high for all outcomes, it was for the majority, including those on which the group placed most emphasis, and thus the group felt confident in using the evidence to develop its recommendations.

Information giving and emotional support

One of the key themes from the qualitative data analysed in the review was the fact that women wanted more information regarding what to expect during their treatment. As expectant management may be an unfamiliar concept to some women, the GDG felt that it was vital that they be informed about the process, including what to expect in terms of pain and bleeding, what pain-relieving measures they might use as well as what options would be available in the event that expectant management does not result in the completion of the miscarriage. The GDG also felt that it was important that women be given details of support organisations, so that they could access support and counselling services. The GDG recognised that there can be a lot of information to give to women and agreed that healthcare professionals should ensure that sufficient time is made available to discuss all of the relevant issues and that this be supported with written information for the women to take away. In some instances, this might also mean arranging an additional appointment.

Although the qualitative studies for this review were looking at women's experiences of different treatment options, the GDG agreed that the evidence highlighted the more general point that women react to complications and the loss of pregnancy in different ways. The GDG therefore wished to stress the importance of giving information in a sensitive way, taking into account each individual woman's emotional response.

7.4 Surgical management compared with medical management of miscarriage

Review question

How effective is surgical management of miscarriage compared with medical management for improving women's clinical and psychological outcomes?

Introduction

The standard procedure for managing miscarriage has been surgical management. Surgical completion of miscarriage carries a risk of complications and often requires a general anaesthetic. Medical management may provide an alternative treatment but needs to be studied in terms of maternal outcomes, including emotional and psychological outcomes, as well as pain, bleeding and adverse clinical events including re-admission and unplanned intervention.

Description of included studies

Twenty-seven studies were included in this review (Chung et al., 1999; Dabash et al. 2010; Dao et al., 2007; Davis et al., 2007; de Jonge et al., 1995; Demetroulis et al., 2001; Egarter et al., 1995; Fang et al., 2009; Graziosi et al., 2004; Graziosi et al., 2005a; Graziosi et al., 2005b; Harwood & Nansel, 2008; Hinshaw, 1997; Lee et al., 2001; Montesinos et al., 2011; Moodliar et al., 2005; Muffley et al., 2002; Niinimaki et al., 2006; Sahin et al., 2001; Shelley et al., 2005; Shwekerela et al., 2007; Smith et al., 2006; Smith et al., 2009; Tam et al., 2005; Taylor et al., 2011; Trinder et al., 2006; Zhang et al., 2005).

One study is a qualitative study which followed up both participants and non-participants of an RCT conducted in the UK (Smith et al., 2006). Another study is a partially randomised trial, conducted in the UK, which included both women who had chosen their method of management and those who had been randomised to medical or surgical management (Hinshaw, 1997). The remainder of the included studies report the outcomes and follow-up data of 16 randomised controlled trials, conducted in the UK (Demetroulis et al., 2001 and a second trial reported on by both Smith et al., 2009 and Trinder et al., 2006), Australia (Shelley et al., 2005), Austria (Egarter et al., 1995), Burkina Faso (Dao et al., 2007), China (Fang et al., 2009), Ecuador (Montesinos et al., 2011), Egypt (Dabash et al., 2010), Finland (Niinimaki et al., 2006), Ghana (Taylor et al., 2011), Hong Kong (one trial reported on

by Chung et al., 1999, Lee et al., 2001 and Tam et al., 2005), the Netherlands (one trial reported on by Graziosi et al., 2004, Graziosi et al., 2005a and Graziosi et al., 2005b), South Africa (two trials: de Jonge et al., 1995; Moodliar et al., 2005), Tanzania (Shwekerela et al., 2007), Turkey (Sahin et al., 2001), and the USA (one trial reported on by Davis et al., 2007, Harwood & Nansel, 2008 and Zhang et al., 2005 and a second trial reported on by Muffley et al., 2002).

All studies compared medical and surgical management of miscarriage and reported at least one priority outcome. The trials were conducted in developed and developing countries, and their populations include women with missed miscarriages and/or women with ongoing miscarriages.

Evidence profile

Sixteen outcomes (grouped into eight broad categories) were prioritised by the GDG to inform recommendations. In outcomes with high heterogeneity (over 60%), the NCC-WCH technical team used a random effects model (the remaining outcomes used fixed effects models) and explored the heterogeneity with sensitivity analyses. Findings from these sensitivity analyses are described here.

Gastro-intestinal side-effects

Overall heterogeneity (89%) was not significantly reduced by considering: only trials in developed countries; trials where only drugs administered vaginally were used; only trials where at least one oral drug was used; or only trials where the surgical arm received general anaesthetic. The technical team also explored the effect of dosage, with and without mode of administration. None of the combinations tested reduced the heterogeneity to below 60%. The high heterogeneity could be as a result of the variety of medical regimens used, the combination of three gastro-intestinal side-effects into one overall outcome, or the fact that it was a patient-reported outcome.

Unplanned visits to a medical facility

Considering only developed countries reduced the heterogeneity from 64% to 25% and resulted in there being no significant difference between the number of unplanned visits in the medical and surgical arms. This could be as a result of different patterns of healthcare-seeking behaviour in developed and developing countries.

Satisfaction

Overall heterogeneity (77%) was not reduced by considering only developed countries or removal of the trials in which the surgical arm received only local or verbal anaesthesia. The high heterogeneity could be a result of factors not generally reported in the trials, for example variable waiting times for surgery (reported in one trial as a contributing factor to dissatisfaction in the surgical patients).

Table 7.4 GRADE summary of findings for comparison of medical management with surgical management

Number of studies	Number of women (%) or average		Effect		Quality
	Medical	Surgical	Relative (95% CI)	Absolute (95% CI)	
Need for unplanned intervention*					
1 meta-analysis of 18 studies[†]	545/2553 (21.3%)	55/2186 (2.5%)	RR 8.13 (6.26 to 10.55)	179 more per 1000 (from 132 more to 240 more)	High
Infection (incidence up to 15 days)					
1 meta-analysis of 7 studies[‡]	23/1455 (1.6%)	24/1113 (2.2%)	RR 0.9 (0.51 to 1.57)	2 fewer per 1000 (from 11 fewer to 12 more)	High

Number of studies	Number of women (%) or average		Effect		Quality
	Medical	Surgical	Relative (95% CI)	Absolute (95% CI)	
Gastro-intestinal side effects (number of events)					
1 meta-analysis of 12 studies[§]	994/4358 (22.8%)	260/3346 (7.8%)	RR 2.36 (1.39 to 4.00)	106 more per 1000 (from 30 more to 233 more)	Moderate
Need for a blood transfusion					
1 meta-analysis of 8 studies[**]	15/1353 (1.1%)	8/1063 (0.8%)	RR 1.6 (0.74 to 3.42)	5 more per 1000 (from 2 fewer to 18 more)	High
Duration of bleeding (days)					
1 meta-analysis of 5 studies (Demetroulis et al., 2001; Egarter et al., 1995; Graziosi et al., 2004; Moodliar et al., 2005; Sahin et al., 2001)	n = 245	n = 241	not calculable (NC)	MD 1.31 higher (0.73 to 1.89 higher) *P* < 0.0001	High
1 study (Trinder et al., 2006)	Median 11 (IQR 7-15) n = 398	Median 8 (IQR 4-14) n = 402	NC	Median 3 higher (confidence interval NC) *P* = 0.0004	High
1 study (Davis et al., 2007)	Median 12 (IQR 9-14) n = 428	Median 10 (IQR 7-12) n = 135	NC	Median 2 higher (confidence interval NC)	Moderate
1 study (Dabash et al. 2010)	Mean 3.23 (SD NR) n = 327	Mean 2.73 (SD NR) n = 316	NC	MD 0.5 higher (confidence interval NC) *P* < 0.01	Moderate
1 study (Taylor et al., 2011)	Mean 2.86 (SD NR)	Mean 1.64 (SD NR)	NC	MD 1.22 higher (confidence interval NC) *P* = 0.001	Moderate
1 study (Chung et al., 1999)	Mean 9.1 (SD not reported (NR)) n = 321	Mean 9.3 (SD NR) n = 314	NC	MD 0.2 lower (confidence interval NC) *P* = 0.48	Low

Number of studies	Number of women (%) or average		Effect		Quality
	Medical	Surgical	Relative (95% CI)	Absolute (95% CI)	
1 study (Montesinos et al., 2011)	Mean 3.4 (SD NR)	Mean 3.0 (SD NR)	NC	MD 0.4 higher (confidence interval NC) *P* = 0.223	Low
1 study (Dao et al., 2007)	Mean 3.1 (SD NR) n = 223	Mean 2.9 (SD NR) n = 224	NC	MD 0.2 higher (confidence interval NC) *P* = 0.09	Very low
Pain: duration (days)					
1 study (Demetroulis et al., 2001)	Mean 4.7 (SD 2.4) n = 36	Mean 2.8 (SD 1.6) n = 35	NC	MD 1.9 higher (0.95 to 2.85 higher) *P* < 0.0001	High
1 study (Dabash et al. 2010)	Mean 2.63 (SD NR) n = 327	Mean 2.63 (SD NR) n = 316	NC	MD 0 higher (confidence interval NC) *P* = 0.98	Moderate
1 study (Shelley et al., 2005)	Median 3.0 (Range 0.2-16.0) n = 11	Median 2.0 (Range 0.2-12.0) n = 12	NC	Median 1 higher (confidence interval NC)	Moderate
1 study (Montesinos et al., 2011)	Mean 2.5 (SD NR)	Mean 2.6 (SD NR)	NC	MD 0.1 lower (confidence interval NC) *P* = 0.739	Moderate
1 study (Taylor et al., 2011)	Mean 1.44 (SD NR)	Mean 1.34 (SD NR)	NC	MD 0.1 higher (confidence interval NC) *P* = 0.44	Low
1 study (Chung et al., 1999)	Mean 0.17 (SD NR) n = 321	Mean 0.25 (SD NR) n = 314	NC	MD 0.08 lower (confidence interval NC) *P* = 0.30	Low
1 study (Dao et al., 2007)	Mean 1.4 (SD NR) n = 223	Mean 1.3 (SD NR) n = 224	NC	MD 0.1 higher (confidence interval NC) *P* = 0.08	Very low

Number of studies	Number of women (%) or average		Effect		Quality
	Medical	Surgical	Relative (95% CI)	Absolute (95% CI)	
Pain: severity score/10					
1 meta-analysis of 3 studies (Graziosi et al., 2004; Moodliar et al., 2005; Zhang et al., 2005)	n = 602	n = 263	NC	MD 2.3 higher (1.92 to 2.68 higher) *P* < 0.00001	High
1 study (Shelley et al., 2005)	Median 3 (Range 1-8) n = 11	Median 3 (Range 1-10) n = 12	NC	Median 0 higher (confidence interval NC)	Moderate
1 study (Fang et al., 2009)	Score <3: 17/45 (37.8%)	Score <3: 12/30 (40%)	RR 0.94 (0.53-1.68)	24 fewer per 1000 (from 188 fewer to 272 more)	Low
Pain: severity score/7					
1 study (Dao et al., 2007)	Mean 2.32 (SD NR) n = 223	Mean 2.73 (SD NR) n = 224	NC	MD 0.41 lower (confidence interval NC) *P* = 0.047	Moderate
1 study (Shwekerela et al., 2007)	Mean 3.0 (SD NR) n = 150	Mean 3.5 (SD NR) n = 150	NC	MD 0.5 lower (NC) *P* < 0.001	Moderate
Unplanned visits to a medical facility					
1 meta-analysis of 5 studies (Chung et al., 1999; Dabash et al. 2010; Dao et al., 2007; Demetroulis et al., 2001; Zhang et al., 2005)	148/1375 (10.8%)	42/1026 (4.1%)	RR 1.67 (0.74 to 3.79)	27 more per 1000 (from 11 fewer to 114 more)	Low
Unplanned admissions[††]					
1 study (Trinder et al., 2006)	72/398 (18.1%)	32/402 (7.9%)	RR 2.27 (1.53 to 3.37)	101 more per 1000 (from 42 more to 189 more)	High

Number of studies	Number of women (%) or average		Effect		Quality
	Medical	Surgical	Relative (95% CI)	Absolute (95% CI)	
Satisfaction: reported incidence					
1 meta-analysis of 9 studies‡‡	1032/1093 (94.4%)	1024/1076 (95.2%)	RR 0.99 (0.96 to 1.03)	10 fewer per 1000 (from 38 fewer to 29 more)	Low
Social function at 2 weeks: SF-36 score/100 (better indicated by higher values)					
1 meta-analysis of 2 studies (Graziosi et al., 2005a; Harwood & Nansel, 2008)	n = 525	n = 205	NC	MD 0.69 lower (2.7 lower to 1.32 higher) *P* = 0.50	High
Social function at 2 weeks: SPS score (better indicated by lower values)					
1 study (Lee et al., 2001)	Mean 0.14 (SD 0.26) n = 104	Mean 0.16 (SD 0.29) n = 111	NC	MD 0.02 lower (0.094 lower to 0.054 higher) *P* = 0.93	High
Mental health at 2 weeks: SF-36 score/100 (better indicated by higher values)					
1 meta-analysis of 2 studies (Graziosi et al., 2005a; Shelley et al., 2005)	n = 79	n = 66	NC	MD 3.43 lower (8.53 lower to 1.68 higher) *P* = 0.19	Low
Live birth rate in a subsequent pregnancy					
1 meta-analysis of 2 studies (Smith et al., 2009; Tam et al., 2005)	290/361 (80.3%)	304/365 (83.3%)	RR 0.96 (0.9 to 1.03)	33 fewer per 1000 (from 83 fewer to 25 more)	Moderate
1 study (Graziosi et al., 2005b)	n = 69	n = 57	RR 0.98 (0.66 to 1.5)	NC	Very low

CI confidence interval, IQR interquartile range, MD mean difference, NC not calculable, NR not reported, *P* probability, RR relative risk, SD standard deviation

* Unplanned interventions include: surgery (including repeat surgery) due to first-line treatment failure, emergency surgery prior to allocated treatment, surgical completion on maternal request, or treatment to deal with a complication of the initial treatment

† 18 studies – Chung et al. 1999; Dabash et al. 2010; Dao et al., 2007; de Jonge et al., 1995; Demetroulis et al., 2001; Egarter et al., 1995; Fang et al., 2009; Graziosi et al., 2004; Montesinos et al., 2011; Moodliar et al., 2005; Muffley et al., 2002; Niinimaki et al., 2006; Sahin et al., 2001; Shelley et al., 2005; Shwekerela et al., 2007; Taylor et al., 2011; Trinder et al., 2006; Zhang et al., 2005

‡ 7 studies - Chung et al., 1999; Moodliar et al., 2005; Sahin et al., 2001; Shelley et al., 2005; Shwekerela et al., 2007; Trinder et al., 2006; Zhang et al., 2005;
§ 12 studies - Chung et al., 1999; Dabash et al., 2010; Dao et al., 2007; Demetroulis et al., 2001; Egarter et al., 1995; Graziosi et al., 2004; Montesinos et al., 2011; Moodliar et al., 2005; Shelley et al., 2005; Shwekerela et al., 2007; Taylor et al., 2011; Zhang et al., 2005
** 8 studies - Dabash et al., 2010; Davis et al., 2007; de Jonge et al., 1995; Demetroulis et al., 2001; Graziosi et al., 2004; Muffley et al., 2002; Shelley et al., 2005; Trinder et al., 2006
†† Unplanned admission is an admission to hospital during the trial that was not pre-specified in the methodology as part of the management protocol
‡‡ 9 studies - Dabash et al. 2010; Dao et al., 2007; Demetroulis et al., 2001; Fang et al., 2009; Montesinos et al., 2011; Niinimaki et al., 2006; Sahin et al., 2001; Shwekerela et al., 2007; Taylor et al., 2011

Two UK studies undertook additional data collection and analysis as a follow-up to RCTs. One study (Smith et al, 2006) used qualitative methods of data collection and analysis, the other used a simple descriptive survey with data reported as descriptive statistics (Hinshaw, 1997). Findings from these studies are summarised in Table 7.5 with quotations used to illustrate key themes identified from the qualitative research.

Table 7.5 Additional findings evaluating medical and surgical miscarriage management strategies

Qualitative data on emotional/psychological outcomes and women's satisfaction with care	
1 study (Smith et al., 2006) (High*)	**Areas with general consensus** *Fear* There was near uniform fear of intervention, especially anaesthetic. *'I was more worried about the anaesthetic, that sort of worries me, just sort of being knocked out, and I'm always afraid about not waking up again....'* *Predictability* Women wanted a predictable end, so they could get on with their lives, and they wanted their management and symptoms to have a predictable course. *'I would have preferred to have a D & C, although I'm not sure what that would be like, exactly what that is, but, at least there would be an end to that, like you know: one minute you're pregnant, and the next minute it's finished and you can get on with your life.'* *Need for more information* Women felt they did not know what to expect in terms of bleeding and pain, and wanted more details on the timing, duration and effects of interventions, particularly in the medical group. *'… and I just thought: I don't want to wait any more, particularly because I don't know what's going to happen, and, oh, the first time I'd read a book about miscarriage, and the most awful stories always get in there, I mean you always get those sorts of stories and you think, "oh my God, you know, what on earth is going to happen?'* **Areas with wider variation in responses** *Appropriateness* Some women queried whether intervention was necessary and wished to be allowed to miscarry naturally themselves, whereas others were in favour of something being done to help expedite completion. *'… it happened the next morning [when] I came home … and it was a sense of relief really, ... it's ended … the medical treatment, it's just speeding it up … it's not actually anyone else going in my body … it's just a little magic tablet … it's midpoint… it's a kind treatment … it's not your baby whipped out of you, which is what a D & C feels like to me.'* *Awareness of the event* Some women felt benefit in experiencing the event, to allow them to say goodbye, whereas others preferred surgery to avoid consciousness of the miscarriage.

Qualitative data on emotional/psychological outcomes and women's satisfaction with care	
	'… it's very clean, very quick, wonderful operation, but, in a way, I think probably letting it miscarry helps to grieve in a funny way, because you're going through your grief all of the time that you are waiting for it to go, and then it goes, and you do a sort of mental realignment or whatever, you know, you have time to sort of prepare yourself.' *The 'baby'* A few women wanted to see it and say goodbye, whereas others were scared about what they might see and wanted to avoid it. Some women wanted to avoid intervention because in the case of a misdiagnosis they felt that they would have been responsible for the baby's death. *'I was very relieved that it had miscarried naturally 'cos I could cope with it dying naturally, that wasn't a problem, with the thought of having it killed on purpose, that's how I would have seen it.'* *Pain and bleeding* Pain and bleeding were mentioned mostly by medical group. Experiences of pain varied considerably, whereas bleeding was generally described as being a lot. *'I suppose to all intents and purposes I had gone through labour, although obviously a different version, but I did feel, my body did feel as though I'd gone through labour, and of course, I had nothing to show for it.'* *Care received* A minority of women described a lack of caring by staff. *'… you felt like you were ... sort of on a conveyor belt and they just whacked this mask over my face, it was almost like, you know: get through, lie down, shut up [laughs] and we can get on with it, because you are slowing down the process …' (woman who had surgical treatment)*
Descriptive data from non-randomised women	
1 study (Hinshaw, 1997) (Very low*)	In a partially randomised trial, 54.2% women had a preference for one method and chose not to be randomised; therefore they were given their preferred method of management. The reasons that women preferred medical management were the avoidance of general anaesthesia/surgery (57.1%) and the feeling that it was more natural or they were in control (35.7%). The reasons that women preferred surgical management were the timescale (72.1%), issues of awareness (42.9%), avoidance of pain/bleeding (40.8%) and perceived effectiveness (12.9%). Generally, acceptability was lower in the medical arm, but was unaffected by whether women were randomised or chose their method of management.

* Qualitative studies not ranked in GRADE but using NICE quality assessment for qualitative studies

Additional analysis of surgical complications

The rate of surgical complications is not reported as an outcome in the GRADE table because it is intuitive that the rate will be higher in women randomised to the surgical arm (the vast majority of whom undergo surgery) when compared to women randomised to the medical arm (a minority of whom end up having surgery). However, the GDG was concerned that potential side-effects of surgery should not be overlooked, and therefore further analysis was done based on data on surgical complications that was reported in the studies.

Five trials (Chung et al., 1999; Egarter et al., 1995; Graziosi et al., 2004; Muffley et al., 2002; Trinder et al., 2006) reported the rates of surgical complications, which included uterine perforation, cervical laceration, haemorrhage and intrauterine synechia. The incidence of surgical complications was generally low, ranging from 2% to 8% among women randomised to surgery. The incidence was under 5% in four out of the five studies that reported it.

The potential for reducing the risk of complications through cervical priming prior to surgery (as hypothesised in Chung et al., 1999) could not be assessed, because none of the studies that assessed surgical complication rates reported priming.

The association of complication rate with type of miscarriage (for example missed or incomplete) could not be explored because three of the studies only included women with missed miscarriage, and in the remaining two studies over 75% of women had a missed miscarriage.

Evidence statements

Need for an unplanned intervention

One meta-analysis of 18 studies found that the need for an unplanned intervention was higher in women who received medical management compared with women who received surgical management. This finding was statistically significant and the evidence for this outcome was of high quality.

Infection

One meta-analysis of seven studies did not find a statistically significant difference in the incidence of infection for women who received medical management compared with women who received surgical management. The evidence for this outcome was of high quality.

Gastro-intestinal side-effects

One meta-analysis of 12 studies found that gastro-intestinal side-effects were higher in women who received medical management compared with women who received surgical management. This finding was statistically significant. The evidence for this outcome was of moderate quality.

Need for a blood transfusion

One meta-analysis of eight studies did not find a statistically significant difference in the need for a blood transfusion for women who received medical management compared with women who received surgical management. The evidence for this outcome was of high quality.

Duration of bleeding

One meta-analysis of five studies and three other studies found that duration of bleeding was longer in women who received medical management compared with women who received surgical management. This finding was statistically significant. The evidence for this finding was of high quality in the meta-analysis and one single study, and moderate quality in the other two studies. Three further studies did not find a statistically significant difference in duration of bleeding between the two groups. The evidence for this finding was low quality in two studies and very low quality in the third. One further study reported duration of bleeding in a manner that did not allow assessment of statistical significance.

Pain

One study found that the duration of pain was longer in women who received medical management compared with women who received surgical management. This finding was statistically significant and the evidence for this finding was of high quality. Five further studies did not find a statistically significant difference in duration of pain between the two groups. The evidence for this finding was of moderate quality in two studies, low in two other studies and very low in the fifth study. One further study reported duration of pain in a manner that did not allow assessment of statistical significance.

One meta-analysis of three studies found that the severity of pain on a ten-point scale was higher in women who received medical management compared with women who received surgical management. This finding was statistically significant. The evidence for this finding was of high quality. One further study did not find a statistically significant difference in severity of pain on a ten-point scale between the two groups. The evidence for this finding was of low quality. One further study reported severity of pain on a ten-point scale in a manner that did not allow assessment of statistical significance.

Two studies found that the severity of pain on a seven-point scale was lower in women who received medical management compared with women who received surgical management. This finding was statistically significant and the evidence for this outcome was of moderate quality.

Unplanned visits to a medical facility

One meta-analysis of five studies did not find a statistically significant difference in the unplanned visits to a medical facility for women who received medical management compared with women who received surgical management. The evidence for this outcome was of low quality.

Unplanned admissions

One study found that unplanned admissions were higher in women who received medical management compared with women who received surgical management. This finding was statistically significant and the evidence for this outcome was of high quality.

Satisfaction

One meta-analysis of nine studies did not find a statistically significant difference in the reported satisfaction for women who received medical management compared with women who received surgical management. The evidence for this outcome was of low quality.

Social function at 2 weeks

Three studies did not find a statistically significant difference in the social function score at 2 weeks for women who received medical management compared with women who received surgical management. The evidence for this outcome was of high quality.

Mental health at 2 weeks

One meta-analysis of two studies did not find a statistically significant difference in the mental health score at 2 weeks for women who received medical management compared with women who received surgical management. The evidence for this outcome was of low quality.

Live birth rate in a subsequent pregnancy

One meta-analysis of two studies and one further study did not find a statistically significant difference in the live birth rate in a subsequent pregnancy for women who received medical management compared with women who received surgical management. The evidence for this outcome was of moderate quality and very low quality respectively.

Women's preferences, emotional and psychological outcomes

One qualitative study found that there was general consensus among women regarding fear of intervention, a desire for their treatment to follow a predictable course and the need for more information. In contrast, there was wider variation in women's feelings about the appropriateness of intervention, awareness of the event, feelings about the 'baby', the degree of pain and bleeding experienced, and the care received. The evidence for these findings was of high quality.

One partially randomised trial provided very low quality evidence that the acceptability of medical management was lower than surgical management, but was unaffected by whether women were randomised to, or had chosen, their method of management. Women who chose surgical management stated timescale, issues of awareness, avoidance of pain/bleeding and perceived effectiveness as the reasons for their preference. Women who chose medical management stated avoidance of general anaesthesia/surgery, and the feeling that it was more natural and that they were in control, as the main reasons for their preference. However, the evidence for these findings was of very low quality.

Evidence to recommendations

Relative value placed on the outcomes considered

For this review, the GDG felt that both quantitative and qualitative evidence were equally valuable. Clinically, the group felt that the need for further intervention, requirement for a blood transfusion and side-effects were important, in addition to other outcomes with cost implications, such as need for admission. From their clinical experience, and the qualitative evidence, the GDG members noted that women's responses to miscarriage and their preferences for mode of management are highly variable, and therefore the views and experiences of women reported in the qualitative study were vital in informing their decision. In contrast, the group did not feel that satisfaction with treatment and psychological scores were particularly useful outcomes. What evidence there was showed little difference between the two treatment arms, but the group felt that these outcomes are often difficult to

capture accurately in randomised populations, and are less informative than qualitative data that explores women's experiences of their mode of management.

Consideration of clinical benefits and harms

Medical management of miscarriage avoids the need for surgery in over 70% of women. The GDG felt that this would be an important consideration for women, as surgery often requires a general anaesthetic and has an associated risk of complications. The risk of surgical complications among women randomised to surgery ranged from 2% to 8%, and included uterine perforation, haemorrhage, cervical lacerations and synechia. However, medical management is also associated with a significantly higher rate of unplanned intervention and unplanned admission. Gastro-intestinal side-effects, such as vomiting, are higher with medical management of miscarriage but the risk of infection and haemorrhage requiring transfusion is similar for both forms of active management. From their experience, the GDG members felt that this small risk of blood transfusion may be an over-estimation as in current clinical practice few women receive one.

The results of the qualitative studies supported the GDG's view that individual women often have very different priorities and expectations of their treatment. They recognised that, while women may strongly wish to avoid undergoing surgery, for some women the predictability, promptness and high likelihood of success following surgical treatment would be an attractive option. The GDG felt that, as the majority of women would have undergone up to 2 weeks of expectant management as a first-line treatment, it was important that they be given a choice about how to proceed at that point. Although the health economics analysis showed that medical management was more cost effective than surgical management, the GDG noted that this was based on estimates of first-line treatment, and therefore could not directly be applied to women in whom expectant management had already failed. The group felt strongly that after a period of expectant management women should have the choice of how to proceed, and therefore recommended that a discussion of the options take place.

The evidence showed that outcomes such as duration of pain seemed comparable in the medical and surgical arms, although the tendency was that pain lasted longer and was more severe after medical management. Similarly, the duration of bleeding was very variable but was generally less in the surgical arm than the medical arm. From their clinical experience, the GDG members felt that women's experiences of pain and bleeding after miscarriage also tend to be extremely variable. The GDG noted that medical management of miscarriage seems to be more successful (in terms of avoiding surgical intervention) in women with incomplete or inevitable miscarriage when compared with those with a missed miscarriage. It also recognised that successful treatment was higher in studies that allowed longer follow-up before surgical intervention and where follow-up was clinical rather than ultrasound orientated. However, due to the differences between the studies, the GDG did not feel that the evidence was strong enough to make a recommendation that might supersede women's choice. Overall, it noted that medical management had both advantages (in terms of avoiding surgery) and disadvantages (in terms of the potential for increased pain and bleeding) and therefore the individual woman's preference and specific clinical situation should inform the choice of second-line management strategy.

Consideration of health benefits and resource uses

While both unplanned admissions and need for an unplanned intervention are higher after medical management of miscarriage compared to surgical treatment, the health economics analysis of first-line treatment options calculated that medical management was more cost-effective than surgical management due to the reduced cost of the initial treatment. However, the GDG felt that, having recommended expectant management (the most cost-effective option) as a first-line management strategy on the grounds of cost, or medical management if expectant management was unacceptable, it was appropriate that women then have a choice of all treatments if the first management strategy failed, particularly as the health economics was based on outcomes of first-line treatment. It noted that, for women in whom expectant management had not been successful, the success of medical management was likely to be reduced, and therefore the associated costs of unplanned interventions and admissions would be increased.

Quality of evidence

Much of the evidence for this review was of high or moderate quality. In particular, the GDG welcomed the inclusion of the MIST trial, a high quality randomised controlled trial conducted in the

UK, with an associated qualitative study investigating women's views of different modes of miscarriage management. Because it explored women's experiences so comprehensively, and it was conducted in the UK, the GDG believed that it was likely to represent the spectrum of different views that women might have regarding their preferred treatment options. However, as it was only one study involving a small group of women, the GDG felt that it was important to recommend that further research be done to evaluate whether different modes of management impact on patient experience and longer term psychological and emotional outcomes.

Information giving and emotional support

The GDG noted that an overarching theme from the qualitative data was the fact that women wanted more information about what to expect, what their course of treatment would entail (including potential complications) and what support would be provided (both immediately and longer term). It was noted that a lack of information often led to uncertainty which could heighten women's anxiety. Therefore, the group felt that it was important that women were informed about the possible course of events following their chosen management course, including what to expect in terms of the duration and severity of bleeding and where and when to get help in an emergency. In addition, it was the experience of some of the group that women are often uncertain about what to expect in the recovery period, and that they therefore need to be given more information about this, including details of how to access counselling and other support services.

Other considerations

Choice of treatment is important for women and satisfaction is higher where women have been offered and exercised their choice. The GDG felt it important to support women's choice following a period of expectant management where this had not been successful. It recognised the potential for increased psychological sequelae if women were denied a choice after 7–14 days of expectant management, during which time they may have been continuing to bleed and desiring a prompt completion of the process. The GDG recognised that for women with greater difficulty in accessing health care (for example women with English as a second language, drug users, travellers or those living in a remote area), surgical management might be preferable as a second-line strategy due to the reduced need for unplanned intervention and unplanned admission. However, as the GDG was recommending that all treatment options should be discussed with women if their first-line treatment is not successful, it did not feel it was necessary to make any specific recommendations for these groups of women.

Recommendations

Number	Recommendation
49	Use expectant management for 7–14 days as the first-line management strategy for women with a confirmed diagnosis of miscarriage. Explore management options other than expectant management if: • the woman is at increased risk of haemorrhage (for example, she is in the late first trimester) **or** • she has previous adverse and/or traumatic experience associated with pregnancy (for example, stillbirth, miscarriage or antepartum haemorrhage) **or** • she is at increased risk from the effects of haemorrhage (for example, if she has coagulopathies or is unable to have a blood transfusion) **or** • there is evidence of infection.
50	Offer medical management to women with a confirmed diagnosis of miscarriage if expectant management is not acceptable to the woman.
51	Explain what expectant management involves and that most women will need no further treatment. Also provide women with oral and written information about further treatment options.

52 Give all women undergoing expectant management of miscarriage oral and written information about what to expect throughout the process, advice on pain relief and where and when to get help in an emergency.*

53 If the resolution of bleeding and pain indicate that the miscarriage has completed during 7–14 days of expectant management, advise the woman to take a urine pregnancy test after 3 weeks, and to return for individualised care if it is positive.

54 Offer a repeat scan if after the period of expectant management the bleeding and pain:

- have not started (suggesting that the process of miscarriage has not begun) **or**
- are persisting and/or increasing (suggesting incomplete miscarriage).

Discuss all treatment options (continued expectant management, medical management, and surgical management) with the woman to allow her to make an informed choice.

55 Review the condition of a woman who opts for continued expectant management of miscarriage at a minimum of 14 days after the first follow-up appointment.

Number	Research recommendation
RR 6	In women with confirmed miscarriage, does the type of management strategy (expectant, medical and surgical) impact on women's experience, including psychological and emotional outcomes?

Why this is important

The management of miscarriage in the UK has changed in many ways over the past 2 decades, particularly in the shift from inpatient to outpatient or day case care and the introduction of medical and expectant management as alternatives to surgery.

Despite these changes there is a lack of research into the effects of these different approaches from the woman's perspective, in particular their psychological and emotional impact. Miscarriage is distressing for most women, and the type of management itself might affect women's need for counselling, with a resulting cost to the NHS. Because of this it is an important area for research.

The deficiency in the literature could be addressed by a comparative study of women having the different management strategies (expectant, medical or surgical) and in a variety of clinical settings (for example, early pregnancy assessment unit, gynaecological ward or gynaecological emergency unit). The data collected could be both quantitative (using validated psychological health questionnaires) and qualitative (focusing particularly on women's experience of the particular type and setting of care).

* See also recommendation 3 for details of further information that should be provided.

7.5 Misoprostol and mifepristone for managing miscarriage

Review question

What is the most appropriate dose of misoprostol and mifepristone to provide for managing miscarriage?

Introduction

Medical management of miscarriage has been offered to women suffering miscarriage for a number of years with varying doses, timing and routes of administration of drugs being used. The reviews carried out for the purposes of this guideline aimed to ascertain the most appropriate and efficacious dose. The GDG considered the data for two groups of women – those having a missed miscarriage and those having an incomplete miscarriage – as some of the clinicians on the GDG reported a difference in treatment outcomes for these groups of women.

Description of included studies

Twenty-one studies were included in this review (Ayudhaya et al., 2006; Bagratee et al., 2004; Blanchard et al., 2004; Blohm et al., 2005; Creinin et al., 1997; Kovavisarach & Jamnansiri, 2005; Kovavisarach & Sathapanachai, 2002; Kushwah & Singh, 2009; Lelaidier et al., 1993; Lister et al., 2005; Ngoc et al., 2004; Ngoc et al., 2005; Pang et al., 2001; Paritakul & Phupong, 2011; Rita et al., 2006; Shah et al., 2010; Stockheim et al., 2006; Tang et al., 2003; Tang et al., 2006; Tanha et al., 2010; Wood & Brain, 2002).

All of the included studies were randomised controlled trials and were conducted in the UK (Bagratee et al., 2004), USA (Creinin et al., 1997; Lister et al., 2005), Canada (Wood & Brain, 2002), France (Lelaidier et al., 1993), Sweden (Blohm et al., 2005), Israel (Stockheim et al., 2006), Hong Kong (Pang et al., 2001; Tang et al., 2003; Tang et al., 2006), Thailand (Ayudhaya et al., 2006; Kovavisarach & Jamnansiri, 2005; Kovavisarach & Sathapanachai, 2002; Paritakul & Phupong, 2011), Vietnam (Blanchard et al., 2004; Ngoc et al., 2004; Ngoc et al., 2005), India (Kushwah & Singh, 2009; Rita et al., 2006), Pakistan (Shah et al., 2010) and Iran (Tanha et al., 2010).

The GDG decided that, for this review question, studies should only be included if they treated women with incomplete miscarriages and women with missed miscarriages as separate populations. Four studies only included women with incomplete miscarriages (Blanchard et al., 2004; Ngoc et al., 2005; Pang et al., 2001; Paritakul & Phupong, 2011) and two studies included women with both incomplete miscarriages and missed miscarriage, but reported at least one outcome separately for the two populations (Bagratee et al., 2004; Blohm et al., 2005). The remainder of the studies only included women with missed miscarriage.

All of the included studies evaluated the use of misoprostol and/or mifepristone for the management of first trimester miscarriage. One study compared the efficacy of misoprostol alone with a combined regimen of mifepristone and misoprostol (Stockheim et al., 2006). Four studies compared different dosages of misoprostol using the same route of administration, of which one evaluated vaginal misoprostol (Kovavisarach & Jamnansiri, 2005), one evaluated sublingual misoprostol (Tang et al., 2006) and two evaluated oral misoprostol (Blanchard et al., 2004; Ngoc et al., 2005). Nine studies compared misoprostol administered via different routes, of which three compared oral and sublingual administration (Ayudhaya et al., 2006; Kushwah & Singh, 2009; Paritakul & Phupong, 2011), three compared sublingual and vaginal administration (Shah et al., 2010; Tang et al., 2003; Tanha et al., 2010), and four compared oral and vaginal administration (Creinin et al., 1997; Ngoc et al., 2004; Pang et al., 2001; Rita et al., 2006). Six trials were placebo controlled, of which five evaluated misoprostol (Bagratee et al., 2004; Blohm et al., 2005; Kovavisarach & Sathapanachai, 2002; Lister et al., 2005; Wood & Brain, 2002) and one evaluated mifepristone (Lelaidier et al., 1993).

Evidence profile

The treatment regimens described in the GRADE tables and evidence statements detail the maximum number of doses that women could receive; some women did not receive repeat doses if expulsion

had started. If multiple doses of misoprostol were given during the same visit, the interval between doses was between 3 and 6 hours, except in one trial whose participants also received supplemental doses after 12 hours (Kushwah & Singh, 2009). In four studies a repeat dose was given if expulsion had not occurred after 24 hours (Bagratee et al., 2004; Creinin et al., 1997; Lister et al., 2005; Wood & Brain, 2002) and in one further study the treatment regimen consisted of two doses administered 48 hours apart (Stockheim et al., 2006). For further details of study regimens please see evidence tables in Appendix H.

Table 7.6 GRADE summary of findings for comparison of vaginal misoprostol with placebo for the management of missed miscarriage

Number of studies	**Details of treatment regimen (dose in micrograms unless stated)**	**Number of women or average**		**Effect**		**Quality**
		Misoprostol (Ms)	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Success of medical treatment						
1 meta-analysis of 2 studies (Blohm et al., 2005; Kovavisarach & Sathapanachai, 2002)	400 vaginal Ms	69/91 (75.8%)	37/89 (41.6%)	RR 2.10 (0.97 to 4.53)	457 more per 1000 (from 12 fewer to 1000 more)	Very low
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24 h)	39/45 (86.7%)	11/38 (28.9%)	RR 2.99 (1.8 to 4.99)	576 more per 1000 (from 232 more to 1000 more)	High
1 meta-analysis of 2 studies (Lister et al., 2005; Wood & Brain, 2002)	800 vaginal Ms (repeat after 24 h)	35/44 (79.5%)	6/42 (14.3%)	RR 5.59 (2.62 to 11.93)	656 more per 1000 (from 237 more to 1000 more)	High
Need for further intervention						
1 study (Blohm et al., 2005)	400 vaginal Ms	8/57 (14%)	23/51 (45.1%)	RR 0.31 (0.15 to 0.63)	311 fewer per 1000 (from 167 fewer to 383 fewer)	High
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24 h)	6/45 (13.3%)	27/38 (71.1%)	RR 0.19 (0.09 to 0.41)	576 fewer per 1000 (from 419 fewer to 647 fewer)	High

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Misoprostol (Ms)	Placebo	Relative (95% CI)	Absolute (95% CI)	
1 meta-analysis of 2 studies (Lister et al., 2005; Wood & Brain, 2002)	800 vaginal Ms (repeat after 24 h)	10/43 (23.3%)	34/41 (82.9%)	RR 0.28 (0.16 to 0.49)	597 fewer per 1000 (from 423 fewer to 697 fewer)	High
Unplanned visits to a medical facility						
1 study (Lister et al., 2005)	800 vaginal Ms (repeat after 24 h)	0/18 (0%)	3/16 (18.8%)	RR 0.13 (0.01 to 2.3)	163 fewer per 1000 (from 186 fewer to 244 more)	Moderate
Adverse effects: incidence of nausea and/or vomiting						
1 study (Kovavisarach & Sathapanachai, 2002)	400 vaginal Ms	2/27 (7.4%)	1/27 (3.7%)	RR 2 (0.19 to 20.77)	37 more per 1000 (from 30 fewer to 732 more)	Very low
Adverse effects: incidence of nausea						
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24 h)	18/52 (34.6%)	16/52 (30.8%)	RR 1.12 (0.65 to 1.96)	37 more per 1000 (from 108 fewer to 295 more)	Low
1 study (Lister et al., 2005)	800 vaginal Ms (repeat after 24 h)	4/18 (22.2%)	3/16 (18.8%)	RR 1.19 (0.31 to 4.51)	36 more per 1000 (from 129 fewer to 658 more)	Moderate
Adverse effects: severity of nausea						
1 study (Blohm et al., 2005)	400 vaginal Ms	Mean 17.4 (SD 24.7) n = 64	Mean 14.9 (SD 23.8) n = 62	not calculable (NC)	MD 2.5 higher (5.97 lower to 10.97 higher) *P* = 0.57	Low

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Misoprostol (Ms)	Placebo	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of vomiting						
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24 h)	8/52 (15.4%)	7/52 (13.5%)	RR 1.14 (0.45 to 2.92)	19 more per 1000 (from 74 fewer to 258 more)	Low
1 study (Lister et al., 2005)	800 vaginal Ms (repeat after 24 h)	1/18 (5.6%)	3/16 (18.8%)	RR 0.3 (0.03 to 2.57)	131 fewer per 1000 (from 182 fewer to 294 more)	Moderate
Adverse effects: severity of vomiting						
1 study (Blohm et al., 2005)	400 vaginal Ms	Mean 8.1 (SD 20.2) n = 64	Mean 7.3 (SD 21.7) n = 62	NC	MD 0.8 higher (6.53 lower to 8.13 higher) *P* = 0.85	Low
Adverse effects: incidence of diarrhoea						
1 study (Kovavisarach & Sathapanachai, 2002)	400 vaginal Ms	2/27 (7.4%)	0/27 (0%)	RR 5 (0.25 to 99.51)	NC	Very low
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24 h)	11/52 (21.2%)	11/52 (21.2%)	RR 1 (0.48 to 2.1)	0 fewer per 1000 (from 110 fewer to 233 more)	Low
1 study (Lister et al., 2005)	800 vaginal Ms (repeat after 24 h)	1/18 (5.6%)	1/16 (6.3%)	RR 0.89 (0.06 to 13.08)	7 fewer per 1000 (from 59 fewer to 755 more)	Moderate
Adverse effects: severity of diarrhoea (maximum potential score not reported)						
1 study (Blohm et al., 2005)	400 vaginal misoprostol	Mean 7.5 (SD 15.0) n = 64	Mean 8.9 (SD 20.4) n = 62	NC	MD 1.4 lower (7.67 lower to 4.87 higher) *P* = 0.69	Low

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Misoprostol (Ms)	Placebo	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of any gastrointestinal side effects						
1 study (Wood & Brain, 2002)	800 vaginal misoprostol (repeat after 24 h)	1/25 (4%)	not reported (NR)	NC	NC	Low
Adverse effects: incidence of fever						
1 study (Kovavisarach & Sathapanachai, 2002)	400 vaginal Ms	4/27 (14.8%)	0/27 (0%)	RR 9 (0.51 to 159.43)	NC	Very low
Adverse effects: incidence of infection						
1 study (Blohm et al., 2005)	400 vaginal Ms	3/64 (4.7%)	0/62 (0%)	RR 6.78 (0.36 to 128.7)	NC	Low
Adverse effects: incidence of pelvic inflammatory disease						
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24 h)	1/52 (1.9%)	0/52 (0%)	RR 3 (0.13 to 71.99)	NC	Low
Duration of bleeding (days)						
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24 h)	Mean 11.65 (SD 4.4) n = 52	Mean 10.88 (SD 4.78) n = 52	NC	MD 0.77 higher (1 lower to 2.54 higher)	Moderate
Pain: incidence of menstrual cramping						
1 study (Lister et al., 2005)	800 vaginal Ms (repeat after 24 h)	11/18 (61.1%)	5/16 (31.3%)	RR 1.96 (0.87 to 4.42)	300 more per 1000 (from 41 fewer to 1000 more)	Moderate
Pain: incidence of lower abdominal pain						
1 study (Kovavisarach & Sathapanachai, 2002)	400 vaginal Ms	20/27 (74.1%)	6/27 (22.2%)	RR 3.33 (1.59 to 6.99)	518 more per 1000 (from 131 more to 1000 more)	Low

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Misoprostol (Ms)	Placebo	Relative (95% CI)	Absolute (95% CI)	
Pain: severity						
1 study (Blohm et al., 2005)	400 vaginal Ms	Mean 60.4 (SD 31.0) n = 64	Mean 43.8 (SD 37.1) n = 62	NC	MD 16.6 higher (4.64 to 28.56 higher) *P* < 0.007	Low
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24 h)	Mean 6.0 (SD 2.7) n = 52	Mean 5.4 (SD 2.7) n = 52	NC	MD 0.6 higher (0.44 lower to 1.64 higher)	Moderate
1 study (Lister et al., 2005)	800 vaginal Ms (repeat after 24 h)	Mean 5.6 (SD NR) n = 16	Mean 5.2 (SD NR) n = 16	NC	MD 0.4 higher (confidence intervals NC) *P* = 0.806	Moderate
Satisfaction: reported incidence						
1 study (Lister et al., 2005)	800 vaginal Ms (repeat after 24 h)	14/15 (93.3%)	12/15 (80%)	RR 1.17 (0.88 to 1.55)	136 more per 1000 (from 96 fewer to 440 more)	Moderate
Satisfaction: score/10						
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24 h)	Mean 8.9 (SD 1.3) n = 52	Mean 8.7 (SD 1.5) n = 52	NC	MD 0.2 higher (0.34 lower to 0.74 higher)	Moderate

CI confidence interval, MD mean difference, Ms misoprostol, NC not calculable, NR not reported, *P* probability, RR relative risk, SD standard deviation

Table 7.7 GRADE summary of findings for comparison of mifepristone with placebo for the management of missed miscarriage

Number of studies	Details of treatment regimen	Number of women or average		Effect		Quality
		Mifepristone (Mf)	Placebo	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 study (Lelaidier et al., 1993)	600 mg oral Mf	19/23 (82.6%)	2/23 (8.7%)	RR 9.5 (2.49 to 36.19)	739 more per 1000 (from 130 more to 1000 more)	Low
Need for further intervention						
1 study (Lelaidier et al., 1993)	600 mg oral Mf	6/23 (26.1%)	19/21 (90.5%)	RR 0.29 (0.14 to 0.58)	642 fewer per 1000 (from 380 fewer to 778 fewer)	Low
Adverse effects: incidence of endometritis						
1 study (Lelaidier et al., 1993)	600 mg oral Mf	1/23 (4.3%)	1/21 (4.8%)	RR 0.91 (0.06 to 13.69)	4 fewer per 1000 (from 45 fewer to 604 more)	Low
Pain: incidence						
1 study (Lelaidier et al., 1993)	600 mg oral Mf	12/23 (52.2%)	5/21 (23.8%)	RR 2.19 (0.93 to 5.17)	283 more per 1000 (from 17 fewer to 993 more)	Low

CI confidence interval, Mf mifepristone, *P* probability, RR relative risk

Table 7.8 GRADE summary of findings for comparison of mifepristone plus misoprostol with misoprostol only for the management of missed miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Mifepristone (Mf) + misoprostol (Ms)	Ms only	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 study (Stockheim et al., 2006)	Mf + Ms: 600 mg oral Mf, followed 48 hours later by 400 oral Ms x 2 Ms only: 400 oral Ms x 2, with a repeat 48 hours later	38/58 (65.5%)	42/57 (73.7%)	RR 0.89 (0.7 to 1.13)	81 fewer per 1000 (from 221 fewer to 96 more)	Moderate
Need for further intervention						
1 study (Stockheim et al., 2006)	Mf + Ms: 600 mg oral Mf, followed 48 hours later by 400 oral Ms x 2 Ms only: 400 oral Ms x 2, with the same 48 hours later	20/58 (34.5%)	15/57 (26.3%)	RR 1.31 (0.75 to 2.3)	82 more per 1000 (from 66 fewer to 342 more)	Moderate

CI confidence interval, Mf mifepristone, Ms misoprostol, RR relative risk

Table 7.9 GRADE summary of findings for comparison of vaginal misoprostol in different dosages for the management of missed miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		600 micrograms vaginal	800 micrograms vaginal	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 study (Kovavisarach & Jamnansiri, 2005)	Vaginal misoprostol (Ms) 600 vs. 800	26/57 (45.6%)	39/57 (68.4%)	RR 0.67 (0.48 to 0.93)	226 fewer per 1000 (from 48 fewer to 356 fewer)	High

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		600 micrograms vaginal	800 micrograms vaginal	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of nausea						
1 study (Kovavisarach & Jamnansiri, 2005)	Vaginal Ms 600 vs. 800	2/57 (3.5%)	7/57 (12.3%)	RR 0.29 (0.06 to 1.32)	87 fewer per 1000 (from 115 fewer to 39 more)	Moderate
Adverse effects: incidence of vomiting						
1 study (Kovavisarach & Jamnansiri, 2005)	Vaginal Ms 600 vs. 800	0/57 (0%)	0/57 (0%)	not calculable (NC)	NC	Moderate
Adverse effects: incidence of diarrhoea						
1 study (Kovavisarach & Jamnansiri, 2005)	Vaginal Ms 600 vs. 800	0/57 (0%)	2/57 (3.5%)	RR 0.2 (0.01 to 4.08)	28 fewer per 1000 (from 35 fewer to 108 more)	Moderate
Adverse effects: incidence of fever						
1 study (Kovavisarach & Jamnansiri, 2005)	Vaginal Ms 600 vs. 800	10/57 (17.5%)	16/57 (28.1%)	RR 0.62 (0.31 to 1.26)	107 fewer per 1000 (from 194 fewer to 73 more)	Moderate
Pain: incidence						
1 study (Kovavisarach & Jamnansiri, 2005)	Vaginal Ms 600 vs. 800	30/57 (52.6%)	42/57 (73.7%)	RR 0.71 (0.53 to 0.96)	214 fewer per 1000 (from 29 fewer to 346 fewer)	High

CI confidence interval, Ms misoprostol, NC not calculable, RR relative risk

Table 7.10 GRADE summary of findings for comparison of sublingual misoprostol in different dosages for the management of missed miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		600 micrograms sublingual	600 micrograms + extended course sublingual	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 study (Tang et al., 2006)	Sublingual misoprostol (Ms) 600 x 3 vs. 600 x 3 + 400 daily for 7 days	83/90 (92.2%)	84/90 (93.3%)	RR 0.99 (0.91 to 1.07)	9 fewer per 1000 (from 84 fewer to 65 more)	Moderate
Adverse effects: incidence of nausea on day 1						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	38/90 (42.2%)	45/90 (50%)	RR 0.84 (0.61 to 1.16)	80 fewer per 1000 (from 195 fewer to 80 more)	Low
Adverse effects: incidence of nausea on days 2–9						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	13/86 (15.1%)	18/86 (20.9%)	RR 0.72 (0.38 to 1.38)	59 fewer per 1000 (from 130 fewer to 80 more)	Low
Adverse effects: incidence of vomiting on day 1						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	13/90 (14.4%)	14/90 (15.6%)	RR 0.93 (0.46 to 1.86)	11 fewer per 1000 (from 84 fewer to 134 more)	Low
Adverse effects: incidence of vomiting on days 2–9						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	1/86 (1.2%)	5/86 (5.8%)	RR 0.2 (0.02 to 1.68)	47 fewer per 1000 (from 57 fewer to 40 more)	Low
Adverse effects: incidence of diarrhoea on day 1						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	61/90 (67.8%)	63/90 (70%)	RR 0.97 (0.8 to 1.18)	21 fewer per 1000 (from 140 fewer to 126 more)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		600 micrograms sublingual	600 micrograms + extended course sublingual	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of diarrhoea on days 2–9						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	19/86 (22.1%)	38/86 (44.2%)	RR 0.5 (0.31 to 0.79)	221 fewer per 1000 (from 93 fewer to 305 fewer)	Moderate
Adverse effects: incidence of fever on day 1						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	52/90 (57.8%)	55/90 (61.1%)	RR 0.95 (0.74 to 1.2)	31 fewer per 1000 (from 159 fewer to 122 more)	Low
Adverse effects: incidence of fever on days 2-9						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	0/86 (0%)	0/86 (0%)	not calculable (NC)	NC	Low
Adverse effects: incidence of chills and rigor on day 1						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	10/90 (11.1%)	13/90 (14.4%)	RR 0.77 (0.36 to 1.66)	33 fewer per 1000 (from 92 fewer to 95 more)	Low
Adverse effects: incidence of chills and rigor on days 2–9						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	0/86 (0%)	0/86 (0%)	NC	NC	Low
Duration of bleeding (days)						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	Median 11.5 (Range 5 - 35)	Median 11.0 (Range 6 - 42)	NC	Median 0.5 higher (confidence interval NC) NS (*P*-value not reported)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		600 micrograms sublingual	600 micrograms + extended course sublingual	Relative (95% CI)	Absolute (95% CI)	
Pain: incidence on day 1						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	88/90 (97.8%)	88/90 (97.8%)	RR 1 (0.96 to 1.05)	0 fewer per 1000 (from 39 fewer to 49 more)	Moderate
Pain: incidence on days 2–9						
1 study (Tang et al., 2006)	Sublingual Ms 600 x 3 vs. 600 x 3 + 400 daily for 7 days	66/86 (76.7%)	74/86 (86%)	RR 0.89 (0.77 to 1.03)	95 fewer per 1000 (from 198 fewer to 26 more)	Moderate

CI confidence interval, Ms misoprostol, NC not calculable, NS not significant, *P* probability, RR relative risk, SD standard deviation

Table 7.11 GRADE summary of findings for comparison of oral misoprostol with sublingual misoprostol for the management of missed miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Sublingual	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 study (Ayudhaya et al., 2006)	Oral: 400 misoprostol (Ms) x 6 Sublingual: 400 Ms x 6	17/66 (25.8%)	15/70 (21.4%)	RR 1.2 (0.65 to 2.21)	43 more per 1000 (from 75 fewer to 259 more)	Low
1 study (Kushwah & Singh, 2009)	200mg oral mifepristone (Mf), plus: Oral: 600 Ms Sublingual: 600 Ms (+ 400 Ms x 3 after 12 hours if needed)	42/50 (84%)	46/50 (92%)	RR 0.91 (0.79 to 1.06)	83 fewer per 1000 (from 193 fewer to 55 more)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Sublingual	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of nausea or vomiting						
1 study (Ayudhaya et al., 2006)	Oral: 400 Ms x 6 Sublingual: 400 Ms x 6	3/66 (4.5%)	2/70 (2.9%)	RR 1.59 (0.27 to 9.22)	17 more per 1000 (from 21 fewer to 235 more)	Moderate
Adverse effects: incidence of nausea						
1 study (Kushwah & Singh, 2009)	200mg oral Mf, plus: Oral: 600 Ms Sublingual: 600 Ms (+ 400 Ms x 3 after 12 hours if needed)	26/50 (52%)	17/50 (34%)	RR 1.53 (0.96 to 2.44)	180 more per 1000 (from 14 fewer to 490 more)	Low
Adverse effects: incidence of vomiting						
1 study (Kushwah & Singh, 2009)	200mg oral Mf, plus: Oral: 600 Ms Sublingual: 600 Ms (+ 400 Ms x 3 after 12 hours if needed)	22/50 (44%)	11/50 (22%)	RR 2 (1.09 to 3.68)	220 more per 1000 (from 20 more to 590 more)	Moderate
Adverse effects: incidence of diarrhoea						
1 study (Ayudhaya et al., 2006)	Oral: 400 Ms x 6 Sublingual: 400 Ms x 6	7/66 (10.6%)	6/70 (8.6%)	RR 1.24 (0.44 to 3.49)	21 more per 1000 (from 48 fewer to 213 more)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Sublingual	Relative (95% CI)	Absolute (95% CI)	
1 study (Kushwah & Singh, 2009)	200mg oral Mf, plus: Oral: 600 Ms Sublingual: 600 Ms (+ 400 Ms x 3 after 12 hours if needed)	28/50 (56%)	24/50 (48%)	RR 1.17 (0.8 to 1.7)	82 more per 1000 (from 96 fewer to 336 more)	Low
Adverse effects: incidence of fever						
1 study (Ayudhaya et al., 2006)	Oral: 400 Ms x 6 Sublingual: 400 Ms x 6	2/66 (3%)	15/70 (21.4%)	RR 0.14 (0.03 to 0.59)	184 fewer per 1000 (from 88 fewer to 208 fewer)	High
1 study (Kushwah & Singh, 2009)	200mg oral Mf, plus: Oral: 600 Ms Sublingual: 600 Ms (+ 400 Ms x 3 after 12 hours if needed)	26/50 (52%)	10/50 (20%)	RR 2.6 (1.41 to 4.81)	320 more per 1000 (from 82 more to 762 more)	Moderate
Adverse effects: incidence of chills						
1 study (Ayudhaya et al., 2006)	Oral: 400 Ms x 6 Sublingual: 400 Ms x 6	0/66 (0%)	4/70 (5.7%)	RR 0.12 (0.01 to 2.15)	50 fewer per 1000 (from 57 fewer to 66 more)	Moderate
Pain: incidence						
1 study (Ayudhaya et al., 2006)	Oral: 400 Ms x 6 Sublingual: 400 Ms x 6	40/66 (60.6%)	47/70 (67.1%)	RR 0.9 (0.7 to 1.16)	67 fewer per 1000 (from 201 fewer to 107 more)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Sublingual	Relative (95% CI)	Absolute (95% CI)	
1 study (Kushwah & Singh, 2009)	200mg oral Mf, plus: Oral: 600 Ms Sublingual: 600 Ms (+ 400 Ms x 3 after 12 hours if needed)	44/50 (88%)	23/50 (46%)	RR 1.91 (1.39 to 2.63)	419 more per 1000 (from 179 more to 750 more)	Moderate
Satisfaction: reported incidence						
1 study (Kushwah & Singh, 2009)	200mg oral Mf, plus: Oral: 600 Ms Sublingual: 600 Ms (+ 400 Ms x 3 after 12 hours if needed)	36/50 (72%)	46/50 (92%)	RR 0.78 (0.65 to 0.95)	202 fewer per 1000 (from 46 fewer to 322 fewer)	Moderate

CI confidence interval, Mf mifepristone, Ms misoprostol, RR relative risk

Table 7.12 GRADE summary of findings for comparison of sublingual misoprostol with vaginal misoprostol for the management of missed miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Sublingual	Vaginal	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 meta-analysis of 2 studies (Shah et al., 2010; Tanha et al., 2010)	Sublingual: 400 x 5/not reported (NR) Vaginal: 400 x 5/NR	104/132 (78.8%)	61/129 (47.3%)	RR 1.4 (0.75 to 2.62)	189 more per 1000 (from 118 fewer to 766 more)	Very low

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Sublingual	Vaginal	Relative (95% CI)	Absolute (95% CI)	
1 study (Tang et al., 2003)	Sublingual: 600 Ms x 3 Vaginal: 600 Ms x 3	35/40 (87.5%)	35/40 (87.5%)	RR 1 (0.85 to 1.18)	0 fewer per 1000 (from 131 fewer to 157 more)	Moderate
Need for further intervention						
1 meta-analysis of 2 studies (Shah et al., 2010; Tanha et al., 2010)	Sublingual: 400 x 5/NR Vaginal: 400 x 5/NR	28/135 (20.7%)	72/135 (53.3%)	RR 0.49 (0.16 to 1.44)	272 fewer per 1000 (from 448 fewer to 235 more)	Very low
1 study (Tang et al., 2003)	Sublingual: 600 Ms x 3 Vaginal: 600 Ms x 3	4/39 (10.3%)	4/39 (10.3%)	RR 1 (0.27 to 3.72)	0 fewer per 1000 (from 75 fewer to 279 more)	Low
Adverse effects: incidence of nausea						
1 study (Shah et al., 2010)	Sublingual: 400 Ms x 5 Vaginal: 400 Ms x 5	5/25 (20%)	1/25 (4%)	RR 5 (0.63 to 39.79)	160 more per 1000 (from 15 fewer to 1552 more)	Low
1 study (Tang et al., 2003)	Sublingual: 600 Ms x 3 Vaginal: 600 Ms x 3	24/40 (60%)	20/40 (50%)	RR 1.2 (0.8 to 1.79)	100 more per 1000 (from 100 fewer to 395 more)	Moderate
Adverse effects: incidence of vomiting						
1 study (Tanha et al., 2010)	Sublingual: 400 Ms x NR Vaginal: 400 Ms x NR	22/110 (20%)	13/110 (11.8%)	RR 1.69 (0.9 to 3.19)	82 more per 1000 (from 12 fewer to 259 more)	Low
1 study (Tang et al., 2003)	Sublingual: 600 Ms x 3 Vaginal: 600 Ms x 3	7/40 (17.5%)	9/40 (22.5%)	RR 0.78 (0.32 to 1.88)	50 fewer per 1000 (from 153 fewer to 198 more)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Sublingual	Vaginal	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of diarrhoea						
1 study (Tanha et al., 2010)	Sublingual: 400 Ms x NR Vaginal: 400 Ms x NR	76/110 (69.1%)	40/110 (36.4%)	RR 1.9 (1.44 to 2.51)	327 more per 1000 (from 160 more to 549 more)	Moderate
1 study (Tang et al., 2003)	Sublingual: 600 Ms x 3 Vaginal: 600 Ms x 3	28/40 (70%)	11/40 (27.5%)	RR 2.55 (1.48 to 4.38)	426 more per 1000 (from 132 more to 930 more)	High
Adverse effects: incidence of fever						
1 study (Tanha et al., 2010)	Sublingual: 400 Ms x NR Vaginal: 400 Ms x NR	26/110 (23.6%)	4/110 (3.6%)	RR 6.5 (2.35 to 18.01)	200 more per 1000 (from 49 more to 619 more)	Moderate
1 study (Tang et al., 2003)	Sublingual: 600 Ms x 3 Vaginal: 600 Ms x 3	23/40 (57.5%)	19/40 (47.5%)	RR 1.21 (0.79 to 1.84)	100 more per 1000 (from 100 fewer to 399 more)	Moderate
Adverse effects: incidence of chills or shivering						
1 study (Shah et al., 2010)	Sublingual: 400 Ms x 5 Vaginal: 400 Ms x 5	6/25 (24%)	4/25 (16%)	RR 1.5 (0.48 to 4.68)	80 more per 1000 (from 83 fewer to 589 more)	Low
1 study (Tang et al., 2003)	Sublingual: 600 Ms x 3 Vaginal: 600 Ms x 3	6/40 (15%)	3/40 (7.5%)	RR 2 (0.54 to 7.45)	75 more per 1000 (from 34 fewer to 484 more)	Moderate
Duration of bleeding (days)						
1 study (Tang et al., 2003)	Sublingual: 600 Ms x 3 Vaginal: 600 Ms x 3	Median 12.5 (Range 4 – 36) n = 40	Median 12.0 (Range 5 – 79) n = 40	not calculable (NC)	Median 0.5 higher (confidence interval NC) NS (*P*-value NR)	High

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Sublingual	Vaginal	Relative (95% CI)	Absolute (95% CI)	
Pain: incidence of cramps						
1 study (Tanha et al., 2010)	Sublingual: 400 Ms x NR Vaginal: 400 Ms x NR	94/110 (85.5%)	62/110 (56.4%)	RR 1.52 (1.26 to 1.82)	293 more per 1000 (from 147 more to 462 more)	Moderate
Pain: incidence of severe pain						
1 study (Tanha et al., 2010)	Sublingual: 400 Ms x NR Vaginal: 400 Ms x NR	77/110 (70%)	42/110 (38.2%)	RR 1.83 (1.4 to 2.4)	317 more per 1000 (from 153 more to 535 more)	Moderate
Pain: incidence of lower abdominal pain						
1 study (Tang et al., 2003)	Sublingual: 600 Ms x 3 Vaginal: 600 Ms x 3	40/40 (100%)	40/40 (100%)	NC	NC	High
Satisfaction: reported incidence						
1 meta-analysis of 2 studies (Shah et al., 2010; Tanha et al., 2010)	Sublingual: 400 x 5/NR Vaginal: 400 x 5/NR	116/135 (85.9%)	71/135 (52.6%)	RR 1.48 (0.94 to 2.32)	252 more per 1000 (from 32 fewer to 694 more)	Very low

CI confidence interval, Ms misoprostol, NC not calculable, NR not reported, NS not significant, *P* probability, RR relative risk

Table 7.13 GRADE summary of findings for comparison of oral misoprostol with vaginal misoprostol for the management of missed miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Vaginal	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 study (Rita et al., 2006)	Oral: 400 misoprostol (Ms) x 3 Vaginal: 600 Ms x 2	18/50 (36%)	40/50 (80%)	RR 0.45 (0.3 to 0.67)	440 fewer per 1000 (from 264 fewer to 560 fewer)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Vaginal	Relative (95% CI)	Absolute (95% CI)	
1 study (Creinin et al., 1997)	Oral: 400 Ms Vaginal: 800 Ms (repeat after 24 h)	3/12 (25%)	7/8 (87.5%)	RR 0.29 (0.1 to 0.79)	621 fewer per 1000 (from 184 fewer to 788 fewer)	Very low
1 study (Ngoc et al., 2004)	Oral: 800 Ms Vaginal: 800 Ms	89/101 (88.1%)	91/99 (91.9%)	RR 0.96 (0.87 to 1.05)	37 fewer per 1000 (from 119 fewer to 46 more)	Moderate
Need for further intervention						
1 study (Rita et al., 2006)	Oral: 400 Ms x 3 Vaginal: 600 Ms x 2	32/50 (64%)	10/50 (20%)	RR 3.2 (1.77 to 5.78)	440 more per 1000 (from 154 more to 956 more)	Moderate
1 study (Ngoc et al., 2004)	Oral: 800 Ms Vaginal: 800 Ms	11/100 (11%)	7/98 (7.1%)	RR 1.54 (0.62 to 3.81)	39 more per 1000 (from 27 fewer to 201 more)	Low
Admission to a medical facility						
1 study (Ngoc et al., 2004)	Oral: 800 Ms Vaginal: 800 Ms	0/100 (0%)	2/98 (2%)	RR 0.2 (0.01 to 4.03)	16 fewer per 1000 (from 20 fewer to 62 more)	Very low
Adverse effects: incidence of nausea						
1 study (Rita et al., 2006)	Oral: 400 Ms x 3 Vaginal: 600 Ms x 2	25/50 (50%)	20/50 (40%)	RR 1.25 (0.81 to 1.94)	100 more per 1000 (from 76 fewer to 376 more)	Low
1 study (Creinin et al., 1997)	Oral: 400 Ms Vaginal: 800 Ms (repeat after 24 h)	6/12 (50%)	5/8 (62.5%)	RR 0.8 (0.37 to 1.74)	125 fewer per 1000 (from 394 fewer to 463 more)	Very low

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Vaginal	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of vomiting						
1 study (Rita et al., 2006)	Oral: 400 Ms x 3 Vaginal: 600 Ms x 2	6/50 (12%)	3/50 (6%)	RR 2 (0.53 to 7.56)	60 more per 1000 (from 28 fewer to 394 more)	Low
1 study (Creinin et al., 1997)	Oral: 400 Ms Vaginal: 800 Ms (repeat after 24 h)	3/12 (25%)	1/8 (12.5%)	RR 2 (0.25 to 15.99)	125 more per 1000 (from 94 fewer to 1874 more)	Very low
1 study (Ngoc et al., 2004)	Oral: 800 Ms Vaginal: 800 Ms	4/95 (4.2%)	14/95 (14.7%)	RR 0.29 (0.1 to 0.84)	105 fewer per 1000 (from 24 fewer to 133 fewer)	High
Adverse effects: incidence of diarrhoea						
1 study (Rita et al., 2006)	Oral: 400 Ms x 3 Vaginal: 600 Ms x 2	5/50 (10%)	5/50 (10%)	RR 1 (0.31 to 3.24)	0 fewer per 1000 (from 69 fewer to 224 more)	Low
1 study (Creinin et al., 1997)	Oral: 400 Ms Vaginal: 800 Ms (repeat after 24 h)	5/12 (41.7%)	3/8 (37.5%)	RR 1.11 (0.36 to 3.4)	41 more per 1000 (from 240 fewer to 900 more)	Very low
1 study (Ngoc et al., 2004)	Oral: 800 Ms Vaginal: 800 Ms	24/95 (25.3%)	23/95 (24.2%)	RR 1.04 (0.64 to 1.71)	10 more per 1000 (from 87 fewer to 172 more)	Moderate
Adverse effects: incidence of hyperpyrexia						
1 study (Rita et al., 2006)	Oral: 400 Ms x 3 Vaginal: 600 Ms x 2	2/50 (4%)	2/50 (4%)	RR 1 (0.15 to 6.82)	0 fewer per 1000 (from 34 fewer to 233 more)	Low

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Vaginal	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of fever or chills						
1 study (Ngoc et al., 2004)	Oral: 800 Ms Vaginal: 800 Ms	7/95 (7.4%)	7/95 (7.4%)	RR 1 (0.36 to 2.74)	0 fewer per 1000 (from 47 fewer to 128 more)	Moderate
Duration of bleeding (days)						
1 study (Creinin et al., 1997)	Oral: 400 Ms Vaginal: 800 Ms (repeat after 24 h)	not reported (NR)	Mean 10.0 (SD 2.8) n = 7	not calculable (NC)	NC	Very low
1 study (Ngoc et al., 2004)	Oral: 800 Ms Vaginal: 800 Ms	Mean 2.87 (SD NR) n = 95	Mean 2.69 (SD NR) n = 95	NC	MD 0.18 higher (confidence interval NC) NS (*P*-value not reported)	Moderate
Pain: incidence						
1 study (Rita et al., 2006)	Oral: 400 Ms x 3 Vaginal: 600 Ms x 2	8/50 (16%)	5/50 (10%)	RR 1.6 (0.56 to 4.56)	60 more per 1000 (from 44 fewer to 356 more)	Low
1 study (Ngoc et al., 2004)	Oral: 800 Ms Vaginal: 800 Ms	84/95 (88.4%)	85/95 (89.5%)	RR 0.99 (0.89 to 1.09)	9 fewer per 1000 (from 98 fewer to 81 more)	High
Pain: severity/10						
1 study (Creinin et al., 1997)	Oral: 400 Ms Vaginal: 800 Ms (repeat after 24 h)	Mean 4.0 (SD 3.6) n = 11	Mean 5.9 (SD 2.7) n = 7	NC	MD 1.9 lower (4.82 lower to 1.02 higher) *P* = 0.33	Very low

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Vaginal	Relative (95% CI)	Absolute (95% CI)	
Satisfaction: reported incidence						
1 study (Ngoc et al., 2004)	Oral: 800 Ms Vaginal: 800 Ms	86/100 (86%)	88/98 (89.8%)	RR 0.96 (0.86 to 1.06)	36 fewer per 1000 (from 126 fewer to 54 more)	High

CI confidence interval, MD mean difference, Ms misoprostol, NC not calculable, NS not significant, *P* probability, RR relative risk, SD standard deviation

Table 7.14 GRADE summary of findings for comparison of vaginal misoprostol with placebo for the management of incomplete miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Misoprostol	Placebo	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 study (Bagratee et al., 2004)	600 vaginal misoprostol (Ms) (repeat after 24h)	7/7 (100%)	12/14 (85.7%)	RR 1.12 (0.84 to 1.5)	103 more per 1000 (from 137 fewer to 429 more)	Low
Need for further intervention						
1 study (Blohm et al., 2005)	400 vaginal Ms	0/7 (0%)	2/11 (18.2%)	RR 0.3 (0.02 to 5.46)	127 fewer per 1000 (from 178 fewer to 811 more)	Low
1 study (Bagratee et al., 2004)	600 vaginal Ms (repeat after 24h)	0/7 (0%)	2/14 (14.3%)	RR 0.38 (0.02 to 6.9)	89 fewer per 1000 (from 140 fewer to 843 more)	Low

CI confidence interval, Ms misoprostol, RR relative risk

Table 7.15 GRADE summary of findings for comparison of oral misoprostol in different dosages for the management of incomplete miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		600 micrograms oral	2 x 600 micrograms oral	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 meta-analysis of 2 studies (Blanchard et al., 2004; Ngoc et al., 2005)	Oral misoprostol (Ms) 600 vs. 2 x 600	199/236 (84.3%)	195/233 (83.7%)	RR 1.01 (0.94 to 1.09)	8 more per 1000 (from 50 fewer to 75 more)	Moderate
Need for further intervention						
1 meta-analysis of 2 studies (Blanchard et al., 2004; Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	35/234 (15%)	32/227 (14.1%)	RR 1.05 (0.69 to 1.59)	7 more per 1000 (from 44 fewer to 83 more)	Low
Adverse effects: incidence of nausea						
1 meta-analysis of 2 studies (Blanchard et al., 2004; Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	48/235 (20.4%)	37/228 (16.2%)	RR 1.19 (0.57 to 2.46)	31 more per 1000 (from 70 fewer to 237 more)	Very low
Adverse effects: incidence of vomiting						
1 meta-analysis of 2 studies (Blanchard et al., 2004; Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	25/235 (10.6%)	24/228 (10.5%)	RR 1.01 (0.6 to 1.72)	1 more per 1000 (from 42 fewer to 76 more)	Low
Adverse effects: incidence of diarrhoea						
1 study (Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	51/149 (34.2%)	68/145 (46.9%)	RR 0.73 (0.55 to 0.97)	127 fewer per 1000 (from 14 fewer to 211 fewer)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		600 micrograms oral	2 x 600 micrograms oral	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of fever or chills						
1 meta-analysis of 2 studies (Blanchard et al., 2004; Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	27/235 (11.5%)	22/228 (9.6%)	RR 1.19 (0.7 to 2.02)	18 more per 1000 (from 29 fewer to 98 more)	Low
Duration of heavy bleeding (days)						
1 study (Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	Mean 0.8 (SD 0.8) n = 149	Mean 0.8 (SD 0.7) n = 145	not calculable (NC)	MD 0 higher (0.17 lower to 0.17 higher) NS (*P*-value NR)	Moderate
1 study (Blanchard et al., 2004)	Oral Ms 600 vs. 2 x 600	Mean 1.31 (SD not reported (NR)) n = 86	Mean 1.63 (SD NR) n = 83	NC	MD 0.32 lower (confidence interval NC) *P* = 0.21	Low
Duration of normal bleeding (days)						
1 study (Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	Mean 1.2 (SD 0.9) n = 149	Mean 1.2 (SD 1.2) n = 145	NC	MD 0 higher (0.24 lower to 0.24 higher) NS (*P* -value NR)	Moderate
1 study (Blanchard et al., 2004)	Oral Ms 600 vs. 2 x 600	Mean 2.86 (SD NR) n = 86	Mean 2.76 (SD NR) n = 83	NC	MD 0.1 higher (confidence interval NC) *P* = 0.79	Low
Duration of light bleeding or spotting (days)						
1 study (Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	Mean 2.1 (SD 2.1) n = 149	Mean 1.8 (SD 2.1) n = 145	NC	MD 0.3 higher (0.18 lower to 0.78 higher) NS (*P* -value NR)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		600 micrograms oral	2 x 600 micrograms oral	Relative (95% CI)	Absolute (95% CI)	
1 study (Blanchard et al., 2004)	Oral Ms 600 vs. 2 x 600	Mean 2.94 (SD NR) n = 86	Mean 2.88 (SD NR) n = 83	NC	MD 0.06 higher (confidence interval NC) *P* = 0.89	Low
Pain: incidence						
1 meta-analysis of 2 studies (Blanchard et al., 2004; Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	182/235 (77.4%)	183/228 (80.3%)	RR 0.97 (0.88 to 1.06)	24 fewer per 1000 (from 96 fewer to 48 more)	Moderate
Pain: severity/7						
1 study (Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	Mean 3.7 (SD NR) n = 149	Mean 3.6 (SD NR) n = 145	NC	MD 0.1 higher (confidence interval NC) NS (*P* -value NR)	Low
1 study (Blanchard et al., 2004)	Oral Ms 600 vs. 2 x 600	Mean 3.65 (SD NR) n = 85	Mean 4.09 (SD NR) n = 81	NC	MD 0.44 lower (confidence interval NC) *P* = 0.20	Low
Satisfaction: reported incidence						
1 meta-analysis of 2 studies (Blanchard et al., 2004; Ngoc et al., 2005)	Oral Ms 600 vs. 2 x 600	211/234 (90.2%)	199/226 (88.1%)	RR 1.02 (0.96 to 1.09)	18 more per 1000 (from 35 fewer to 79 more)	Moderate

CI confidence interval, MD mean difference, Ms misoprostol, NC not calculable, NR not reported, *P* probability, RR relative risk, SD standard deviation

Table 7.16 GRADE summary of findings for comparison of oral misoprostol with vaginal misoprostol for the management of incomplete miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Vaginal	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 study (Pang et al., 2001)	Oral: 800 misoprostol (Ms) x 2 Vaginal: 800 Ms x 2	67/105 (63.8%)	58/96 (60.4%)	RR 1.06 (0.85 to 1.31)	36 more per 1000 (from 91 fewer to 197 more)	Very low
Need for further intervention						
1 study (Pang et al., 2001)	Oral: 800 Ms x 2 Vaginal: 800 Ms x 2	36/103 (35%)	37/95 (38.9%)	RR 0.9 (0.62 to 1.29)	39 fewer per 1000 (from 148 fewer to 113 more)	Very low
Adverse effects: incidence of nausea						
1 study (Pang et al., 2001)	Oral: 800Ms x 2 Vaginal: 800 Ms x 2	12/103 (11.7%)	7/95 (7.4%)	RR 1.58 (0.65 to 3.85)	43 more per 1000 (from 26 fewer to 210 more)	Low
Adverse effects: incidence of vomiting						
1 study (Pang et al., 2001)	Oral: 800 Ms x 2 Vaginal: 800 Ms x 2	6/103 (5.8%)	2/95 (2.1%)	RR 2.77 (0.57 to 13.38)	37 more per 1000 (from 9 fewer to 261 more)	Low
Adverse effects: incidence of diarrhoea						
1 study (Pang et al., 2001)	Oral: 800 Ms x 2 Vaginal: 800 Ms x 2	62/103 (60.2%)	12/95 (12.6%)	RR 4.77 (2.74 to 8.27)	476 more per 1000 (from 220 more to 918 more)	Moderate
Adverse effects: incidence of fever						
1 study (Pang et al., 2001)	Oral: 800 Ms x 2 Vaginal: 800 Ms x 2	6/103 (5.8%)	11/95 (11.6%)	RR 0.5 (0.19 to 1.31)	58 fewer per 1000 (from 94 fewer to 36 more)	Low

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Vaginal	Relative (95% CI)	Absolute (95% CI)	
Duration of bleeding (days)						
1 study (Pang et al., 2001)	Oral: 800 Ms x 2 Vaginal: 800 Ms x 2	Median 8 (Range 0 - 14) n = 97	Median 8 (Range 0 - 14) n = 89	not calculable (NC)	Median 0 higher (confidence intervals NC) NS (*P*-value not reported [NR])	Moderate
Pain: duration of pelvic pain (days)						
1 study (Pang et al., 2001)	Oral: 800 Ms x 2 Vaginal: 800 Ms x 2	Median 1 (Range 0 - 14) n = 97	Median 2 (Range 0 - 11) n = 89	NC	Median 1 lower (confidence interval NC) *P* = 0.02	Moderate

CI confidence interval, Ms misoprostol, NC not calculable, *P* probability, RR relative risk

Table 7.17 GRADE summary of findings for comparison of oral misoprostol with sublingual misoprostol for the management of incomplete miscarriage

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Sublingual	Relative (95% CI)	Absolute (95% CI)	
Success of medical treatment						
1 study (Paritakul & Phupong, 2011)	Oral: 600 misoprostol (Ms) Sublingual: 600 Ms	28/32 (87.5%)	27/32 (84.4%)	RR 1.04 (0.85 to 1.26)	34 more per 1000 (from 127 fewer to 219 more)	Low
Need for further intervention						
1 study (Paritakul & Phupong, 2011)	Oral: 600 Ms Sublingual: 600 Ms	2/32 (6.3%)	5/32 (15.6%)	RR 0.4 (0.08 to 1.91)	94 fewer per 1000 (from 144 fewer to 142 more)	Low

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Sublingual	Relative (95% CI)	Absolute (95% CI)	
Adverse effects: incidence of nausea						
1 study (Paritakul & Phupong, 2011)	Oral: 600 Ms Sublingual: 600 Ms	7/32 (21.9%)	8/32 (25%)	RR 0.88 (0.36 to 2.13)	30 fewer per 1000 (from 160 fewer to 283 more)	Moderate
Adverse effects: incidence of vomiting						
1 study (Paritakul & Phupong, 2011)	Oral: 600 Ms Sublingual: 600 Ms	0/32 (0%)	0/32 (0%)	not calculable (NC)	NC	Moderate
Adverse effects: incidence of diarrhoea						
1 study (Paritakul & Phupong, 2011)	Oral: 600 Ms Sublingual: 600 Ms	5/32 (15.6%)	9/32 (28.1%)	RR 0.56 (0.21 to 1.48)	124 fewer per 1000 (from 222 fewer to 135 more)	Moderate
Adverse effects: incidence of fever/chills						
1 study (Paritakul & Phupong, 2011)	Oral: 600 Ms Sublingual: 600 Ms	9/32 (28.1%)	14/32 (43.8%)	RR 0.64 (0.33 to 1.27)	157 fewer per 1000 (from 293 fewer to 118 more)	Moderate
Incidence of heavy bleeding						
1 study (Paritakul & Phupong, 2011)	Oral: 600 Ms Sublingual: 600 Ms	0/32 (0%)	0/32 (0%)	NC	NC	Moderate
Pain: incidence of pain/cramps						
1 study (Paritakul & Phupong, 2011)	Oral: 600 Ms Sublingual: 600 Ms	8/32 (25%)	10/32 (31.3%)	RR 0.8 (0.36 to 1.76)	62 fewer per 1000 (from 200 fewer to 237 more)	Moderate

Number of studies	Details of treatment regimen (dose in micrograms unless stated)	Number of women or average		Effect		Quality
		Oral	Sublingual	Relative (95% CI)	Absolute (95% CI)	
Pain: severity/100						
1 study (Paritakul & Phupong, 2011)	Oral: 600 Ms Sublingual: 600 Ms	Mean 22.2 (SD 15.0) n = 32	Mean 29.1 (SD 21.2) n = 32	NC	MD 6.9 lower (15.9 lower to 2.1 higher) (*P* = 0.139)	High
Satisfaction: reported incidence						
1 study (Paritakul & Phupong, 2011)	Oral: 600 Ms Sublingual: 600 Ms	28/32 (87.5%)	27/32 (84.4%)	RR 1.04 (0.85 to 1.26)	34 more per 1000 (from 127 fewer to 219 more)	Moderate

CI confidence interval, MD mean difference, Ms misoprostol, NC not calculable, *P* probability, RR relative risk, SD standard deviation

Evidence statements

Management of missed miscarriage: comparison of vaginal misoprostol and placebo

Success of medical treatment

One study found that the success of medical treatment was higher in women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. A meta-analysis of two studies also found that the success of medical treatment was higher in women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) compared with women who received a placebo. These findings were statistically significant and the evidence for these findings was of high quality. However, another meta-analysis of two studies did not find a statistically significant difference in this outcome between women who received vaginal misoprostol (400 micrograms, one dose) and women who received a placebo. The evidence for this finding was of very low quality.

Need for further intervention

One study found that the need for further intervention was lower in women who received vaginal misoprostol (400 micrograms, 1 dose) compared with women who received a placebo. A second study found that the need for further intervention was lower in women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. A meta-analysis of two studies also found that the need for further intervention was lower in women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) compared with women who received a placebo. These findings were statistically significant and the evidence for these outcomes was of high quality.

Unplanned visits to a medical facility

One study did not find a statistically significant difference in the unplanned visits to a medical facility for women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) compared with women who received a placebo. The evidence for this outcome was of moderate quality.

Adverse effects

One study did not find a statistically significant difference in the incidence of nausea and/or vomiting for women who received vaginal misoprostol (400 micrograms) compared with women who received a placebo. The evidence for this outcome was of very low quality.

One study did not find a statistically significant difference in the incidence of nausea for women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. One further study did not find a statistically significant difference in the incidence of nausea for women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) compared with women who received a placebo. The quality of evidence for this outcome was low in one study and moderate in the other.

One study did not find a statistically significant difference in the severity of nausea for women who received vaginal misoprostol (400 micrograms) compared with women who received a placebo. The evidence for this outcome was of low quality.

One study did not find a statistically significant difference in the incidence of vomiting for women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. One further study did not find a statistically significant difference in the incidence of nausea for women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) compared with women who received a placebo. The quality of evidence for this outcome was low in one study and moderate in the other.

One study did not find a statistically significant difference in the severity of vomiting for women who received vaginal misoprostol (400 micrograms) compared with women who received a placebo. The evidence for this outcome was of low quality.

One study did not find a statistically significant difference in the incidence of diarrhoea for women who received vaginal misoprostol (400 micrograms) compared with women who received a placebo. Another study did not find a statistically significant difference in the incidence of diarrhoea for women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. One further study did not find a statistically significant difference in the incidence of nausea for women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) compared with women who received a placebo. The quality of evidence for this outcome was very low in one study, low in the second study and moderate in the third.

One study did not find a statistically significant difference in the severity of diarrhoea for women who received vaginal misoprostol (400 micrograms) compared with women who received a placebo. The evidence for this outcome was of low quality.

One study reported the incidence of any gastrointestinal side-effects in a manner that did not permit statistical comparison between the two arms. The evidence for this outcome was of low quality.

One study did not find a statistically significant difference in the incidence of fever for women who received vaginal misoprostol (400 micrograms) compared with women who received a placebo. The evidence for this outcome was of very low quality.

One study did not find a statistically significant difference in the incidence of infection for women who received vaginal misoprostol (400 micrograms) compared with women who received a placebo. The evidence for this outcome was of low quality.

One study did not find a statistically significant difference in the incidence of pelvic inflammatory disease for women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. The evidence for this outcome was of low quality.

Duration of bleeding

One study did not find a statistically significant difference in the duration of bleeding for women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. The evidence for this outcome was of moderate quality.

Pain

One study did not find a statistically significant difference in the incidence of menstrual cramping for women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) compared with women who received a placebo. The evidence for this outcome was of moderate quality.

One study found that the incidence of lower abdominal pain was higher in women who received vaginal misoprostol (400 micrograms, one dose) compared with women who received a placebo. This finding was statistically significant. The evidence for this outcome was of low quality.

One study found that the severity of pain was higher in women who received vaginal misoprostol (400 micrograms, one dose) compared with women who received a placebo. This finding was statistically significant and the evidence for this finding was of low quality. However, another study did not find a statistically significant difference in this outcome between women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) and women who received a placebo. A further study did not find a statistically significant difference in this outcome between women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) and women who received a placebo. The evidence for this finding was of moderate quality.

Satisfaction

One study did not find a statistically significant difference in the incidence of satisfaction for women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) compared with women who received a placebo. The evidence for this outcome was of moderate quality.

One study did not find a statistically significant difference in the satisfaction score for women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. The evidence for this outcome was of moderate quality.

Management of missed miscarriage: comparison of mifepristone and placebo

Success of medical treatment

One study found that the success of medical treatment was higher in women who received mifepristone compared with women who received a placebo. This finding was statistically significant and the evidence for this outcome was of low quality.

Need for further intervention

One study found that the need for further intervention was lower in women who received mifepristone compared with women who received a placebo. This finding was statistically significant and the evidence for this outcome was of low quality.

Adverse effects

One study did not find a statistically significant difference in the incidence of endometritis for women who received mifepristone compared with women who received a placebo. The evidence for this outcome was of low quality.

Pain

One study did not find a statistically significant difference in the incidence of pain for women who received mifepristone compared with women who received a placebo. The evidence for this outcome was of low quality.

Management of missed miscarriage: comparison of a combined regimen of mifepristone plus misoprostol and misoprostol only

Success of medical treatment

One study did not find a statistically significant difference in the success of medical treatment for women who received mifepristone plus misoprostol compared with women who received misoprostol only. The evidence for this outcome was of moderate quality.

Need for further intervention

One study did not find a statistically significant difference in the need for further intervention for women who received mifepristone plus misoprostol compared with women who received misoprostol only. The evidence for this outcome was of moderate quality.

Management of missed miscarriage: comparison of vaginal misoprostol dosages

Success of medical treatment

One study found that the success of medical treatment was higher in women who received 800 micrograms of vaginal misoprostol compared with women who received 600 micrograms of vaginal misoprostol. This finding was statistically significant. The evidence for this outcome was of high quality.

Adverse effects

One study did not find a statistically significant difference in the incidence of nausea for women who received 800 micrograms of vaginal misoprostol compared with women who received 600 micrograms of vaginal misoprostol. The evidence for this outcome was of moderate quality.

There were no events in either arm for the outcome of incidence of vomiting. The evidence for this outcome was of moderate quality.

One study did not find a statistically significant difference in the incidence of diarrhoea for women who received 800 micrograms of vaginal misoprostol compared with women who received 600 micrograms of vaginal misoprostol. The evidence for this outcome was of moderate quality.

One study did not find a statistically significant difference in the incidence of fever for women who received 800 micrograms of vaginal misoprostol compared with women who received 600 micrograms of vaginal misoprostol. The evidence for this outcome was of moderate quality.

Pain

One study found that the incidence of pain was higher in women who received 800 micrograms of vaginal misoprostol compared with women who received 600 micrograms of vaginal misoprostol. This finding was statistically significant. The evidence for this outcome was of high quality.

Management of missed miscarriage: comparison of sublingual misoprostol dosages

Success of medical treatment

One study did not find a statistically significant difference in the success of medical treatment for women who received a single dose of sublingual misoprostol (600 micrograms) compared with women who received an extended course of sublingual misoprostol (600 micrograms on day 1 and then 400 micrograms daily on days 2 to 9). The evidence for this outcome was of moderate quality.

Adverse effects

One study did not find a statistically significant difference in the incidence of nausea on day 1 or days 2 to 9 for women who received a single dose of sublingual misoprostol (600 micrograms) compared with women who received an extended course of sublingual misoprostol (600 micrograms on day 1 and then 400 micrograms daily on days 2 to 9). The evidence for these outcomes was of low quality.

One study did not find a statistically significant difference in the incidence of vomiting on day 1 or days 2 to 9 for women who received a single dose of sublingual misoprostol (600 micrograms) compared with women who received an extended course of sublingual misoprostol (600 micrograms on day 1 and then 400 micrograms daily on days 2 to 9). The evidence for these outcomes was of low quality.

One study did not find a statistically significant difference in the incidence of diarrhoea on day 1 for women who received a single dose of sublingual misoprostol (600 micrograms) compared with women who received an extended course of sublingual misoprostol (600 micrograms on day 1 and then 400 micrograms daily on days 2 to 9). The same study found that the incidence of diarrhoea on days 2 to 9 after treatment was higher in women who received an extended course of sublingual misoprostol (600 micrograms on day 1 and then 400 micrograms daily on days 2 to 9) compared with women who received a single dose of sublingual misoprostol (600 micrograms). The evidence for these outcomes was of moderate quality.

One study did not find a statistically significant difference in the incidence of fever on day 1 for women who received a single dose of sublingual misoprostol (600 micrograms) compared with women who received an extended course of sublingual misoprostol (600 micrograms on day 1 and then 400 micrograms daily on days 2 to 9). The same study reported no events in either arm for the incidence of fever on days 2 to 9. The evidence for these outcomes was of low quality.

One study did not find a statistically significant difference in the incidence of chills and rigour on day 1 for women who received a single dose of sublingual misoprostol (600 micrograms) compared with women who received an extended course of sublingual misoprostol (600 micrograms on day 1 and then 400 micrograms daily on days 2 to 9). The same study reported no events in either arm for the incidence of chills and rigour on days 2 to 9. The evidence for these outcomes was of low quality.

Duration of bleeding

One study did not find a statistically significant difference in the duration of bleeding for women who received a single dose of sublingual misoprostol (600 micrograms) compared with women who received an extended course of sublingual misoprostol (600 micrograms on day 1 and then 400 micrograms daily on days 2 to 9). The evidence for this outcome was of moderate quality.

Pain

One study did not find a statistically significant difference in the incidence of pain on day 1 or days 2 to 9 for women who received a single dose of sublingual misoprostol (600 micrograms) compared with women who received an extended course of sublingual misoprostol (600 micrograms on day 1 and then 400 micrograms daily on days 2 to 9). The evidence for these outcomes was of moderate quality.

Management of missed miscarriage: comparison of oral and sublingual misoprostol

Success of medical treatment

One study did not find a statistically significant difference in the success of medical treatment for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (400 micrograms, six doses). Another study did not find a statistically significant difference in the success of medical treatment for women who received oral misoprostol compared with women who receive the same dose of sublingual misoprostol (200 mg of mifepristone plus 600 micrograms of misoprostol, with three supplemental doses of 400 micrograms of misoprostol after 12 hours). The quality of evidence for this outcome was low quality in one study and moderate in the other.

Adverse effects

One study did not find a statistically significant difference in the incidence of nausea or vomiting for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (400 micrograms, six doses). The evidence for this outcome was of moderate quality.

One study did not find a statistically significant difference in the incidence of nausea for women who received oral misoprostol compared with women who receive the same dose of sublingual misoprostol (200 mg of mifepristone plus 600 micrograms of misoprostol, with three supplemental doses of 400 micrograms of misoprostol after 12 hours). The evidence for this outcome was of low quality.

One study found that the incidence of vomiting was higher in women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (200 mg of mifepristone plus 600 micrograms of misoprostol, with three supplemental doses of 400 micrograms of misoprostol after 12 hours). This finding was statistically significant. The evidence for this outcome was of moderate quality.

One study found that the incidence of fever was higher in women who received sublingual misoprostol compared with women who received the same dose of oral misoprostol (400 micrograms, six doses). This finding was statistically significant and the evidence for this finding was of high quality. However, another study found that the incidence of fever was higher in women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (200 mg of mifepristone plus 600 micrograms of misoprostol, with three supplemental doses of 400 micrograms of misoprostol after 12 hours). This finding was statistically significant and the evidence for this finding was of moderate quality.

One study did not find a statistically significant difference in the incidence of chills for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (400 micrograms, six doses). The evidence for this outcome was of moderate quality.

Pain

One study found that the incidence of pain was higher in women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (regimen for both study groups: 200 mg of mifepristone plus 600 micrograms of misoprostol, with three supplemental doses of 400 micrograms of misoprostol after 12 hours). This finding was statistically significant and the evidence for this finding was of moderate quality. However, another study found that there was no statistically significant difference in the incidence of pain in women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (400 micrograms, six doses). The evidence for this finding was of moderate quality.

Satisfaction

One study found that the reported incidence of satisfaction was higher in women who received sublingual misoprostol compared with women who received the same dose of oral misoprostol (regimen for both study groups: 200 mg of mifepristone plus 600 micrograms of misoprostol, with three supplemental doses of 400 micrograms of misoprostol after 12 hours). This finding was statistically significant and the evidence for this finding was of moderate quality.

Management of missed miscarriage: comparison of sublingual and vaginal misoprostol

Success of medical treatment

One meta-analysis of two studies did not find a statistically significant difference in the success of medical treatment for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, five doses in one study and maximum not reported in the other). A second study did not find a statistically significant difference in the success of medical treatment for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (600 micrograms, three doses). The quality of evidence for this finding was very low in the meta-analysis and moderate in the other study.

Need for further intervention

One meta-analysis of two studies did not find a statistically significant difference in the need for further intervention for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, five doses in one study and maximum not reported in the other). A second study did not find a statistically significant difference in the need for further intervention for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (600 micrograms, three doses). The quality of evidence for this finding was very low in the meta-analysis and low in the other study.

Adverse effects

One study did not find a statistically significant difference in the incidence of nausea for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, five doses). A second study did not find a statistically significant difference in the incidence of nausea for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (600 micrograms, three doses). The quality of evidence for this finding was low in one study and moderate in the other.

One study did not find a statistically significant difference in the incidence of vomiting for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, maximum number of doses not reported). A second study did not find a statistically significant difference in the incidence of vomiting for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (600 micrograms, three doses). The quality of evidence for this finding was low in one study and moderate in the other.

One study found that the incidence of diarrhoea was higher in women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, maximum number of doses not reported). A second study found that the incidence

of diarrhoea was higher in women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (600 micrograms, three doses). These findings were statistically significant. The quality of evidence for this finding was moderate in one study and high in the other.

One study found that the incidence of fever was higher in women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, maximum number of doses not reported). This finding was statistically significant and the evidence for this finding was of moderate quality. However, another study did not find a statistically significant difference in this outcome between women who received sublingual misoprostol and women who received the same dose of vaginal misoprostol (600 micrograms, three doses). The evidence for this finding was of moderate quality.

One study did not find a statistically significant difference in the incidence of chills or shivering for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, five doses). A second study did not find a statistically significant difference in the incidence of chills or shivering for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (600 micrograms, three doses). The quality of evidence for this finding was low in one study and moderate in the other.

Duration of bleeding

One study did not find a statistically significant difference in the duration of bleeding for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (600 micrograms, three doses). The evidence for this outcome was of high quality.

Pain

One study found that the incidence of cramps was higher in women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, maximum number of doses not reported). This finding was statistically significant and the evidence for this finding was of moderate quality.

One study found that the incidence of severe pain was higher in women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, maximum number of doses not reported). This finding was statistically significant and the evidence for this finding was of moderate quality.

One study reported 100% incidence of lower abdominal pain in women who received sublingual misoprostol and women who received the same dose of vaginal misoprostol (600 micrograms, three doses). The evidence for this outcome was of high quality.

Satisfaction

One meta-analysis of two studies did not find a statistically significant difference in the reported incidence of satisfaction for women who received sublingual misoprostol compared with women who received the same dose of vaginal misoprostol (400 micrograms, five doses in one study and maximum not reported in the other). The evidence for this outcome was of very low quality.

Management of missed miscarriage: comparison of oral and vaginal misoprostol

Success of medical treatment

One study found that the success of medical treatment was higher in women who received vaginal misoprostol (600 micrograms, two doses) compared with women who received oral misoprostol (400 micrograms, three doses). A second study found that the success of medical treatment was higher in women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) compared with women who received oral misoprostol (400 micrograms, repeat after 24 hours). These findings were statistically significant. The quality of evidence for this finding was moderate in one study and very low in the other. One further study did not find a statistically significant difference in this outcome between women who received the same dose of vaginal and oral misoprostol (800 micrograms, one dose). The evidence for this finding was of moderate quality.

Need for further intervention

One study found that the need for a further intervention was higher in women who received oral misoprostol (400 micrograms, three doses) compared with women who received vaginal misoprostol

(600 micrograms, two doses). This finding was statistically significant and the evidence for this finding was of moderate quality. One further study did not find a statistically significant difference in this outcome between women who received the same dose of vaginal and oral misoprostol (800 micrograms, one dose). The evidence for this finding was of low quality.

Admission to a medical facility

One study did not find a statistically significant difference in the incidence of admission to a medical facility for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, one dose). The evidence for this outcome was of very low quality.

Adverse effects

One study did not find a statistically significant difference in the incidence of nausea for women who received oral misoprostol (400 micrograms, three doses) compared with women who received vaginal misoprostol (600 micrograms, two doses). A second study did not find a statistically significant difference in the incidence of nausea for women who received oral misoprostol (400 micrograms, one dose) compared with women who received vaginal misoprostol (800 micrograms, one dose). The quality of evidence for this outcome was low in one study and very low in the other.

One study found that the incidence of vomiting was higher in women who received vaginal misoprostol (800 micrograms, one dose) compared with women who received oral misoprostol (800 micrograms, one dose). This finding was statistically significant and the evidence for this finding was of high quality. However, another study found that there was no statistically significant difference in this outcome between women who received vaginal misoprostol (600 micrograms, two doses) and oral misoprostol (400 micrograms, three doses). A further study found that there was no statistically significant difference this outcome between women who received vaginal misoprostol (800 micrograms, repeat after 24 hours) and women who received oral misoprostol (400 micrograms, repeat after 24 hours). The quality of evidence for this finding was low in one study and very low in the other.

One study did not find a statistically significant difference in the incidence of diarrhoea for women who received oral misoprostol (400 micrograms, three doses) compared with women who received vaginal misoprostol (600 micrograms, two doses). A second study did not find a statistically significant difference in the incidence of diarrhoea for women who received oral misoprostol (400 micrograms, one dose) compared with women who received vaginal misoprostol (800 micrograms, one dose). Another study did not find a statistically significant difference in the incidence of diarrhoea for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, one dose). The quality of evidence for this outcome was low in one study, very low in the second study and moderate in the third study.

One study did not find a statistically significant difference in the incidence of hyperpyrexia for women who received oral misoprostol (400 micrograms, three doses) compared with women who received vaginal misoprostol (600 micrograms, two doses). The evidence for this outcome was of low quality.

One study did not find a statistically significant difference in the incidence of fever or chills for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, one dose). The evidence for this outcome was of moderate quality.

Duration of bleeding

One study did not find a statistically significant difference in the duration of bleeding for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, one dose). The evidence for this finding was of moderate quality. One further study reported duration of bleeding in a manner that did not permit a comparison between the two arms. The evidence for this finding was of very low quality.

Pain

One study did not find a statistically significant difference in the incidence of pain for women who received oral misoprostol (400 micrograms, three doses) compared with women who received vaginal misoprostol (600 micrograms, two doses). A second study did not find a statistically significant difference in the incidence of pain for women who received oral misoprostol compared with women

who received the same dose of vaginal misoprostol (800 micrograms, one dose). The quality of evidence for this outcome was low in one study and high in the other.

One study did not find a statistically significant difference in the severity of pain for women who received oral misoprostol (400 micrograms, one dose) compared with women who received vaginal misoprostol (800 micrograms, one dose). The evidence for this outcome was of very low quality.

Satisfaction

One study did not find a statistically significant difference in the reported incidence of satisfaction for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, one dose). The evidence for this outcome was of high quality.

Management of incomplete miscarriage: comparison of vaginal misoprostol and placebo

Success of medical treatment

One study did not find a statistically significant difference in the success of medical treatment for women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. The evidence for this outcome was of low quality.

Need for further intervention

One study did not find a statistically significant difference in the need for further intervention for women who received vaginal misoprostol (400 micrograms, one dose) compared with women who received a placebo. A second study did not find a statistically significant difference in the need for further intervention for women who received vaginal misoprostol (600 micrograms, repeat after 24 hours) compared with women who received a placebo. The evidence for this outcome was of low quality.

Management of incomplete miscarriage: comparison of oral misoprostol dosages

Success of medical treatment

One meta-analysis of two studies did not find a statistically significant difference in the success of medical treatment for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The evidence for this outcome was of moderate quality.

Need for further intervention

One meta-analysis of two studies did not find a statistically significant difference in the need for further intervention for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The evidence for this outcome was of low quality.

Adverse effects

One meta-analysis of two studies did not find a statistically significant difference in the incidence of nausea for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The evidence for this outcome was of very low quality.

One meta-analysis of two studies did not find a statistically significant difference in the incidence of vomiting for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The evidence for this outcome was of low quality.

One study found that the incidence of diarrhoea was higher in women who received two 600 microgram doses of oral misoprostol compared with women who received a single 600 microgram dose of oral misoprostol. This difference was statistically significant. The evidence for this finding was of moderate quality.

One meta-analysis of two studies did not find a statistically significant difference in the incidence of fever or chills for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The evidence for this outcome was of low quality.

Duration of bleeding

Two studies did not find a statistically significant difference in the duration of heavy bleeding for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The quality of evidence for this outcome was moderate in one study and low in the other.

Two studies did not find a statistically significant difference in the duration of normal bleeding for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The quality of evidence for this outcome was moderate in one study and low in the other.

Two studies did not find a statistically significant difference in the duration of light bleeding for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The quality of evidence for this outcome was moderate in one study and low in the other.

Pain

One meta-analysis of two studies did not find a statistically significant difference in the incidence of pain for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The evidence for this outcome was of moderate quality.

Two studies did not find a statistically significant difference in the severity of pain for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The evidence for this outcome was of low quality.

Satisfaction

One meta-analysis of two studies did not find a statistically significant difference in the reported incidence of satisfaction for women who received two 600 microgram doses of oral misoprostol compared with women who received a single dose of 600 microgram oral misoprostol. The evidence for this outcome was of moderate quality.

Management of incomplete miscarriage: comparison of oral and vaginal misoprostol

Success of medical treatment

One study did not find a statistically significant difference in the success of medical treatment for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, two doses). The evidence for this outcome was of very low quality.

Need for further intervention

One study did not find a statistically significant difference in the need for further intervention for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, two doses). The evidence for this outcome was of very low quality.

Adverse effects

One study did not find a statistically significant difference in the incidence of nausea for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, two doses). The evidence for this outcome was of low quality.

One study did not find a statistically significant difference in the incidence of vomiting for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, two doses). The evidence for this outcome was of low quality.

One study found that the incidence of diarrhoea was higher in women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, two doses). This finding was statistically significant and the evidence for this finding was of moderate quality.

One study did not find a statistically significant difference in the incidence of fever for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, two doses). The evidence for this outcome was of low quality.

Duration of bleeding

One study did not find a statistically significant difference in the duration of bleeding for women who received oral misoprostol compared with women who received the same dose of vaginal misoprostol (800 micrograms, two doses). The evidence for this outcome was of moderate quality.

Pain

One study found that the duration of pelvic pain was longer in women who received vaginal misoprostol compared with women who received the same dose of oral misoprostol (800 micrograms, two doses). This finding was statistically significant and the evidence for this finding was of moderate quality.

Management of incomplete miscarriage: comparison of oral and sublingual misoprostol

Success of medical treatment

One study did not find a statistically significant difference in the success of medical treatment for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of low quality.

Need for further intervention

One study did not find a statistically significant difference in the need for further intervention for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of low quality.

Adverse effects

One study did not find a statistically significant difference in the incidence of nausea for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of moderate quality.

One study reported no incidences of vomiting in women who received oral misoprostol and women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of moderate quality.

One study did not find a statistically significant difference in the incidence of diarrhoea for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of moderate quality.

One study did not find a statistically significant difference in the incidence of fever/chills for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of moderate quality.

Incidence of heavy bleeding

One study reported no incidences of heavy bleeding in women who received oral misoprostol and women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of moderate quality.

Pain

One study did not find a statistically significant difference in the incidence of pain/cramps for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of moderate quality.

One study did not find a statistically significant difference in the severity of pain for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of high quality.

Satisfaction

One study did not find a statistically significant difference in the incidence of reported satisfaction for women who received oral misoprostol compared with women who received the same dose of sublingual misoprostol (600 micrograms). The evidence for this outcome was of moderate quality.

Evidence to recommendations

Relative value placed on the outcomes considered

The primary outcome measures for this question were the success rate of the treatment and the need for further interventions. The secondary outcomes were the various side-effects associated with treatment. Of these, the group felt that pain was less informative than the others, as all women would be likely to experience a degree of pain as a natural consequence of the miscarriage. It was also evident from the placebo trials that gastro-intestinal symptoms may accompany miscarriage.

Consideration of clinical benefits and harms

When considering the appropriate dose and mode of administration, the group considered the main priority to be the efficacy of the treatment. The evidence compared a number of different doses and regimens. For women with missed miscarriage, a single dose of 800 micrograms (oral or vaginal) of misoprostol was the most effective overall. For women with an incomplete miscarriage, the evidence suggested that a single dose of 600 micrograms of misoprostol was effective, but the group recognised that units might prefer to use 800 micrograms for alignment of protocols.

For women with missed miscarriage, the group noted that, used at the same dose, both vaginal and oral routes of administration had similar effectiveness, and that both were more effective than sub-lingual administration. The majority of side-effects did not show a difference by route. There was contradictory evidence regarding diarrhoea: one study showed more diarrhoea associated with a vaginal route of administration than with an oral route, but two further studies showed no statistically significant difference and this matched the GDG members' clinical experience. The evidence suggested that there were more side-effects from sub-lingual administration than with vaginal administration. In addition, the GDG members recognised from their own clinical experience that there can often be difficulties with sub-lingual administration as women are expected to hold up to four relatively large tablets under their tongue for a long period of time.

For women with an incomplete miscarriage, one study found there was a significantly lower incidence of diarrhoea with vaginal administration compared with oral administration. A second study showed no significant differences between oral and sub-lingual administration for all outcomes.

The group felt that an additional benefit of vaginal administration is that if women vomit after receiving medication orally, this can interfere with the absorption of the drug and it can be difficult to determine if the dose should be repeated.

Overall, the GDG agreed that vaginal misoprostol is the preferred treatment. However, it recognised that it is important to take into account women's preferences and thus agreed that the oral route would be appropriate if vaginal administration was not acceptable to the woman.

Consideration of health benefits and resource uses

The group recognised that there was very little evidence which compared the efficacy of misoprostol in combination with mifepristone compared with misoprostol alone for the treatment of miscarriage. However, what evidence there was suggested that there was no difference in effectiveness. Given the large cost of mifepristone compared with misoprostol[*], the group agreed that mifepristone should not be used routinely in the management of miscarriage. It was recognised that mifepristone is currently used in UK practice for this indication and that it would therefore be helpful to conduct further research. The GDG agreed that a trial was needed to determine definitively whether the addition of mifepristone improves the success rate of medical management, the results of which could then be used to evaluate whether it is a cost-effective treatment.

Quality of evidence

The evidence for this question was drawn from RCTs; however, the quality was mixed and ranged from high to very low. Generally, the group felt that the evidence was of sufficient quality to make recommendations, although it recognised that it would have been helpful to have had further evidence related to the efficacy of mifepristone and misoprostol in combination.

* A pack of three 200 mg mifepristone tablets costs approximately £50, whilst a pack of sixty 200 microgram misoprostol tablets costs approximately £10.

Information giving and emotional support

The group stressed the importance of providing women with information about the treatment, what to expect as the miscarriage progresses, the potential side-effects of treatment and the next steps if the treatment is ineffective. It felt that informing women about the likely length and extent of bleeding was a particular consideration, as this could be particularly distressing or worrying.

Other considerations

The GDG discussed the fact that the majority of women receiving medical treatment would now be receiving it as second-line treatment, as a result of recommendations about first-line expectant management made in Section 7.4. All of the studies evaluated medical management as first-line treatment. However, the group noted that the women participating in the studies were likely to have presented at different points in the course of their miscarriage, depending on their symptoms and ability to access health care. For example, women with no symptoms might have sought care, and been diagnosed with a missed miscarriage, weeks after the miscarriage had actually occurred, and therefore would be reasonably comparable to women presenting earlier who had then been expectantly managed for a period of time. Despite this, the group accepted that the treatment success rates reported in the trials might be higher than would be expected in women in whom expectant management had already failed, and that this would be a consideration for women choosing their preferred second-line treatment. However, it also felt that the *relative* efficacy of different routes of administration would be unlikely to vary according to whether the treatment was first or second line, and, therefore, that the results of the comparisons reported in the trials could safely be extrapolated to women actively choosing medical management after a period of expectant management.

The GDG recognised that there are a number of side-effects associated with miscarriage itself and with the drugs used in its management, and that clinicians should treat these side-effects at the same time as providing miscarriage management.

The group agreed that, for women with a missed miscarriage, if the treatment is ineffective (that is, bleeding has not started) after 24 hours, there should be a clinical review, which could just be a telephone conversation rather than a formal appointment. The group also recognised the importance of having a follow-up process in place to ensure that there is no molar or ectopic pregnancy. The group agreed that all women should be advised to check that a urine pregnancy test is negative 3 weeks after receiving medical treatment to determine if it has been effective, and that they should return for clinical review if the test is still positive.

While misoprostol is commonly used to treat miscarriage, it is not currently licensed for use for this indication and so women's consent should be obtained before it is used.

Recommendations

Number	Recommendation
56	Do not offer mifepristone as a treatment for missed or incomplete miscarriage.
57	Offer vaginal misoprostol for the medical treatment of missed or incomplete miscarriage. Oral administration is an acceptable alternative if this is the woman's preference.*
58	For women with a missed miscarriage, use a single dose of 800 micrograms of misoprostol.*
59	Advise the woman that if bleeding has not started 24 hours after treatment, she should contact her healthcare professional to determine ongoing individualised care.

* Although this use is common in UK clinical practice, at the time of publication (December 2012), misoprostol did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

60	For women with an incomplete miscarriage, use a single dose of 600 micrograms of misoprostol. (800 micrograms can be used as an alternative to allow alignment of treatment protocols for both missed and incomplete miscarriage.)*
61	Offer all women receiving medical management of miscarriage pain relief and anti-emetics as needed.
62	Inform women undergoing medical management of miscarriage about what to expect throughout the process, including the length and extent of bleeding and the potential side effects of treatment including pain, diarrhoea and vomiting.
63	Advise women to take a urine pregnancy test 3 weeks after medical management of miscarriage unless they experience worsening symptoms, in which case advise them to return to the healthcare professional responsible for providing their medical management.
64	Advise women with a positive urine pregnancy test after 3 weeks to return for a review by a healthcare professional to ensure that there is no molar or ectopic pregnancy.

Number	Research recommendation
RR 7	Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of miscarriage?

7.6 Setting for surgical management of miscarriage

Review question

What is the effectiveness of surgical management of miscarriage in an outpatient (office) setting compared with any other setting for improving women's clinical and psychological outcomes?

Introduction

Historically women diagnosed with a miscarriage who opted for surgical management would undergo the procedure in a traditional theatre setting under a general anaesthetic. Recent advances in surgical techniques and equipment have seen the introduction of surgical procedures being performed without a general anaesthetic (but with some other form of anaesthesia, analgesia or sedation) in an outpatient setting. This review sought to identify which settings are associated with better outcomes.

Description of included studies

Four studies were included in this review. Three studies were conducted in the USA (Blumenthal et al., 1994; Dalton et al., 2006; Edwards et al., 2007) and one in South Africa (De Jonge et al., 1994).

One retrospective observational study (Edwards et al., 2007) assessed and compared the efficiency, post procedure quality of life and acceptability of manual vacuum aspiration (MVA) performed in an outpatient setting with electric vacuum aspiration (EVA) performed in a hospital in-patient setting in women experiencing a first-trimester miscarriage. EVA was performed under either general anaesthesia, 'monitored anaesthesia care' (MAC) or spinal anaesthesia. Analgesia for MVA was provided with a paracervical block of lidocaine.

One randomised clinical trial (De Jonge et al., 1994) assessed evacuation under systemic analgesia (fentanyl and midazolam) in a treatment room compared with evacuation under general anaesthesia in an operating theatre.

One prospective observational study (Dalton et al., 2006) examined women's satisfaction with an office-based surgical procedure for early pregnancy failure and compared the resource use and cost

between office and operating room management. Anaesthesia for the MVA performed in an office setting consisted of oral lorazepam, ibuprofen and/or propoxyphene napsylate, with paracervical block. EVA was performed under anaesthesia that included intravenous sedation, regional anaesthesia or general anaesthesia.

One quasi experimental study (Blumenthal et al., 1994) also examined the cost effectiveness of performing manual vacuum aspiration curettage (MVAC) either in an emergency room or in a labour room as an alternative to the traditional suction curettage (SC) in the operating room. For the SC procedure, sedation was achieved with a combination of short-acting benzodiazepines and narcotics and MVAC was performed under systemic analgesia (fentanyl and midazolam). None of the women had general anaesthesia in this study.

Evidence profile

The evidence from all four studies is presented in one profile.

Table 7.18 GRADE summary of findings for comparison of operating room with office setting for surgical management of miscarriage

Number of studies	**Number of women**		**Effect**		**Quality**
	Operating room/theatre	**Outpatient/office setting or similar**	**Relative (95% CI)**	**Absolute (95% CI)**	
Emergency hospital visit on the same day of treatment					
1 study (Edwards et al., 2007)	4/88 (4.6%)	3/67 (4.5%)	RR 1.01 (0.26 to 3.95)*	0 per 1000 (from 33 fewer to 132 more)*	Very low
Tissue passed (reported within 48 hours after treatment)					
1 study (Edwards et al., 2007)	14/79 (17.7%)	16/59 (27.1%)	RR 0.65 (0.35 to 1.22)*	95 fewer per 1000 (from 176 fewer to 60 more)* *P* = 0.19	Very low
Pain severity score (reported within 48 hours after treatment)					
1 study (Edwards et al., 2007)	Mean 2.8 (SD 2.4) (n = 79)	Mean 3.7 (SD 2.3) (n = 62)	not calculable (NC)	*P* = 0.03	Very low
Success rate (within 30 days after treatment)					
1 study (Edwards et al., 2007)	81/83 (97.6%)	59/62 (95.2)	RR 1.02 (0.95 to 1.12)*	19 more per 1000 (from 48 fewer to 114 more)* *P* = 0.43	Very low

Number of studies	Number of women		Effect		Quality
	Operating room/theatre	Outpatient/office setting or similar	Relative (95% CI)	Absolute (95% CI)	
Fever (> 38°C) following treatment					
1 study (Edwards et al., 2007)	4/83 (4.8%)	1/63 (1.6%)	RR 3.03 (0.47 to 19.9)*	32 more per 1000 (from 8 fewer to 300 more)* *P* = 0.29	Very low
Waiting time: from emergency room admission to procedure (hours)					
1 study (Blumenthal et al., 1994)	Mean 7.18 (SD 4.9)	Mean 3.45 (SD 2.0)	NC	MD 3.73 higher (from 1 higher to 6 higher) *P* < 0.01	Very low
1 study (De Jonge et al., 1994)	Mean 12.63 (range 1.08–70.25)	Mean 7.25 (0.25–63)	NC	Median 5.38 higher (CI NC) *P* < 0.0003	Moderate
Blood transfusion (number of women)					
1 study (De Jonge et al., 1994)	24/68 (32.2%)	13/73 (17.8%)	1.98 (1.11 to 3.57)*	175 more per 1000 (from 18 more to 458 more)* *P* < 0.03	Low
Maximum total satisfaction (defined as maximum score on both satisfaction-related items)					
1 study (Dalton et al., 2006)	26/46 (56%)	51/110 (46%)	1.21 (0.86 to 1.66)*	97 more per 1000 (from 65 fewer to 306 more)* *P* = 0.15	Very low
Post procedure infection					
1 study (Dalton et al., 2006)	1/50 (2%)	2/115 (2%)	1.15 (0.15 to 8.55)*	3 more per 1000 (15 fewer to 131 more)* *P* = 0.99	Very low
Blood loss (millilitres)					
1 study (Dalton et al., 2006)	Mean 311 (SD 344)	Mean 70 (SD 106)	NC	241 higher (171 higher to 310 higher) *P* < 0.001	Very low

Number of studies	Number of women		Effect		Quality
	Operating room/theatre	Outpatient/office setting or similar	Relative (95% CI)	Absolute (95% CI)	
Need for re-evacuation					
1 study (Dalton et al., 2006)	1/50 (2%)	4/115 (3%)	0.57 (0.08 to 3.67)*	15 fewer per 1000 (from32 fewer to 93 more)* *P* = 0.68	Very low

CI confidence interval, NC not calculable, *P* probability, RR relative risk, SD standard deviation

* NCC calculation

Evidence statements

Evidence was identified from four studies that reported efficiency of MVA performed as an outpatient compared with EVA performed in an operating room in women experiencing a first-trimester miscarriage.

One study found lower pain severity within 48 hours of treatment in women following EVA in an operating room compared to MVA in an office setting. This finding was statistically significant and the evidence for this outcome was of very low quality.

Two studies study found longer waiting times from admission to procedure in women undergoing EVA in an operating room compared with MVA in office setting. This finding was statistically significant and the evidence for this outcome was of moderate and very low quality.

One study found a higher proportion of women receiving a blood transfusion following EVA in an operating room compared with MVA in an office setting. This finding was statistically significant and the evidence for this outcome was of low quality.

One study found higher mean blood loss in women following EVA in an operating room compared with MVA in an office setting. This finding was statistically significant and the evidence for this outcome was of very low quality.

One study did not find a statistically significant difference in the proportion of women who presented to an emergency department on the same day of treatment following EVA in an operating room compared with MVA in an office setting. The evidence for this outcome was of very low quality.

One study did not find a statistically significant difference in the proportion of women who reported passing tissue within 48 hours of treatment following EVA in an operating room compared with MVA in an office setting. The evidence for this outcome was of very low quality.

One study did not find a statistically significant difference in success rate 30 days after treatment in women following EVA in an operating room compared with MVA in an office setting. The evidence for this outcome was of very low quality.

One study did not find a statistically significant difference in the proportion of women who developed fever after treatment following EVA in an operating room compared with MVA in an office setting. The evidence for this outcome was of very low quality.

One study did not find a statistically significant difference in maximum total satisfaction score in women following EVA in an operating room compared with MVA in an office setting. The evidence for this outcome was of very low quality.

One study did not find a statistically significant difference in post procedure infection in women following EVA in an operating room compared with MVA in an office setting. The evidence for this outcome was of very low quality.

One study did not find a statistically significant difference of need for re-evacuation in women following EVA in an operating room compared with MVA in an office setting. The evidence for this outcome was of very low quality.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG considered the success rate of the treatment to be the most important outcome for this question. In addition, the group felt that need for an emergency hospital visit was also an important measure as an indicator of the comparative safety of the procedure in the different settings.

Consideration of clinical benefits and harms

The evidence showed that the median waiting time, the number of women requiring a blood transfusion, and the mean blood loss were all lower in an outpatient setting. The group recognised that although women's pain severity scores 48 hours after treatment were significantly lower in an inpatient setting, the average scores were relatively low for both groups. The group noted that the rate of blood transfusions in the study which reported this outcome was particularly high in both arms and that this evidence was unlikely to be applicable to a UK setting. In addition, the group noted that the study which reported the mean blood loss outcome had more than twice as many women in one arm as in the other and that this was likely to have affected the results.

Consideration of health benefits and resource uses

It was recognised that there would be an initial cost for units to set up the facility for performing manual vacuum aspiration as an outpatient procedure. However, once these costs have been met, it is likely that an outpatient setting would be cost effective, given the reduced time for conducting the procedure.

Quality of evidence

The evidence was generally of very low quality and so the group did not feel able to make a strong recommendation that all surgical management should routinely be conducted as an outpatient procedure. However, the group did feel that the evidence about reduced waiting times justified a recommendation that units should be able to offer surgical management as an outpatient procedure in order to provide women with a choice.

Information giving and emotional support

The GDG felt that it was important that women were given appropriate information about the different treatment options and what to expect during the procedure, in order that they could make an informed choice about their treatment. In addition, it agreed that women should be provided with information about what to expect during the recovery period.

Other considerations

The group recognised that some women will prefer to have the procedure conducted under general rather than local anaesthetic (that is, in a theatre setting). In addition, it recognised that at later gestations it may not always be clinically appropriate to offer the procedure without a general anaesthetic. As a result, the GDG did not feel it appropriate to recommend that all surgical procedures be conducted as outpatient procedures.

Recommendations

Number	Recommendation
65	Where clinically appropriate, offer women undergoing a miscarriage a choice of: • manual vacuum aspiration under local anaesthetic in an outpatient or clinic setting **or** • surgical management in a theatre under general anaesthetic.
66	Provide oral and written information to all women undergoing surgical management of miscarriage about the treatment options available and what to expect during and after the procedure.*

* See also recommendation 3 for details of further information that should be provided.

8 Management of ectopic pregnancy

8.1 Introduction

The early diagnosis of ectopic pregnancy has increased with the advent of ultrasound and serum β-human chorionic gonadotrophin (hCG) level assessment. Treatment options include surgical, medical and, rarely, expectant management. Surgery, by means of salpingectomy or salpingotomy, is performed laparoscopically or by open surgery. The most commonly used drug for the medical treatment of ectopic pregnancies is methotrexate. This can be administered either systemically or locally, or both, by various routes and requires constant vigilance of effect and evaluation by serial follow-up.

The broader range of treatments for ectopic pregnancy has allowed women's choice to be an integral part of the decision-making process. This chapter examines the evidence for the effectiveness and safety of surgical and medical treatment of tubal ectopic pregnancy in view of primary treatment success, tubal preservation and future fertility.

8.2 Surgical compared with medical management of ectopic pregnancy

Review question

How effective is surgical management of tubal ectopic pregnancy compared with medical management for improving women's clinical and psychological outcomes?

Description of included studies

Ten studies were included in this review (Colacurci et al., 1998; Dias Pereira et al., 1998; Fernandez et al., 1995; Fernandez et al., 1998; Hajenius et al., 1997; Moeller et al., 2009; Nieuwkerk et al., 1998; Saraj et al., 1998; Sowter et al., 2001b; Zilber et al., 1996).

All the included studies are randomised trials: three were conducted in the Netherlands (Hajenius et al., 1997; Dias Pereira et al., 1998; Nieuwkerk et al., 1998), two in France (Fernandez et al., 1995; Fernandez et al., 1998), one in Denmark (Moeller et al., 2009), one in the USA (Saraj et al.,1998;), one in Israel (Zilber et al., 1996), one in New Zealand (Sowter et al., 2001b) and one in Italy (Colacurci et al., 1998).

All included studies compared medical and surgical management of ectopic pregnancy and reported at least one priority outcome. Surgical management consisted of salpingotomy/salpingostomy in all of the included trials except for one (Sowter et al., 2001b) where some women (n = 7/28) were treated with salpingectomy for various reasons. Medical management in all included trials consisted of systemic or local injection of methotrexate. Eight trials (Colacurci et al., 1998; Dias Pereira et al., 1998; Fernandez et al., 1998; Hajenius et al., 1997; Moeller et al., 2009; Nieuwkerk et al., 1998; Saraj et al., 1998; Sowter et al., 2001b) compared systemic methotrexate with surgery. In three of these trials (Nieuwkerk et al., 1998; Dias Pereira et al., 1998; Hajenius et al., 1997) women were treated with multiple doses of methotrexate and in the remaining five trials they were treated with a single dose of intramuscular methotrexate injection. Three trials (Fernandez et al., 1995; Fernandez et al., 1998; Zilber et al., 1996) compared local injection of methotrexate to surgery for management of ectopic pregnancy. Local injection in the three trials consisted of direct injection of methotrexate into

the pregnancy site under laparoscopic guidance. One trial (Fernandez et al., 1998) compared local or systemic injection of methotrexate to surgery for management of ectopic pregnancy.

The trials were conducted in economically developed countries and their populations include women with confirmed ectopic pregnancy. Further details, including the duration of follow-up, can be found in the evidence tables in Appendix H.

Evidence profile

Outcomes are reported in three evidence profiles:

- surgery compared with systemic methotrexate
- surgery compared with local methotrexate
- surgery compared with systemic or local methotrexate

In the outcomes with high heterogeneity (I^2 greater than 60%), the technical team used a random effects model (the remaining outcomes used fixed effects models) and explored the heterogeneity with sensitivity analyses.

Success rate (surgery compared with systemic methotrexate)

Overall heterogeneity (69%) was not reduced by excluding the trial with multi-dose methotrexate; however, the heterogeneity was reduced to some extent (56%) by excluding the trial that treated some women (n = 6/28) with salpingectomy.

Hospital stay (surgery compared with local methotrexate)

Excluding the study with small sample size (less than 50) reduced the heterogeneity from 100% to 0%. The change could be a result of different hospitals' policies regarding the hospital stay following the treatment.

Table 8.1 GRADE summary of findings for comparison of surgery with systemic methotrexate

Number of studies	**Number of women**		**Effect**		**Quality**
	Surgery	**Systemic methotrexate**	**Relative (95% CI)**	**Absolute (95% CI) and *P*-value if reported**	
Success rate					
1 meta-analysis of 5 studies (Fernandez et al., 1998; Hajenius et al., 1997; Moeller et al., 2009; Saraj et al.,1998; Sowter et al., 2001b)	187/215 (87%)	157/198 (79.3%)	RR 1.08 (0.99 to 1.19)*	63 more per 1000 (from 8 fewer to 143 more)*	Moderate

Number of studies	Number of women		Effect		Quality
	Surgery	Systemic methotrexate	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
Future pregnancy rate					
1 meta-analysis of 2 studies (Dias Pereira et al., 1998; Moeller et al., 2009)	48/92 (52.2%)	50/86 (58.1%)	RR 0.92 (0.71 to 1.18)*	47 fewer per 1000 (from 192 fewer to 87 more)*	Low
Recurrent ectopic pregnancy					
1 meta-analysis of 2 studies (Dias Pereira et al., 1998; Moeller et al., 2009)	6/92 (6.5%)	3/86 (3.5%)	RR 1.65 (0.48 to 5.7)*	23 more per 1000 (from 18 fewer to 164 more)*	Moderate
Resolution time (days)					
1 meta-analysis of 3 studies (Colacurci et al., 1998; Fernandez et al., 1995; Fernandez et al., 1998)	n = 84	n = 57	not calculable (NC)	MD 8.8 lower (11.99 to 5.62 lower)* *P* < 0.0001	Moderate
Hospital stay (hours)					
1 study (Fernandez et al., 1998)	Mean 46 (SD 8.4) n = 49	Mean 24 (SD 1.2) n = 22	NC	MD 22 longer (19.6 longer to 24.4 longer)* *P* < 0.0001	Moderate
Need for further intervention					
1 meta-analysis of 3 studies (Fernandez et al., 1998; Hajenius et al., 1997; Moeller et al., 2009)	8/130 (6.2%)	29/109 (26.6%)	RR 0.26 (0.12 to 0.55)*	197 fewer per 1000 (120 fewer to 234 fewer)*	High

Number of studies	Number of women		Effect		Quality
	Surgery	**Systemic methotrexate**	**Relative (95% CI)**	**Absolute (95% CI) and *P*-value if reported**	
Tubal preservation					
1 study (Hajenius et al., 1997)	45/49 (91.8%)	46/51 (90.2%)	RR 1.02 (0.9 to 1.15)*	18 more per 1000 (from 90 fewer to 135 more)*	High
Homolateral tubal patency					
1 study (Hajenius et al., 1997)	23/39 (59%)	23/42 (54.8%)	RR 1.08 (0.74 to 1.57)*	44 more per 1000 (from 142 fewer to 312 more)*	Moderate
Pain score 2 days after confirmative laparoscopy					
1 study (Nieuwkerk et al., 1998)	Mean 68 (SD 23) n = 34	Mean 79 (SD 21) n = 38	NC	MD 11 lower (21.22 to 0.78 lower)* *P* = NS† (as reported in paper)	Moderate
Pain score 2 weeks after confirmative laparoscopy					
1 study (Nieuwkerk et al., 1998)	Mean 38 (SD 26) n = 35	Mean 51 (SD 33) n = 37	NC	MD 13 lower (26.68 lower to 0.68 higher)* *P* = 0.06†	Moderate
Pain score 16 weeks after confirmative laparoscopy					
1 study (Nieuwkerk et al., 1998)	Mean 15 (SD 21) n = 30	Mean 19 (SD 27) n = 34	NC	MD 4 lower (15.78 lower to 7.78 higher)* *P* = NS†	Moderate
Depression score 2 weeks after confirmative laparoscopy					
1 study (Nieuwkerk et al., 1998)	Mean 44 (SD 11) n = 35	Mean 49 (SD 12) n = 37	NC	MD 5 lower (10.31 lower to 0.31 higher)* *P* = NS	Moderate
Depression score 16 weeks after confirmative laparoscopy					
1 study (Nieuwkerk et al., 1998)	Mean 33 (SD 12) n = 30	Mean 38 (SD 11) n = 34	NC	MD 5 lower (10.67 lower to 0.67 higher)* *P* = NS	Moderate

Number of studies	Number of women		Effect		Quality
	Surgery	Systemic methotrexate	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
Overall quality of life score 2 days after confirmative laparoscopy					
1 study (Nieuwkerk et al., 1998)	Mean 52 (SD 28) n = 34	Mean 67 (SD 20) n = 38	NC	MD 15 lower (26.36 to 3.64 lower)* *P* < 0.05	Moderate
Overall quality of life score 2 weeks after confirmative laparoscopy					
1 study (Nieuwkerk et al., 1998)	Mean 44 (SD 11) n = 35	Mean 49 (SD 12) n = 37	NC	MD 5 lower (10.31 lower to 0.31 higher)* *P* < 0.05‡	Moderate
Overall quality of life score 16 weeks after confirmative laparoscopy					
1 study (Nieuwkerk et al., 1998)	Mean 23 (SD 20) n = 30	Mean 27 (SD 20) n = 34	NC	MD 4 lower (5.82 lower to 13.82 higher)* *P* = NS	Moderate

CI confidence interval, MD mean difference, NC not calculable, NS not significant, *P* probability, RR relative risk, SD standard deviation

* NCC-WCH calculation

† Women treated with methotrexate had consistently more pain than women treated with surgery at each separate time point following laparoscopy. Based on the NCC-WCH calculation the pain difference 2 days following laparoscopy was statistically significant (*P* < 0.03). This was not reported in the paper; however a significant treatment effect was demonstrated between the 2 groups when examined across all time points (2 days, 2 weeks, 4 weeks and 16 weeks; multivariate analysis of variance, *P* = 0.02) with more pain reported by women in the medical group at all time points.

‡ This was the *P* value reported in the paper. However, an NCC-WCH calculation gave a *P* value of 0.07.

Table 8.2 GRADE summary of findings for comparison of surgery with local methotrexate

Number of studies	Number of women		Effect		Quality
	Surgery	Local methotrexate	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
Success rate					
1 meta-analysis of 2 studies (Fernandez et al., 1995; Fernandez, et al. 1998)	66/69 (95.7%)	46/49 (93.9%)	RR 1.02 (0.93 to 1.11)*	19 more per 1000 (from 66 fewer to 103 more)*	High

Number of studies	Number of women		Effect		Quality
	Surgery	Local methotrexate	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
Future pregnancy rate					
1 meta-analysis of 2 studies (Fernandez, et al. 1998; Zilber et al., 1996)	16/28 (57.1%)	19/26 (73.1%)	RR 0.77 (0.53 to 1.12)*	168 fewer per 1000 (from 343 fewer to 88 more)*	Low
Recurrent ectopic pregnancy					
1 meta-analysis of 2 studies (Fernandez et al., 1998; Zilber et al., 1996)	2/38 (5.3%)	0/36 (0%)	RR 2.84 (0.31 to 26.08)*	not calculable (NC)	Moderate
Resolution time (days)					
1 study (Fernandez et al., 1998)	Mean 13.6 (SD 6.1) n = 49	Mean 28.6 (SD 18.6) n = 51	NC	MD 15 lower (20.38 to 9.62 lower)* *P* < 0.0001	Moderate
1 study (Zilber et al., 1996)	Mean 13.9 (SD not reported[NR]) n = 24	Mean 13.7 (SD NR) n = 24	NC	MD 0.2 higher (CI NC) *P* = NS	Moderate
Hospital stay (hours)					
1 meta-analysis of 3 studies (Fernandez et al., 1995; Fernandez et al., 1998; Zilber et al., 1996)	n = 69	n = 71	NC	MD 22 higher (19.3 to 24.7 higher)* *P* < 0.0001	Moderate

Number of studies	Number of women		Effect		Quality
	Surgery	Local methotrexate	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
Need for further intervention					
1 meta-analysis of 2 studies (Fernandez et al., 1998; Zilber et al., 1996)	3/75 (4%)	8/75 (10.7%)	RR 0.38 (0.1 to 1.36)*	66 fewer per 1000 (from 96 fewer to 38 more)*	Moderate

CI confidence interval, MD mean difference, NC not calculable, NR not reported, *P* probability, RR relative risk, SD standard deviation

* NCC-WCH calculation

Table 8.3 GRADE summary of findings for comparison of surgery with systemic and local methotrexate

Number of studies	Number of women		Effect		Quality
	Surgery	Methotrexate (systemic or local)	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
Future spontaneous ongoing or term pregnancy					
1 study (Fernandez et al., 1998)	15/37 (40.5%)†	21/37 (56.8%)†	RR 0.71 (0.44 to 1.16)*	165 fewer per 1000 (from 318 fewer to 91 more)*	Low
Recurrent ectopic pregnancy					
1 study (Fernandez et al., 1998)	5/49 (10.2%)	1/51 (2%)	RR 5.2 (0.63 to 42.96)*	82 more per 1000 (from 7 fewer to 823 more)*	Low

CI confidence interval, *P* probability, RR relative risk

* NCC-WCH calculation

† Excludes those who did not desire a pregnancy. Lost to follow-up included

Evidence statements

Surgery compared with systemic methotrexate

Success rate

One meta-analysis of five studies did not find a statistically significant difference in the success rate in women who received surgical management compared with women who received medical management. The evidence for this finding was of moderate quality.

Future pregnancy rate

One meta-analysis of two studies did not find a statistically significant difference in future pregnancy rate in women who received surgical management compared with women who received medical management with systemic methotrexate. The evidence for this finding was of low quality.

Recurrent ectopic pregnancy

One meta-analysis of two studies did not find a statistically significant difference in recurrent ectopic pregnancy rate in women who received surgical management compared with women who received medical management with systemic methotrexate. The evidence for this finding was of moderate quality.

Resolution time

One meta-analysis of three studies found that resolution time was shorter in women who received surgical management compared with women who received medical management with systemic methotrexate. This finding was statistically significant. The evidence for this finding was of moderate quality.

Hospital stay

One study found that hospital stay was longer in women who received surgical management compared with women who received medical management with systemic methotrexate. This finding was statistically significant. The evidence for this finding was of moderate quality.

Need for further intervention

One meta-analysis of three studies found that the need for further intervention was lower in women who received surgical management compared with women who received medical management with systemic methotrexate. This finding was statistically significant. The evidence for this finding was of high quality.

Tubal preservation

One study did not find a statistically significant difference in tubal preservation in women who received salpingotomy compared with women who received medical management with systemic methotrexate. The evidence for this finding was of high quality.

Homolateral tubal patency

One study did not find a statistically significant difference in homolateral tubal patency in women who received surgical management compared with women who received medical management with systemic methotrexate. The evidence for this finding was of moderate quality.

Pain score 2 days after confirmative laparoscopy

One study did not find a statistically significant difference in pain scores 2 days after confirmative laparoscopy in women who received surgical management compared with women who received medical management with systemic methotrexate. The evidence for this finding was of moderate quality.

Pain score 2 weeks after confirmative laparoscopy

One study did not find a statistically significant difference in pain scores 2 weeks after confirmative laparoscopy in women who received surgical management compared with women who received medical management with systemic methotrexate. The evidence for this finding was of moderate quality.

Pain score 16 weeks after confirmative laparoscopy

One study did not find a statistically significant difference in pain scores 16 weeks after confirmative laparoscopy in women who received surgical management compared with women who received medical management with systemic methotrexate. The evidence for this finding was of moderate quality.

Depression score 2 weeks after confirmative laparoscopy

One study did not find a statistically significant difference in depression scores 2 weeks after confirmative laparoscopy in women who received surgical management compared with women who received medical management with systemic methotrexate. The evidence for this finding was of moderate quality.

Depression score 16 weeks after confirmative laparoscopy

One study did not find a statistically significant difference in depression scores 16 weeks after confirmative laparoscopy in women who received surgical management compared with women who

received medical management with systemic methotrexate. The evidence for this finding was of moderate quality.

Overall quality of life score 2 days after confirmative laparoscopy

One study found that overall quality of life scores 2 days after confirmative laparoscopy were lower in women who received surgical management compared with women who received medical management with systemic methotrexate. This finding was statistically significant and the evidence for this finding was of moderate quality.

Overall quality of life score 2 weeks after confirmative laparoscopy

One study found that overall quality of life scores 2 weeks after confirmative laparoscopy was lower in women who received surgical management compared with women who received medical management with systemic methotrexate. This finding was statistically significant and the evidence for this finding was of moderate quality.

Overall quality of life score 16 weeks after confirmative laparoscopy

One study did not find a statistically significant difference in overall quality of life scores 16 weeks after confirmative laparoscopy in women who received surgical management compared with women who received medical management with systemic methotrexate. The evidence for this finding was of moderate quality.

Surgery compared with local methotrexate

Success rate

One meta-analysis of two studies did not find a statistically significant difference in the success rate in women who received surgical management compared with women who received medical management with local methotrexate. The evidence for this finding was of moderate quality.

Future pregnancy rate

One meta-analysis of two studies did not find a statistically significant difference in future pregnancy rate in women who received surgical management compared with women who received medical management with local methotrexate. The evidence for this finding was of low quality.

Recurrent ectopic pregnancy

One meta-analysis of two studies did not find a statistically significant difference in pregnancy rate in women who received surgical management compared with women who received medical management with local methotrexate. The evidence for this finding was of moderate quality.

Resolution time

One study found that resolution time was shorter in women who received surgical management compared with women who received medical management with local methotrexate. This finding was statistically significant. The evidence for this finding was of moderate quality.

One study did not find a statistically significant difference in resolution time in women who received surgical management compared with women who received medical management with local methotrexate. The evidence for this finding was of moderate quality.

Hospital stay

One meta-analysis of three studies found that hospital stay was longer in women who received surgical management compared with women who received medical management with local methotrexate. This finding was statistically significant and the evidence for this finding was of moderate quality.

Need for further intervention

One meta-analysis of two studies did not find a statistically significant difference in the need for further intervention in women who received surgical management compared with women who received medical management with local methotrexate. The evidence for this finding was of moderate quality.

Surgery compared with methotrexate (systemic and local)

Future spontaneous ongoing or term pregnancy

One study did not find a statistically significant difference in the rate of future spontaneous continuing or term pregnancy in women who received surgical management compared with women who received medical management with methotrexate (systemic or local). The evidence for this finding was of low quality.

Recurrent ectopic pregnancy

One study did not find a statistically significant difference in recurrent ectopic pregnancy in women who received surgical management compared with women who received medical management with methotrexate (systemic or local). The evidence for this finding was of low quality.

Health economics

A new economic model was developed for this guideline to assess the cost effectiveness of different treatment strategies for ectopic pregnancy. The model is described in more detail in Section 10.4.

The model compared the cost effectiveness of three treatment strategies in a population of women diagnosed with an ectopic pregnancy but not requiring urgent surgical intervention:

- laparoscopic salpingectomy
- laparoscopic salpingotomy
- methotrexate.

In the base–case analysis the evaluation took the form of a cost minimisation analysis with the assumption that all women recover and that any differences in morbidity only exist in the very short term. Methotrexate was the cheapest option at £1432 followed by laparoscopic salpingectomy at £1608. Laparoscopic salpingotomy, because of its relatively high re-intervention rate and follow-up costs, was the most expensive strategy at £2205. A probabilistic sensitivity analysis of one million Monte Carlo simulations found that methotrexate was cheapest in 99.65% of the simulations with a 0.35% probability that laparoscopic salpingectomy was cheapest.

A number of one-way sensitivity analyses suggested that the ordinal ranking of strategies in terms of their cost was not affected by large changes in parameter values. A further sensitivity analysis relaxed the assumption about equivalence in treatment outcomes and estimated an incremental gain in quality adjusted life years (QALYs) for the surgical alternatives when compared to methotrexate. This found that laparoscopic salpingotomy was dominated by laparoscopic salpingectomy (a higher cost than laparoscopic salpingectomy with no QALY gain). The incremental cost effectiveness ratio of laparoscopic salpingectomy against methotrexate was calculated to be almost £84,000 per QALY which would not normally be considered cost effective using advisory willingness to pay thresholds suggested by NICE (NICE, 2009).

Evidence to recommendations

Relative value placed on the outcomes considered

The guideline development group (GDG) identified future reproductive outcomes as very important from the woman's perspective.

The group also felt that outcomes such as the chances of treatment success, the likelihood of needing another intervention and the length of time required for follow-up would be important considerations for women, as well as having cost implications.

Women's experiences of care and psychological outcomes were identified as being important. However, evidence was only found for psychological outcomes and was not available for women's experience of care. The effects demonstrated were short term, with no significant differences shown after 2 weeks in most cases and 4 months in the remainder.

Consideration of clinical benefits and harms

The evidence in this review showed that women undergoing medical treatment required a longer period of recovery and follow-up than women who had laparoscopic surgery. In some women, the

time to resolution was up to 6–7 weeks. Medical treatment was also associated with a higher need for further intervention, which could include surgery or an additional dose of methotrexate. In addition, the GDG recognised that some women may have contraindications to surgery or have a personal desire to avoid a surgical procedure; therefore medical treatment would be appropriate in such circumstances. For women choosing to have methotrexate treatment, the GDG agreed that systemic administration was preferable, as it is easier to administer, less invasive and in line with current practice.

The GDG noted that the studies considered in this review had specific inclusion criteria for women with an ectopic pregnancy who were felt to be at low risk for tubal rupture. Thus they felt that for women who fell outside of these criteria, methotrexate treatment was not an appropriate choice of treatment. Evidence from Sowter et al. (2001b) showed that the chance of treatment failure was increased in women with higher initial hCG levels. At an initial hCG below 1000 international units per litre (IU/l), women had a 12% chance of requiring further treatment, but at an hCG over 1500 IU/l this rose to 70%. Given this finding, the group recommended that methotrexate only be offered as a first-line treatment for women with an hCG of less than 1500 IU/l (and with an ectopic pregnancy with an adnexal mass smaller than 35 mm).

The evidence from Sowter et al. (2001b) also showed that at an hCG level below 5000 IU/l, women had an 85% chance of successful treatment with either a first or second dose of methotrexate administration. Given this, they felt that for women with hCG levels between 1500 IU/l and 5000 IU/l, it would still be appropriate to offer medical management, but that surgery should also be offered as a choice, given that women in this group were more likely to require further interventions following medical management.

The GDG members agreed that for women with an hCG level greater than 5000 IU/l, with an adnexal mass greater than 35 mm or with an ectopic pregnancy with a fetal heartbeat visible on ultrasound, surgery should be offered as a first-line treatment, as they were aware of studies that showed an increased risk of rupture for all of these women.

The GDG was aware of cases of women who had experienced a failure of medical treatment and then re-presented later with tubal rupture or other severe symptoms: it was felt, therefore, that follow-up should be mandatory after any medical treatment and that women needed access to 24 hour emergency care. Using their clinical experience, the GDG members agreed that women should have two follow-up appointments in the first week following treatment, and then one appointment per week until a negative pregnancy test is performed. This follow-up protocol would ensure that women in whom medical treatment was not effective would be identified early, before their condition became serious. The GDG agreed that an hCG level which plateaued or rose following medical management should prompt a reassessment of the woman's treatment. Given the potential risks if medical management fails, the group highlighted the importance of this follow-up protocol, and decided that if any difficulties in follow-up were anticipated, women should be advised to have surgery as a first-line treatment.

Consideration of health benefits and resource uses

The GDG noted that, while surgery has the advantage of a shorter resolution time and a reduced need for further intervention, medical management is associated with a shorter stay in hospital. Therefore, the group decided that this area was appropriate for a health economics analysis. Using a cost minimisation approach, the model determined that methotrexate was the preferred treatment approach. Taking this finding into account, but also the potential risks inherent in tubal rupture, the GDG decided to recommend methotrexate as the first-line treatment for women meeting the criteria discussed above; namely those with an unruptured ectopic pregnancy which is smaller than 35 mm with no visible heartbeat and who have an hCG level less than 1500 IU/l.

Quality of evidence

The evidence was derived from randomised controlled trials and ranged in quality from high to low for the outcomes considered. The GDG felt that it was disappointing that studies had not reported more information about outcomes among women with different initial hCG levels and size of ectopic pregnancy. Four studies only included ectopic pregnancies below a certain size (ranging from 35 mm to 40 mm) and only two discussed the effect of hCG values on outcomes.

Information giving and emotional support

The GDG emphasised the importance of providing good quality information to women who are in a clinically stable condition, including accurate information on local management options and appropriate counselling regarding the proposed procedure. The GDG was aware that, for some women, methotrexate might be a clinically appropriate treatment option but would not be acceptable to the woman personally. In these circumstances, the GDG felt that the woman's choice should be supported. For all women with an ectopic pregnancy, the GDG thought that it was important that women were given sufficient information about what to expect during the course of their treatment and recovery. In particular, GDG members felt women should be made aware of the amount of pain and/or bleeding that might be expected, so that women knew that it was a normal part of the treatment process.

It was recognised that ongoing psychological support should be offered from the diagnostic period and during discussions regarding treatment options and the relevant outcomes and into the post-operative period, including information regarding resuming usual activity and details of patient groups to contact for support. The information needs to cover details regarding both physical and emotional recovery.

Other considerations

The GDG noted that these studies looked specifically at women with unruptured ectopic pregnancies and therefore these women were not in extreme pain. The GDG did not feel that women in significant pain were suitable for medical management and therefore they should be offered surgery.

The group also wished to highlight that medical management should only be undertaken once it was confirmed on an ultrasound scan that there was no intrauterine pregnancy.

Recommendations

Number	Recommendation
67	Inform women who have had an ectopic pregnancy that they can self-refer to an early pregnancy assessment service in future pregnancies if they have any early concerns.
68	Give all women with an ectopic pregnancy oral and written information about: • how they can contact a healthcare professional for post-operative advice if needed, and who this will be **and** • where and when to get help in an emergency.[*]
69	Offer systemic methotrexate[†] as a first-line treatment to women who are able to return for follow-up and who have all of the following: • no significant pain • an unruptured ectopic pregnancy with an adnexal mass smaller than 35 mm with no visible heartbeat • a serum hCG level less than 1500 IU/litre • no intrauterine pregnancy (as confirmed on an ultrasound scan). Offer surgery where treatment with methotrexate is not acceptable to the woman.

[*] See also recommendation 3 for details of further information that should be provided.
[†] Although this use is common in UK clinical practice, at the time of publication (December 2012), methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

70 Offer surgery as a first-line treatment to women who are unable to return for follow-up after methotrexate treatment or who have any of the following:

- an ectopic pregnancy and significant pain
- an ectopic pregnancy with an adnexal mass of 35 mm or larger
- an ectopic pregnancy with a fetal heartbeat visible on an ultrasound scan
- an ectopic pregnancy and a serum hCG level of 5000 IU/litre or more.

71 Offer the choice of either methotrexate* or surgical management to women with an ectopic pregnancy who have a serum hCG level of at least 1500 IU/litre and less than 5000 IU/litre, who are able to return for follow-up and who meet all of the following criteria:

- no significant pain
- an unruptured ectopic pregnancy with an adnexal mass smaller than 35 mm with no visible heartbeat
- no intrauterine pregnancy (as confirmed on an ultrasound scan).

Advise women who choose methotrexate that their chance of needing further intervention is increased and they may need to be urgently admitted if their condition deteriorates.

72 For women with ectopic pregnancy who have had methotrexate, take 2 serum hCG measurements in the first week (days 4 and 7) after treatment and then 1 serum hCG measurement per week until a negative result is obtained. If hCG levels plateau or rise, reassess the woman's condition for further treatment.

Number	Research recommendation
RR 8	In women with ectopic pregnancy, does the type of intervention (laparoscopy or medical management) impact on women's experience, including psychological and emotional outcomes? **Why this is important** Currently there is no evidence exploring the psychological impact of the different treatments for ectopic pregnancy. However, the emotional impact of the condition can be significant, in some circumstances leading to post-traumatic stress disorder. A qualitative comparative study should be carried out to assess how this impact can be reduced. This would help to maximise women's emotional recovery in the short and long term, enable women and clinicians to decide the optimum treatment method and identify what support is needed for women during and after the process. It could also reduce the cost to the NHS of providing long-term counselling for affected women.

8.3 Laparotomy compared with laparoscopy for ectopic pregnancy

Review question

What is the effectiveness of laparotomy compared with laparoscopic techniques for managing tubal ectopic pregnancy?

* Although this use is common in UK clinical practice, at the time of publication (December 2012), methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Introduction

Many women with ectopic pregnancies are managed surgically using either laparoscopy and/or laparotomy. There is, however, some variation in practice in the way women with an ectopic pregnancy with similar clinical characteristics are managed. The reasons for this variability are multifactorial, but include differences in surgical training, availability of equipment and surgeon preference. This review aims to consider the evidence comparing laparoscopy and laparotomy to investigate which approach is more effective.

Description of included studies

Fourteen studies were included in this review (Baumann et al., 1991; Chatwani et al., 1992; El Tabbakh & El Sayes, 2002; Federici et al., 1994; Lo et al., 1999; Lundorff et al., 1991; Lundorff et al., 1992; Lundorff, 1997; Mehra et al., 1998; Mol et al., 1997; Murphy et al., 1992; Rizzuto et al., 2008; Vermesh et al., 1989; Vermesh & Presser, 1992).

Five of the included studies reported the initial outcomes and follow-up data of two randomised controlled trials conducted in Sweden (Lundorff et al., 1991; Lundorff et al., 1992; Lundorff, 1997) and the USA (Vermesh et al., 1989; Vermesh & Presser, 1992). Nine of the included studies were prospective comparative observational studies conducted in the UK (Baumann et al., 1991; Rizzuto et al., 2008), the USA (Chatwani et al., 1992; Murphy et al., 1992), Italy (Federici et al., 1994), the Netherlands (Mol et al., 1997), Hong Kong (Lo et al., 1999), Kuwait (El Tabbakh & El Sayes, 2002) and India (Mehra et al., 1998).

All studies compared laparotomy with laparoscopy for the management of tubal ectopic pregnancies and reported at least one outcome of interest. However, one observational study also included seven women with non-tubal ectopic pregnancies (Baumann et al., 1991) and another had a specific study population of women with a ruptured ectopic pregnancy and significant haemoperitoneum (Rizzuto et al., 2008) (The findings from this study are reported separately at the end of the evidence profile below).

Evidence profile

Table 8.4 GRADE summary of findings for comparison of laparotomy with laparoscopy for the management of tubal ectopic pregnancy

Number of studies	**Number of women or mean (SD)**		**Effect**		**Quality**
	Laparotomy	**Laparoscopy**	**Relative** (95% CI)	**Absolute** (95% CI) and *P*-value if reported	
Subsequent viable intrauterine pregnancy					
1 meta-analysis of 2 studies (Lundorff et al., 1992; Vermesh & Presser, 1992)	27/66 (40.9%)	26/61 (42.6%)	RR 0.96 (0.64 to 1.45)	17 fewer per 1000 (from 155 fewer to 191 more)	Low
Subsequent intrauterine pregnancy					

Number of studies	Number of women or mean (SD)		Effect		Quality
	Laparotomy	Laparoscopy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 meta-analysis of 2 studies (Lundorff et al., 1992; Vermesh & Presser, 1992)	35/66 (53%)	35/61 (57.4%)	RR 0.92 (0.68 to 1.26)	43 fewer per 1000 (from 186 fewer to 152 more)	Low
1 study (Chatwani et al., 1992)	12/35 (34.3%)	9/33 (27.3%)	RR 1.26 (0.61 to 2.59)	70 more per 1000 (from 106 fewer to 433 more)	Very low
1 study (Mehra et al., 1998)	11/25 (44%)	46/86 (53.5%)	RR 0.82 (0.51 to 1.33)	95 fewer per 1000 (from 264 fewer to 179 more)	Very low
1 study (Murphy et al., 1992)	5/10 (50%)	7/8 (87.5%)	RR 0.57 (0.29 to 1.12)	375 fewer per 1000 (from 620 fewer to 105 more)	Very low
Recurrent ectopic pregnancy					
1 meta-analysis of 2 studies (Lundorff et al., 1992; Vermesh & Presser, 1992)	9/66 (13.6%)	5/61 (8.2%)	RR 1.66 (0.59 to 4.69)	54 more per 1000 (from 34 fewer to 302 more)	Low
1 study (Mehra et al., 1998)	1/25 (4%)	4/86 (4.7%)	RR 0.86 (0.10 to 7.35)	7 fewer per 1000 (from 42 fewer to 295 more)	Very low
1 study (Murphy et al., 1992)	2/10 (20%)	0/8 (0%)	RR 4.09 (0.22 to 74.78)	200 more per 1000 (from 155 fewer to 510 more)	Very low
Length of hospital stay (days)					

Number of studies	Number of women or mean (SD)		Effect		Quality
	Laparotomy	Laparoscopy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 meta-analysis of 2 studies (Lundorff et al., 1991; Vermesh et al., 1989)	Means 5.4 and 3.3 (SD 1.5 and 1.1) n = 87	Means 2.2 and 1.4 (SD 0.69 and 0.55) n = 78	not calculable (NC)	MD 2.55 higher (1.28 to 3.83 higher)	Moderate
1 study (Baumann et al., 1991)	Mean 5.2 (SD 1.4) n = 27	Mean 1.7 (SD 1.2) n = 65	NC	MD 3.5 higher (3.05 to 3.95 higher) *P* < 0.001	Very low
1 study (Chatwani et al., 1992)	Mean 4.70 (SD not reported (NR)) n = 61	Mean 1.27 (SD NR) n = 56	NC	MD 3.43 higher (confidence intervals NC) *P* < 0.05	Very low
1 study (El Tabbakh & El Sayes, 2002)	Mean 5.25 (SD 3.16) n = 23	Mean 2.14 (SD 1.81) n = 184	NC	MD 3.11 higher (2.24 to 3.98 higher)	Very low
1 study (Federici et al., 1994)	Mean 7.3 (SD 0.9) n = 7	Mean 2.8 (SD 0.7) n = 23	NC	MD 4.5 higher (3.84 to 5.16 higher) *P* < 0.001	Very low
1 study (Lo et al., 1999)	Mean 5.3 (SD NR) n = 164	Mean 2.65 (SD NR) n = 371	NC	MD 2.65 higher (confidence intervals NC) *P* = 0.0001	Very low
1 study (Mehra et al., 1998)	Mean 3.52 (SD 0.51)* n = 25	Mean 1.48 (SD 0.59)* n = 86	NC	MD 2.04 higher (1.80 to 2.27 higher) *P* < 0.05	Very low
1 study (Mol et al., 1997)	Mean 8.89 (SD 2.33) n = 140	Mean 2.93 (SD 1.08) n = 115	NC	MD 5.96 higher (5.49 to 6.43 higher)	Very low

Number of studies	Number of women or mean (SD)		Effect		Quality
	Laparotomy	Laparoscopy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 study (Murphy et al., 1992)	Mean 26.42 (SD 0.71)* n = 37	Mean 1.08 (SD 0.79)* n = 26	NC	MD 25.34 higher (24.96 to 25.72 higher) *P* < 0.005	Very low
Need for further surgery					
1 meta-analysis of 2 studies (Lundorff et al., 1991; Vermesh et al., 1989)	3/87 (3.4%)	8/78 (10.3%)	RR 0.34 (0.09 to 1.22)	68 fewer per 1000 (from 93 fewer to 23 more)	Low
1 study (Baumann et al., 1991)	0/27 (0%)	2/65 (3.1%)	RR 0.47 (0.02 to 9.51)	16 fewer per 1000 (from 30 fewer to 262 more)	Very low
1 study (Federici et al., 1994)	0/7 (0%)	0/23 (0%)	NC	NC	Very low
1 study (Lo et al., 1999)	1/164 (0.61%)	3/371 (0.81%)	RR 0.75 (0.08 to 7.20)	2 fewer per 1000 (from 7 fewer to 50 more)	Very low
1 study (Murphy et al., 1992)	0/37 (0%)	2/26 (7.7%)	RR 0.14 (0.01 to 2.84)	66 fewer per 1000 (from 76 fewer to 142 more)	Very low
Need for methotrexate					
1 study (Lundorff, 1997)	0/57 (0%)	2/48 (4.2%)	RR 0.17 (0.01 to 3.44)	35 fewer per 1000 (from 41 fewer to 102 more)	Low
1 study (Murphy et al., 1992)	0/37 (0%)	1/26 (3.8%)	RR 0.24 (0.01 to 5.6)	29 fewer per 1000 (from 38 fewer to 177 more)	Very low
Need for surgery, methotrexate or expectant management					

Number of studies	Number of women or mean (SD)		Effect		Quality
	Laparotomy	Laparoscopy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 study (Mol et al., 1997)	1/140 (0.71%)	18/115 (15.7%)	RR 0.05 (0.006 to 0.34)	149 fewer per 1000 (from 104 fewer to 156 fewer)	Very low
Readmission to hospital					
1 study (Chatwani et al., 1992)	1/61 (1.6%)	1/56 (1.8%)	RR 0.92 (0.06 to 14.33)	1 fewer per 1000 (from 17 fewer to 238 more)	Very low
1 study (Lo et al., 1999)	2/164 (1.2%)	8/371 (2.2%)	RR 0.57 (0.12 to 2.63)	9 fewer per 1000 (from 19 fewer to 35 more)	Very low
Abdominal pain					
1 study (Lundorff, 1997)	3/57 (5.3%)	1/48 (2.1%)	RR 2.53 (0.27 to 23.50)	32 more per 1000 (from 15 fewer to 469 more)	Low
Thromboembolic disease					
1 study (Mol et al., 1997)	1/140 (0.71%)	0/115 (0%)	RR 2.47 (0.1 to 60.02)	7 more per 1000 (from 26 fewer to 39 more)	Very low
Respiratory morbidity					
1 study (Mol et al., 1997)	2/140 (1.4%)	0/115 (0%)	RR 4.11 (0.2 to 84.83)	14 more per 1000 (from 20 fewer to 51 more)	Very low
1 study (Murphy et al., 1992)	1/37 (2.7%)	0/26 (0%)	RR 2.13 (0.09 to 50.36)	27 more per 1000 (from 104 fewer to 138 more)	Very low
Need for a blood transfusion					
1 study (El Tabbakh & El Sayes, 2002)	6/23 (26.1%)	13/184 (7.1%)	RR 3.69 (1.56 to 8.77)	190 more per 1000 (from 40 more to 549 more)	Very low

Number of studies	Number of women or mean (SD)		Effect		Quality
	Laparotomy	Laparoscopy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 study (Mol et al., 1997)	10/140 (7.1%)	1/115 (0.87%)	RR 8.21 (1.07 to 63.22)	63 more per 1000 (from 1 more to 541 more)	Very low
1 study (Murphy et al., 1992)	2/37 (5.4%)	1/26 (3.8%)	RR 1.41 (0.13 to 14.70)	16 more per 1000 (from 33 fewer to 527 more)	Very low
Intraoperative blood loss (millilitres)					
1 study (Vermesh et al., 1989)	Mean 195 (SD 131.45) n = 30	Mean 79 (SD 98.59) n = 30	NC	MD 116 higher (55.95 to 176.05 higher) *P* < 0.001	Moderate
1 study (Baumann et al., 1991)	Mean 269.0 (SD 258.90) n = 27	Mean 206.1 (SD 235.0) n = 65	NC	MD 63 higher (47.53 lower to 173.33 higher) NS (*P* value NR)	Very low
1 study (El Tabbakh & El Sayes, 2002)	Mean 270.7 (SD 138.4) n = 23	Mean 79.6 (SD 96.7) n = 184	NC	MD 191.08 higher (146.61 to 235.55 higher) *P* < 0.0001	Very low
1 study (Lo et al., 1999)	Mean 110.4 (SD NR) n = 164	Mean 129.2 (SD NR) n = 371	NC	MD 18.8 lower (confidence intervals NC) NS (*P* value NR)	Very low
1 study (Mehra et al., 1998)	Mean 150 (SD 44.9) n = 25	Mean 140 (SD 51.9) n = 86	NC	MD 10 higher (12.72 lower to 32.72 higher) NS (*P* value NR)	Very low
1 study (Murphy et al., 1992)	Mean 115 (SD 115) n = 36	Mean 62 (SD 61) n = 26	NC	MD 53 higher (3.45 to 102.55 higher) *P* < 0.001	Very low
Length of hospital stay (days)[†]					

Number of studies	Number of women or mean (SD)		Effect		Quality
	Laparotomy	Laparoscopy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 study (Rizzuto et al., 2008)	All patients discharged after 3–4 days n = 5	All patients discharged after 1–2 days n = 32	NC	NC	Very low
Need for further surgery†					
1 study (Rizzuto et al., 2008)	0/5 (0%)	0/32 (0%)	NC	NC	Very low

CI confidence interval, MD mean difference, NC not calculable, NR not reported, NS not significant, *P* probability, RR relative risk, SD standard deviation

* Calculated by the NCC-WCH technical team from data reported in hours in the study

† The results of Rizzuto et al., 2008 are reported separately due to the specific nature of the study population (women with a ruptured ectopic pregnancy and significant haemoperitoneum)

Evidence statements

Subsequent viable intrauterine pregnancy

One meta-analysis of two studies did not find a statistically significant difference in the incidence of subsequent viable intrauterine pregnancy for women who received a laparotomy compared with women who received a laparoscopy. The evidence for this outcome was of low quality.

Subsequent intrauterine pregnancy

Three studies and one meta-analysis of two studies did not find a statistically significant difference in the incidence of subsequent intrauterine pregnancy for women who received a laparotomy compared with women who received a laparoscopy. The evidence for this outcome was of very low and quality.

Recurrent ectopic pregnancy

Two studies and one meta-analysis of two studies did not find a statistically significant difference in the incidence of recurrent ectopic pregnancy for women who received a laparotomy compared with women who received a laparoscopy. The evidence for this outcome was of very low and low quality.

Length of hospital stay

Eight studies and one meta-analysis of two studies found that the length of hospital stay was longer in women who received a laparotomy compared with women who received a laparoscopy. This finding was statistically significant. The evidence for this finding was of moderate quality in the meta-analysis of two studies and very low in the other studies.

Need for further surgery

Four studies and one meta-analysis of two studies did not find a statistically significant difference in the need for further surgery for women who received a laparotomy compared with women who received a laparoscopy. The evidence for this outcome was of very low and low quality.

Need for methotrexate

Two studies did not find a statistically significant difference in the need for methotrexate for women who received a laparotomy compared with women who received a laparoscopy. The evidence for this outcome was of low and very low quality.

Need for surgery, methotrexate or expectant management

One study found that the need for surgery, methotrexate or expectant management was lower in women who received a laparotomy compared with women who received a laparoscopy. This finding was statistically significant and the evidence for this finding was of very low quality.

Readmission to hospital

Two studies did not find a statistically significant difference in the need for readmission to hospital for women who received a laparotomy compared with women who received a laparoscopy. The evidence for this outcome was of very low quality.

Abdominal pain

One study did not find a statistically significant difference in the incidence of abdominal pain for women who received a laparotomy compared with women who received a laparoscopy. The evidence for this outcome was of low quality.

Thromboembolic disease

One study did not find a statistically significant difference in the incidence of thromboembolic disease for women who received a laparotomy compared with women who received a laparoscopy. The evidence for this outcome was of very low quality.

Respiratory morbidity

Two studies did not find a statistically significant difference in the incidence of respiratory morbidity for women who received a laparotomy compared with women who received a laparoscopy. The evidence for this outcome was of very low quality.

Need for a blood transfusion

Two studies found that the need for a blood transfusion was higher in women who received a laparotomy compared with women who received a laparoscopy. This finding was statistically significant and the evidence for this finding was of very low quality in both studies. One further study did not find a statistically significant difference in the need for a blood transfusion between the two groups. The evidence for this finding was of very low quality.

Intraoperative blood loss

Three studies found that intraoperative blood loss was higher in women who received a laparotomy compared with women who received a laparoscopy. This finding was statistically significant. The evidence for this finding was moderate in one study and very low in the others. Three further studies did not find a statistically significant difference in intraoperative blood loss between the two groups. The evidence for this finding was of very low quality.

One study that only included women with tubal rupture and significant haemoperitoneum reported length of hospital stay in a manner that did not allow assessment of statistical significance. In the same study there were no events in either arm for the outcome of need for further surgery. The evidence for these outcomes was of very low quality.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG identified future reproductive outcomes as the most important outcomes from the woman's perspective.

Length of hospital stay was also considered very important, both from a woman's point of view and in terms of cost to the NHS.

Other outcomes relating to women's experience of care were also seen as important, particularly pain experienced and incidence of complications requiring further care, such as the need for blood transfusion, further surgery and readmission to hospital.

Although reported by many studies, the GDG agreed that intraoperative blood loss is not a useful outcome as it is very difficult to measure/assess accurately. More importantly, even in those studies which reported statistically significant differences in blood loss, the GDG did not consider these differences to be clinically significant.

Consideration of clinical benefits and harms

The evidence suggested there is little difference in clinically significant outcomes between laparotomy and laparoscopy. Laparoscopy is superior in terms of length of hospital stay, with no evidence of any harm compared to laparotomy, including no difference in need for further treatment (either surgical or medical). Two studies showed that fewer women required a blood transfusion following laparoscopy compared with laparotomy (although a third study found no difference between the two treatments) While it was noted that one study (Mol et al., 1997) showed fewer incidences of methotrexate administration, expectant management or further surgery with laparotomy, the GDG believed that this finding was due to the fact that most (84%) of the women in the laparotomy arm received excision surgery to remove the tube and ectopic pregnancy (reported in the paper as 'radical' surgery), while the majority (66%) in the laparoscopy arm received conservative surgery.

The group did not feel able to make a strong recommendation due to the poor level of evidence regarding clinical benefits.

Consideration of health benefits and resource uses

The evidence suggested that there is no difference in terms of health benefits between laparoscopy and laparotomy, including the key outcome of subsequent successful pregnancy.

The length of hospital stay is shorter following laparoscopy compared with laparotomy, thus this aspect of care, when combined with the reduced likelihood of a blood transfusion, would use fewer resources. The GDG noted that laparoscopy is associated with the use of expensive equipment which is prone to malfunction if not well maintained and/or renewed regularly. In addition, hospital units that employ disposable equipment will consume limited resources. However, on balance, the group felt that the capital cost of the laparoscopic equipment, when spread across the number of procedures that would be undertaken, would be outweighed by the saving in the number of hospital in-patient bed days. Therefore, the GDG felt it appropriate to recommend laparoscopy as the first-line technique for most surgeries, although it was aware that the availability and presence of competent trained surgical personnel on a 24/7 basis may limit the minimally invasive option of treatment.

Quality of evidence

The quality of the evidence was moderate to very low. Some of the studies included few women so it was difficult to draw any conclusions as the number of adverse events was very low in the study groups. Thus the GDG was unable to draw conclusions about the incidence of thromboembolic complications, need for blood transfusion, abdominal pain or respiratory complications. This was unfortunate, as all of these were considered important outcomes which would impact on women's experience of care as well as resource use.

It is regrettable that there was no evidence about emotional outcomes as these are also considered important.

Information giving and psychological support

While the GDG had prioritised women's experience of care as a key outcome for this review, no data was reported for this. The GDG recognised that the shorter hospital stay associated with laparoscopic surgery was likely to be valued by most women and that being separated from their family and friends for a shorter time was likely to be beneficial in terms of emotional support and reduce the negative psychological impact of surgery.

Other considerations

The GDG was aware that there may be some practitioners who are not competent to perform laparoscopy, particularly in more complex cases. In addition, some surgeons are not comfortable with laparoscopic surgery where the woman is collapsed or haemodynamically unstable.

An additional problem can arise where the laparoscopic equipment is unavailable or not working. The GDG members recognised from their clinical experience that equipment failures may lead to unnecessarily lengthy operations. The decision as to which intervention is most appropriate therefore depends on the relative expertise of the doctor, the equipment available, the complexity of the surgery required and the condition of the woman.

The GDG felt that each unit should have at least some practitioners who are competent to perform laparoscopy. In order to achieve this, further investment in training and equipment may be necessary.

Recommendations

Number	Recommendation
73	When surgical treatment is indicated for women with an ectopic pregnancy, it should be performed laparoscopically whenever possible, taking into account the condition of the woman and the complexity of the surgical procedure.
74	Surgeons providing care to women with ectopic pregnancy should be competent to perform laparoscopic surgery.
75	Commissioners and managers should ensure that equipment for laparoscopic surgery is available.

8.4 Salpingectomy compared with salpingotomy for ectopic pregnancy

Review question

What is the effectiveness of salpingectomy compared with salpingotomy in improving outcomes in women with tubal ectopic pregnancy?

Introduction

Surgical treatment of ectopic pregnancy can be conservative (preserving the Fallopian tube) or radical (removing the Fallopian tube). Salpingotomy is surgical incision of a Fallopian tube to remove the ectopic pregnancy. Salpingostomy is the surgical formation of an opening in the Fallopian tube where the fimbrial end has been closed by infection or chronic inflammation. In the literature there appears to be a blurring of this definition, with authors apparently using the terms interchangeably and sometimes referring to salpingotomy and salpingostomy within the same paper. The term 'salpingotomy' will be used in this review to cover both salpingotomy and salpingostomy.

Salpingotomy is a conservative approach which preserves the tube but bears the risk of incomplete removal of the pregnancy tissue (persistent trophoblast). Salpingectomy is a radical approach which bears no risk of persistent trophoblast but leaves only one tube for reproductive capacity. It is unknown which type of operation is better, especially for future fertility. The risk of additional treatment in the case of persistent trophoblast after salpingotomy may be acceptable if compensated for by retention of the Fallopian tube and a small rise in intrauterine pregnancy rate.

Description of included studies

Twenty-one studies were included in this review (Bangsgaard et al., 2003; Becker et al., 2011; Bouyer et al., 2000; Colacurci et al., 1998; DeCherney & Kase, 1979; dela Cruz & Cumming, 1997; Giambelli et al., 1996; Gruft et al., 1994; Kuroda et al., 2009; Langebrekke et al., 1993; Mecke et al., 1989; Mol et al., 1997; Mol et al., 1998; Ory et al., 1993; Parker et al., 1994; Sherman et al., 1982; Silva et al., 1993; Tahseen & Wyldes, 2003; Tulandi & Guralnick, 1991; Turan, 2011; Tuomivaara & Kauppila, 1988).

There were no relevant randomised controlled trials identified for this review question. Four of the included studies were prospective observational studies (Becker et al., 2011; Bouyer et al., 2000; Mol et al., 1997; Silva et al., 1993) and the remainder were retrospective observational studies. The studies were conducted in the UK (Tahseen & Wyldes, 2003), Denmark (Bangsgaard et al., 2003), Finland (Tuomivaara & Kauppila, 1988), France (Bouyer et al., 2000), Germany (Becker et al., 2011; Mecke et al., 1989), Italy (Colacurci et al., 1998; Giambelli et al., 1996; Gruft et al., 1994), the Netherlands (Mol et al., 1997; Mol et al., 1998), Norway (Langebrekke et al., 1993), Australia (Parker et al., 1994), the USA (DeCherney & Kase, 1979; Ory et al., 1993; Silva et al., 1993), Canada (dela Cruz & Cumming, 1997; Tulandi & Guralnick, 1991), Turkey (Turan, 2011), Israel (Sherman et al., 1982) and Japan (Kuroda et al., 2009).

The majority of the included studies compared salpingectomy with salpingotomy for the management of tubal ectopic pregnancy: however, in four of the studies some of the participants received a different type of radical or conservative surgery, such as a salpingo-oophorectomy or milking of the tube (DeCherney & Kase, 1979; Mol et al., 1997; Sherman et al., 1982; Tuomivaara & Kauppila, 1988).

Evidence profile

Table 8.5 GRADE summary of findings for comparison of salpingectomy with salpingotomy for the management of tubal ectopic pregnancy

Number of studies	**Number of women or cumulative probability**		**Effect**		**Quality**
	Salpingectomy	**Salpingotomy**	**Relative** (95% CI)	**Absolute** (95% CI) and *P*-value if reported	
Subsequent live birth or full-term birth					
1 study (Silva et al., 1993)	10/26 (38.5%)	19/60 (31.7%)	RR 1.21 (0.66 to 2.24)	67 more per 1000 (from 108 fewer to 393 more)	Very low
1 study (dela Cruz & Cumming, 1997)	21/56 (37.5%)	16/34 (47.1%)	RR 0.8 (0.49 to 1.3)	94 fewer per 1000 (from 240 fewer to 141 more)	Very low
1 study (Mol et al., 1998)	18/79 (22.8%)	22/56 (39.3%)	RR 0.58 (0.34 to 0.98)	165 fewer per 1000 (from 8 fewer to 259 fewer)	Very low
1 study (Langebrekke et al., 1993)	18/40 (45%)	38/58 (65.5%)	RR 0.69 (0.46 to 1.01)	203 fewer per 1000 (from 354 fewer to 7 more)	Very low
1 study (Gruft et al., 1994)	23/71 (32.4%)	12/44 (27.3%)	RR 1.19 (0.66 to 2.14)	52 more per 1000 (from 93 fewer to 311 more)	Very low
1 study (Bangsgaard et al., 2003)	21/68 (30.9%)	88/208 (42.3%)	RR 0.73 (0.49 to 1.08)	114 fewer per 1000 (from 216 fewer to 34 more)	Very low
1 study (Ory et al., 1993)	29/50 (58%)	17/33 (51.5%)	RR 1.13 (0.75 to 1.69)	67 more per 1000 (from 129 fewer to 355 more)	Very low

Number of studies	Number of women or cumulative probability		Effect		Quality
	Salpingectomy	Salpingotomy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 study (DeCherney & Kase, 1979)	21/50 (42%)	19/48 (39.6%)	RR 1.06 (0.66 to 1.71)	24 more per 1000 (from 135 fewer to 281 more)	Very low
Subsequent intrauterine pregnancy					
1 study (Bouyer et al., 2000)	18-month cumulative rate (95% CI): 57% (44 to 70) n = 100	18-month cumulative rate (95% CI): 73% (65 to 80) n = 166	Hazard ratio 0.56 (0.39 to 0.81)*	160 fewer per 1000 (confidence interval not calculable [NC])	Very low
1 study (Becker et al., 2011)	25/51 (49%)	122/145 (84.1%)	RR 0.58 (0.44 to 0.78)*	353 fewer per 1000 (from 185 fewer to 471 fewer)	Very low
1 study (Silva et al., 1993)	14/26 (53.8%)	36/60 (60%)	RR 0.9 (0.59 to 1.35)	60 fewer per 1000 (from 246 fewer to 210 more)	Very low
1 study (Langebrekke et al., 1993)	19/40 (47.5%)	40/58 (69%)	RR 0.69 (0.48 to 1)	214 fewer per 1000 (from 359 fewer to 0 more)	Very low
1 study (dela Cruz & Cumming, 1997)	27/56 (48.2%)	23/34 (67.6%)	RR 0.71 (0.5 to 1.02)	196 fewer per 1000 (from 338 fewer to 14 more)	Very low
1 study (Mol et al., 1998)	24/79 (30.4%)	30/56 (53.6%)	RR 0.57 (0.38 to 0.86)*	230 fewer per 1000 (from 75 fewer to 332 fewer)	Very low
1 study (Bangsgaard et al., 2003)	39/68 (57.4%)	161/208 (77.4%)	RR 0.74 (0.6 to 0.92)	201 fewer per 1000 (from 62 fewer to 310 fewer)	Very low
1 study (Turan, 2011)	33/55 (60%)	23/35 (65.7%)	RR 0.91 (0.66 to 1.26)	59 fewer per 1000 (from 223 fewer to 171 more)	Very low

Number of studies	Number of women or cumulative probability		Effect		Quality
	Salpingectomy	Salpingotomy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 study (Tuomivaara & Kauppila, 1988)	170/237 (71.7%)	59/86 (68.6%)	RR 1.05 (0.89 to 1.23)	34 more per 1000 (from 75 fewer to 158 more)	Very low
1 study (Sherman et al., 1982)	75/104 (72.1%)	39/47 (83%)	RR 0.87 (0.73 to 1.04)*	108 fewer per 1000 (from 224 fewer to 33 more)	Very low
1 study (Giambelli et al., 1996)	6-month cumulative rate: 62.5% (denominator NR)	6-month cumulative rate: 53.8% (denominator NR)	NC	87 more per 1000 (confidence interval NC) NS (*P*-value NR)	Very low
1 study (Tulandi & Guralnick, 1991)	24-month cumulative probability: 26% n = 24	24-month cumulative probability: 47% n = 34	NC	210 fewer per 1000 (confidence interval NC) *P* < 0.05	Very low
1 study (Tahseen & Wyldes, 2003)	38/97 (39.2%)	12/25 (48%)	RR 0.82 (0.51 to 1.32)	86 fewer per 1000 (from 235 fewer to 154 more)	Very low
1 study (Kuroda et al., 2009)	17/40 (42.5%)	24/43 (55.8%)	RR 0.76 (0.49 to 1.19)	134 fewer per 1000 (from 285 fewer to 106 more)	Very low
1 study (Colacurci et al., 1998)	2/11 (18.2%)	10/26 (38.5%)	RR 0.47 (0.12 to 1.81)	204 fewer per 1000 (from 338 fewer to 312 more)	Very low
Recurrent ectopic pregnancy					
1 study (Bouyer et al., 2000)	10/100 (10%)	17/166 (10.2%)	RR 0.98 (0.47 to 2.05)	2 fewer per 1000 (from 54 fewer to 108 more)	Very low

Number of studies	Number of women or cumulative probability		Effect		Quality
	Salpingectomy	Salpingotomy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 study (Becker et al., 2011)	7/51 (13.7%)	11/145 (7.6%)	RR 1.81 (0.74 to 4.42)	61 more per 1000 (from 20 fewer to 259 more)	Very low
1 study (Silva et al., 1993)	2/26 (7.7%)	11/60 (18.3%)	RR 0.42 (0.1 to 1.76)	106 fewer per 1000 (from 165 fewer to 139 more)	Very low
1 study (Langebrekke et al., 1993)	4/40 (10%)	4/58 (6.9%)	RR 1.45 (0.39 to 5.46)	31 more per 1000 (from 42 fewer to 308 more)	Very low
1 study (dela Cruz & Cumming, 1997)	10/56 (17.9%)	4/34 (11.8%)	RR 1.52 (0.52 to 4.46)	61 more per 1000 (from 56 fewer to 407 more)	Very low
1 study (Ory et al., 1993)	3/50 (6%)	8/33 (24.2%)	RR 0.25 (0.07 to 0.87)*	182 fewer per 1000 (from 32 fewer to 225 fewer)	Very low
1 study (Mol et al., 1998)	7/79 (8.9%)	5/56 (8.9%)	RR 0.99 (0.33 to 2.97)	1 fewer per 1000 (from 60 fewer to 176 more)	Very low
1 study (Bangsgaard et al., 2003)	8/68 (11.8%)	28/208 (13.5%)	RR 0.87 (0.42 to 1.83)	18 fewer per 1000 (from 78 fewer to 112 more)	Very low
1 study (Turan, 2011)	2/55 (3.6%)	6/35 (17.1%)	RR 0.21 (0.05 to 0.99)	135 fewer per 1000 (from 2 fewer to 163 fewer)	Very low
1 study (Sherman et al., 1982)	6/104 (5.8%)	3/47 (6.4%)	RR 0.9 (0.24 to 3.46)	6 fewer per 1000 (from 49 fewer to 157 more)	Very low
1 study (Tuomivaara & Kauppila, 1988)	25/237 (10.5%)	10/86 (11.6%)	RR 0.91 (0.45 to 1.81)	10 fewer per 1000 (from 64 fewer to 94 more)	Very low

Number of studies	Number of women or cumulative probability		Effect		Quality
	Salpingectomy	Salpingotomy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 study (Giambelli et al., 1996)	6-month cumulative rate: 5.1% (denominator NR)	6-month cumulative rate: 7.8% (denominator NR)	NC	27 fewer per 1000 (confidence interval NC) NS (*P*-value NR)	Very low
1 study (DeCherney & Kase, 1979)	6/50 (12%)	9/48 (18.8%)	RR 0.64 (0.25 to 1.66)	68 fewer per 1000 (from 141 fewer to 124 more)	Very low
1 study (Tulandi & Guralnick, 1991)	24-month cumulative probability: 13% n = 24	24-month cumulative probability: 31% n = 34	NC	180 fewer per 1000 (confidence interval NC) *P* < 0.05	Very low
1 study (Kuroda et al., 2009)	7/40 (17.5%)	4/43 (9.3%)	RR 1.88 (0.6 to 5.94)	82 more per 1000 (from 37 fewer to 460 more)	Very low
1 study (Colacurci et al., 1998)	1/11 (9.1%)	1/26 (3.8%)	RR 2.36 (0.16 to 34.5)	52 more per 1000 (from 32 fewer to 1000 more)	Very low
Need for further intervention					
1 study (Bouyer et al., 2000)	1/178 (0.56%)	14/262 (5.3%)	RR 0.11 (0.01 to 0.79)	48 fewer per 1000 (from 11 fewer to 53 fewer)	Very low
1 study (Mol et al., 1997)	1/157 (0.64%)	18/98 (18.4%)	RR 0.03 (0 to 0.26)	178 fewer per 1000 (from 136 fewer to 184 fewer)	Very low
1 study (Parker et al., 1994)	1/103 (0.97%)	6/50 (12%)	RR 0.08 0.01 to 0.65)	110 fewer per 1000 (from 42 fewer to 119 fewer)	Very low

Number of studies	Number of women or cumulative probability		Effect		Quality
	Salpingectomy	Salpingotomy	Relative (95% CI)	Absolute (95% CI) and *P*-value if reported	
1 study (Mecke et al., 1989)	0/25 (0%)	14/153 (9.2%)	RR 0.2 (0.01 to 3.32)	73 fewer per 1000 (from 91 fewer to 212 more)	Very low
1 study (Giambelli et al., 1996)	0/59 (0%)	4/55 (7.3%)	RR 0.1 (0.01 to 1.88)	65 fewer per 1000 (from 72 fewer to 64 more)	Very low
Need for a blood transfusion					
1 study (Mol et al., 1997)	10/157 (6.4%)	1/98 (1%)	RR 6.24 (0.81 to 48.01)	53 more per 1000 (from 2 fewer to 480 more)	Very low
1 study (Colacurci et al., 1998)	0/13 (0%)	1/32 (3.1%)	RR 0.79 (0.03 to 18.13)	7 fewer per 1000 (from 30 fewer to 535 more)	Very low
Surgical complications					
1 study (Mol et al., 1997)	2/157 (1.3%)	3/98 (3.1%)	RR 0.42 (0.07 to 2.45)	18 fewer per 1000 (from 28 fewer to 44 more)	Very low
1 study (Mecke et al., 1989)	0/25 (0%)	6/153 (3.9%)	RR 0.46 (0.03 to 7.85)	21 fewer per 1000 (from 38 fewer to 269 more)	Very low

CI confidence interval, NC not calculable, NR not reported, NS not significant, *P* probability, RR relative risk

* Significance is altered when other factors influencing fertility are controlled for (using multivariate analysis or stratification)

Evidence statements

The studies identified for this review question were generally of poor quality. Using GRADE criteria, the evidence was of very low quality for every outcome.

Subsequent live birth or full-term birth

One study found that the proportion of women with a subsequent live birth or full-term birth was lower in women who received a salpingectomy compared with women who received a salpingotomy. This finding was statistically significant. A further seven studies did not find a statistically significant difference in subsequent live birth or full-term birth between the two groups.

Subsequent intrauterine pregnancy

Five studies found that the proportion of women with a subsequent intrauterine pregnancy was lower in women who received a salpingectomy compared with women who received a salpingotomy. This

finding was statistically significant. A further ten studies did not find a statistically significant difference in subsequent intrauterine pregnancy between the two groups.

Recurrent ectopic pregnancy

Three studies found that the proportion of women with a recurrent ectopic pregnancy was lower in women who received a salpingectomy compared with women who received a salpingotomy. This finding was statistically significant. A further 12 studies did not find a statistically significant difference in recurrent ectopic pregnancy between the two groups.

Need for further intervention

Three studies found that the need for further intervention was lower in women who received a salpingectomy compared with women who received a salpingotomy. This finding was statistically significant. Two further studies did not find a statistically significant difference in the need for further intervention between the two groups.

Need for a blood transfusion

Two studies did not find a statistically significant difference in the need for a blood transfusion for women who received a salpingectomy compared with women who received a salpingotomy.

Surgical complications

Two studies did not find a statistically significant difference in the incidence of surgical complications for women who received a salpingectomy compared with women who received a salpingotomy.

Health economics

A new economic model was developed for this guideline to assess the cost effectiveness of different treatment strategies for ectopic pregnancy. Please see Section 7.2 for a summary of the model's findings and Section 10.4 for full details of the model.

Evidence to recommendations

Relative value placed on the outcomes considered

The primary outcomes for this question were the reproductive outcomes and the need for further intervention. The likelihood of a future viable intrauterine pregnancy and the possibility of a repeat ectopic pregnancy are thought to be outcomes that are very important to most women. The chance of a further intervention is important for informing women about the likely course of their recovery, as well as having health economic implications. Secondary outcomes for this review included the need for a blood transfusion, incidence of surgical complications and ongoing pain, although evidence was not available for the last of these.

Consideration of clinical benefits and harms

When considering which mode of surgery to recommend, the GDG felt that maintaining the woman's reproductive potential was a priority. Six of the studies showed that the proportion of women with an intrauterine pregnancy or a subsequent live or full-term birth was lower in women who received a salpingectomy, while the remainder showed no significant difference. However, the group noted that the evidence was derived from observational studies, and in many of the papers it was reported that a woman's future reproductive desires and other fertility factors influenced the mode of surgery performed, therefore biasing the results. When multivariate or stratified analysis was performed (adjusting for other factors contributing to fertility, such as tubal pathology and history of infertility), the effect became non-significant in two studies. In two other studies, the difference in the proportion of women with an intrauterine pregnancy or a subsequent live or full-term birth was significant for women with other factors prognostic of infertility, but not for the remainder of the women.

Three out of five studies showed that the need for a further intervention was significantly higher following a salpingotomy. The GDG recognised that this would be an important consideration for women, particularly as the second intervention might include the more radical procedure of salpingectomy.

For the outcome of recurrent ectopic pregnancy, there was a general trend that the incidence was lower among women who received a salpingectomy: however, due to the poor quality of the evidence, the GDG did not feel that the effect was certain enough to base a recommendation on.

Overall, the GDG felt that for women without any coexistent fertility factors, future reproductive potential was unlikely to be strongly affected by which mode of surgery was performed. However, for women with factors prognostic of infertility, the evidence suggested that salpingotomy was associated with a higher chance of a subsequent intrauterine pregnancy (please refer to evidence tables in Appendix H where stratified or adjusted analyses are reported for Becker et al., 2011; Bouyer et al., 2000 and Sherman et al., 1982).

Consideration of health benefits and resource uses

The GDG noted that the evidence showed a higher incidence of further intervention following a salpingotomy, and therefore that the comparison of salpingectomy and salpingotomy should be incorporated in the health economic analysis for management of ectopic pregnancy. The cost minimisation model (see Section 10.4) showed that salpingectomy was preferable to salpingotomy in terms of resource use. Given that the evidence around reproductive outcomes following salpingectomy and salpingotomy was inconclusive, the group felt that for women without any coexistent fertility factors, the recommended surgical treatment should be a salpingectomy.

Quality of evidence

The evidence for this review was of very low quality because it was drawn from observational studies, the majority of which were retrospective. There was a high likelihood of bias in many of the studies, because they had a select population and a woman's future fertility desires and reproductive history contributed to the choice of treatment. However, the GDG felt that the studies which performed stratified or multivariate analyses controlled for some of these factors and therefore presented a more accurate estimate of reproductive outcomes.

Information giving and psychological support

The likelihood of a future viable intrauterine pregnancy and the possibility of a repeat ectopic pregnancy were prioritised as key outcomes as these were felt to be the most important to women. The chance of a further intervention is important for informing women about the likely course of their recovery and a recommendation was made to reflect this.

Other considerations

The GDG also discussed the ongoing European Study in Ectopic Pregnancy (ESEP) study, which is a large multi-centre randomised controlled trial that compares salpingectomy and salpingotomy. Unfortunately, the trial will not be published in time for inclusion in this guideline: however, in light of the fact that this study is being conducted, the GDG did not feel that this area was a priority for a research recommendation.

Recommendations

Number	Recommendation
76	Offer a salpingectomy to women undergoing surgery for an ectopic pregnancy unless they have other risk factors for infertility.
77	Consider salpingotomy as an alternative to salpingectomy for women with risk factors for infertility such as contralateral tube damage.
78	Inform women having a salpingotomy that up to 1 in 5 women may need further treatment. This treatment may include methotrexate and/or a salpingectomy.
79	For women who have had a salpingotomy, take 1 serum hCG measurement at 7 days after surgery, then 1 serum hCG measurement per week until a negative result is obtained.
80	Advise women who have had a salpingectomy that they should take a urine pregnancy test after 3 weeks. Advise women to return for further assessment if the test is positive.

9 Anti-D rhesus prophylaxis

9.1 Introduction

Haemolytic disease of the newborn is caused by the destruction of fetal red blood cells by maternal antibodies against red cell antigens acquired from the father. Fifteen percent of all women are rhesus (D) protein negative and therefore historically the vast majority of cases of haemolytic disease of the newborn have been caused by the production of antibodies against the rhesus D antigen. Currently there is confusion about whether anti-D prophylaxis is required to prevent sensitisation during bleeding in the first trimester of pregnancy. The group therefore considered the risk of sensitisation in the first 13 weeks of a pregnancy complicated by bleeding. In women in whom anti-D is required, the group then looked at the most appropriate dose of anti-D that should be recommended to prevent sensitisation.

9.2 Anti-D rhesus prophylaxis for threatened miscarriage, miscarriage and ectopic pregnancy

Review question

Should anti-D rhesus prophylaxis be given to women with a threatened miscarriage, miscarriage or ectopic pregnancy in the first trimester?

Description of included studies

Eight studies were included in this review (Gavin, 1972; Katz & Marcus, 1973; Murray & Barron, 1971; Murray et al., 1970; Simonovits et al., 1974; Simonovits et al., 1980; Visscher & Visscher, 1972; Walsh & Lewis, 1970).

Of the included papers, five were non-comparative, descriptive studies reporting the incidence of sensitisation in women receiving no anti-D rhesus prophylaxis following first trimester obstetric events (Katz & Marcus, 1973; Murray & Barron, 1971; Murray et al., 1970; Simonovits et al., 1980; Walsh & Lewis, 1970). The remaining three papers were comparative studies examining the effect of anti-D rhesus prophylaxis on outcomes. One randomised controlled trial compared 300 micrograms of anti-D rhesus prophylaxis with placebo, with the authors also reporting an additional prospective case series of nine women who did not receive any intervention (Visscher & Visscher, 1972). One study was a non-randomised trial, comparing anti-D rhesus prophylaxis (dose not stated) with placebo (Gavin, 1972). One prospective observational study compared outcomes in women who received anti-D rhesus prophylaxis following a previous therapeutic abortion with those who did not receive any prophylaxis (Simonovits et al., 1974).

No studies were found that evaluated the use of anti-D rhesus prophylaxis after a threatened miscarriage or ectopic pregnancy. Two studies evaluated outcomes in women who were diagnosed with a miscarriage (Katz & Marcus, 1973; Visscher & Visscher, 1972). Three studies had a mixed population, comprising women receiving surgery for a miscarriage and women undergoing a therapeutic abortion (Gavin, 1972; Murray & Barron, 1971; Murray et al., 1970). Three studies only included women having a therapeutic abortion (Simonovits et al., 1974; Simonovits et al., 1980; Walsh & Lewis, 1970). The GDG felt that, for this review, it was appropriate to include studies of women having a therapeutic abortion because of the lack of evidence in the populations of interest,

the comparability of the surgical procedures and the fact that the outcomes of interest are biochemical rather than psychological.

Findings for the outcomes of interest reported are presented in two evidence profiles. The first profile includes the five non-comparative studies and the second includes the three comparative studies.

Evidence profile

Table 9.1 GRADE summary of findings for series of women receiving no anti-D rhesus prophylaxis (non-comparative data)

Number of studies	Test used for antibody detection*	Number of patients	Quality
Incidence of sensitisation at 5–9 months following miscarriage/abortion			
1 study (Katz & Marcus, 1973)	Use of multiple tests reported	1/36[†] (2.8%)	Very low
1 study (Visscher & Visscher, 1972)	Enzyme-Coombs screening procedure	0/9 (0%)	Very low
1 study (Murray & Barron, 1971)	Indirect Coombs test	2/96 (2.1%)	Very low
	Enzyme-treated cells	9/96 (9.4%)	
1 study (Murray et al., 1970)	Indirect Coombs test	1/23 (4.3%)	Very low
	Low's papain	2/23 (8.7%)	
	Papain-treated cells	3/23 (13.0%)	
1 study (Walsh & Lewis, 1970)	Indirect Coombs test	1/18 (5.6%)	Very low
1 study (Katz & Marcus, 1973)	Use of multiple tests reported	5/25 (20%)	Very low
Evidence of sensitisation in subsequent pregnancy			
1 study (Simonovits et al., 1980)	Indirect Coombs test	3/386 (0.8%)[‡]	Very low
	Papain-treated cells	6/386 (1.6%)[‡]	
1 study (Visscher & Visscher, 1972)	Enzyme-Coombs screening procedure	0/2 (0%)	Very low

Number of studies	Test used for antibody detection*	Number of patients	Quality
Neonatal outcomes in sensitised women: delivery of hydropic infant or baby with hyperbilirubinemia			
1 study (Katz & Marcus, 1973)	N/A	3/4 (75%)	Very low
Neonatal outcomes in sensitised women: positive direct Coombs test in baby born following subsequent pregnancy			
1 study (Katz & Marcus, 1973)	Direct Coombs test	2/3 (66.7%)	Very low

* The indirect Coombs test (also known as the indirect antiglobulin test) is currently the standard test for detecting whether a Rh- woman has antibodies against the Rh D antigen present in her blood, and therefore whether she has been sensitised. Historically, enzyme-treated red blood cells (such as those treated with papain) were used to improve the sensitivity of antibody screening tests and were part of the screen for anti-D. However, tests using treated red blood cells detect a lot of non-specific antibodies in addition to anti-D, and therefore in current practice they are only used in confirmatory tests and reference labs. The direct Coombs test (also known as the direct antiglobulin test) is used to test a baby's blood, and determine whether maternal antibodies have bound to the baby's red blood cells. This can be used to establish whether the baby is suffering from, or is at risk of, haemolytic disease of the newborn.

† The woman had weak antibody titre on admission, and then a titre of 1:4 at 5 months

‡ These are test results from the 2nd to 3rd month of second pregnancy. Test results from month 8–9 have also been reported in the study, but are not reported here.

Table 9.2 GRADE summary of findings for anti-D rhesus prophylaxis compared with no intervention or placebo (comparative data)

Number of studies	Test used for antibody detection*	Number of women		Effect		Quality
		Anti-D prophylaxis	Placebo / no intervention	Relative (95% CI)	Absolute (95% CI)	
Incidence of sensitisation at 4–6 months following miscarriage/abortion						
1 study (Visscher & Visscher, 1972)	Enzyme-Coombs screening procedure	0/19 (0%)	0/29 (0%)	Not calculable (NC)	NC	Very low
1 study (Gavin, 1972)	Indirect Coombs test	0/21 (0%)	2/36 (5.6%)	RR 0.34 (0.02 to 6.69)	37 fewer per 1000 (from 54 fewer to 316 more)	Very low
Evidence of sensitisation in subsequent pregnancy						
1 study (Visscher & Visscher, 1972)	Enzyme-Coombs screening procedure	0/3 (0%)	0/6 (0%)	NC	NC	Very low

Number of studies	Test used for antibody detection*	Number of women		Effect		Quality
		Anti-D prophylaxis	Placebo / no intervention	Relative (95% CI)	Absolute (95% CI)	
1 study (Simonovits et al., 1974)	**Anti-D:** papain-treated cells **No intervention:** indirect Coombs test and papain-treated cells for one woman; not reported for other	1/96† (1.0%)	2/145 (1.4%)	RR 0.76 (0.07 to 8.21)	3 fewer per 1000 (from 13 fewer to 99 more)	Very low

CI confidence interval, NC not calculable, RR relative risk

* The indirect Coombs test (also known as the indirect antiglobulin test) is currently the standard test for detecting whether a Rh- woman has antibodies against the Rh D antigen present in her blood, and therefore whether she has been sensitised. Historically, enzyme-treated red blood cells (such as those treated with papain) were used to improve the sensitivity of antibody screening tests and were part of the screen for anti-D. However, tests using treated red blood cells detect a lot of non-specific antibodies in addition to anti-D, and therefore in current practice they are only used in confirmatory tests and reference labs. The direct Coombs test (also known as the direct antiglobulin test) is used to test a baby's blood, and determine whether maternal antibodies have bound to the baby's red blood cells. This can be used to establish whether the baby is suffering from, or is at risk of, haemolytic disease of the newborn.

† This woman delivered a Rh+ baby at the end of her second pregnancy and tested negative 6 months before birth; therefore she is likely to have been sensitised in her second, full-term pregnancy

Evidence statements

The evidence for each of the reported studies and outcomes is of very low quality.

Non-comparative data (see Table 9.1)

Incidence of sensitisation at 5–9 months following miscarriage/abortion

One study found that the incidence of sensitisation was 2.8% among women who did not receive any prophylaxis following a miscarriage: however, the only case of sensitisation occurred in a woman who had a weak antibody titre on admission.

One study did not report any incidences of sensitisation (using the enzyme-Coombs screening procedure) among women who did not receive any prophylaxis following a miscarriage.

One study reported that among women who did not receive any prophylaxis following a miscarriage or therapeutic abortion the incidence of sensitisation was 2.1% using the indirect Coombs test and 9.4% using enzyme-treated cells.

One study reported that among women who did not receive any prophylaxis following a miscarriage or therapeutic abortion, the incidence of sensitisation was 4.3% using the indirect Coombs test, 8.7% using Low's papain and 13.0% using papainised cells.

One study reported that the incidence of sensitisation was 5.6% using the indirect Coombs test among women who did not receive any prophylaxis following a therapeutic abortion.

One study reported that the incidence of sensitisation was 20% among women who did not receive any prophylaxis following a miscarriage or therapeutic abortion: however, definitive proof that the miscarriage or therapeutic abortion was the cause of sensitisation was only available in 2/5 cases.

Evidence of sensitisation in subsequent pregnancy

One study reported that the incidence of sensitisation during a subsequent pregnancy in women who did not receive any prophylaxis following a therapeutic abortion was 0.8% using the indirect Coombs test and 1.6% using papain-treated red blood cells.

One study reported no incidences of sensitisation during a subsequent pregnancy (using the enzyme-Coombs screening procedure) in two women who did not receive any prophylaxis following a miscarriage.

Neonatal outcomes in sensitised women

One study found that three out of four women who were sensitised following a miscarriage delivered a hydropic infant or baby with hyperbilirubinemia in a subsequent pregnancy. The same study found that two out of three babies born to women sensitised after a miscarriage had a positive direct Coombs test.

Comparative data (see Table 9.2)

Incidence of sensitisation at 4–6 months following miscarriage/abortion

One study did not find a statistically significant difference in the incidence of sensitisation for women receiving anti-D rhesus prophylaxis following a miscarriage or therapeutic abortion compared with women receiving a placebo. One further study did not report any incidences of sensitisation in women receiving anti-D rhesus prophylaxis following a miscarriage and women receiving a placebo.

Evidence of sensitisation in subsequent pregnancy

One study did not find a statistically significant difference in the incidence of sensitisation during subsequent pregnancies for women receiving anti-D rhesus prophylaxis following a therapeutic abortion compared with women receiving a placebo. One further study did not report any incidences of sensitisation during subsequent pregnancies in women receiving anti-D rhesus prophylaxis following a miscarriage and women receiving a placebo.

Evidence to recommendations

Please see recommendations in Section 9.3, where the evidence from all of the anti-D rhesus prophylaxis reviews has been considered.

9.3 Anti-D rhesus prophylaxis – dose

Review question

What is the appropriate dose of anti-D that should be administered to women with a threatened miscarriage, miscarriage or ectopic pregnancy in the first trimester?

Description of included studies

Three studies were included in this review (Hensleigh et al., 1977; Keith & Bozorgi, 1977; Stewart et al., 1978). All of the studies were randomised controlled trials conducted in the USA, and evaluated the administration of different doses of anti-D rhesus prophylaxis to women following first trimester therapeutic abortion. Two studies compared doses of 50 micrograms and 300 micrograms (Keith & Bozorgi, 1977; Stewart et al., 1978). The third study compared three different doses of 73, 155 and 499 micrograms (Hensleigh et al., 1977). No studies were identified that compared different doses following an ectopic pregnancy or miscarriage.

Evidence profile

Table 9.3 GRADE summary of findings for comparison of 50 micrograms and 300 micrograms of anti-D prophylaxis

Number of studies	Number of women		Effect		Quality
	50 micrograms	300 micrograms	Relative (95% CI)	Absolute (95% CI)	
Detection of Rhesus antibodies at 6 months follow-up					
1 meta-analysis of 2 studies (Keith & Bozorgi, 1977; Stewart et al., 1978)	0/989 (0%)	0/81 (0%)	NC	NC	Very low
Adverse drug reaction					
1 meta-analysis of 2 studies (Keith & Bozorgi, 1977; Stewart et al., 1978)	1/1218 (0.08%)	0/111 (0%)	RR 0.31 (0.01 to 7.61)	1 more (from 33 fewer to 5 more)*	Very low

CI confidence interval, NC not calculable, RR relative risk

Table 9.4 GRADE summary of findings for comparison of 73, 155 and 499 micrograms of anti-D prophylaxis

Number of studies	Number of women			Effect		Quality
	73 micrograms	155 micrograms	499 micrograms	Relative (95% CI)	Absolute (95% CI)	
Incidence of sensitisation						
1 study (Hensleigh et al., 1977)	0/8	0/83	0/25	NC	NC	Very low
Adverse drug reaction						
1 study (Hensleigh et al., 1977)	0/8	0/83	0/25	NC	NC	Very low

CI confidence interval, NC not calculable

Evidence statements

The evidence for each of the reported studies and outcomes is of very low quality.

Comparison of 50 and 300 micrograms

Detection of rhesus antibodies at 6 months

One meta-analysis of two studies did not find any incidences of rhesus antibody detection in women who received 50 micrograms or 300 micrograms of anti-D.

Adverse drug reaction

One meta-analysis of two studies did not find a statistically significant difference in the incidence of adverse drug reaction for women who received 50 micrograms of anti-D compared with women who received 300 micrograms of anti-D.

Comparison of 73, 155 and 499 micrograms

Incidence of sensitisation

One study did not find any incidences of sensitisation in women who received 73 micrograms, 155 micrograms or 499 micrograms of anti-D.

Adverse drug reaction

One study did not find any incidences of adverse drug reaction in women who received 73 micrograms, 155 micrograms or 499 micrograms of anti-D.

Evidence to recommendations

Relative value placed on the outcomes considered

For the review looking at the provision of anti-D rhesus prophylaxis, the key outcome of interest for the guideline development group (GDG) was the incidence of sensitisation following a miscarriage or therapeutic abortion, as it is this which anti-D rhesus prophylaxis is supposed to prevent. This included both sensitisation in the current pregnancy and sensitisation in subsequent pregnancies.

For the review looking at the appropriate dose, the key outcome was the effectiveness of the prophylaxis at different doses.

Trade-off between clinical benefits and harms

The group recognised that there is little harm associated with the provision of anti-D rhesus prophylaxis. While there is always a potential risk of transferring blood-borne disease when administering blood products, this risk is very low given the screening that is conducted before their use. The group was not aware of any other adverse outcomes associated with the use of anti-D rhesus prophylaxis and there was only one such outcome reported in the available evidence.

By contrast, the group recognised that there is a clear health benefit in avoiding sensitisation if possible. Sensitisation increases the chance of miscarriage in a later pregnancy and also increases the chance that subsequent babies will develop a range of conditions including fetal heart failure, hydrops (fluid retention), oedema, anaemia and rhesus disease. Rhesus disease, in turn, increases the chance of the baby developing kernicterus which can cause brain damage or even death.

Quality of evidence

The group recognised that all of the evidence available for this topic was of very low quality. There were only three studies looking at the use of anti-D rhesus prophylaxis which reported comparative data. None of the studies was very large and it is unlikely that any were sufficiently powered to detect a statistically significant difference. The group had hoped to see evidence in women with a threatened miscarriage and in women with ectopic pregnancy. However, none was available which met the inclusion criteria. All of the studies reported data in women with either a miscarriage (the vast majority of which were managed with surgery) or a therapeutic abortion. There was no evidence for women undergoing medical management of miscarriage and a very small proportion of women had a complete miscarriage without intervention.

For the question of the appropriate dose, again there were only three comparative studies. While one was relatively large, all were of very low quality.

Given the paucity of available evidence, the GDG's recommendations were mainly developed through the members' own clinical experience and that of the clinical adviser for this topic.

Trade-off between net health benefits and resource use

Although the quality of the evidence was very low for the descriptive studies, the group felt that, taken as a whole, there was evidence of a risk of sensitisation for women if they did not receive anti-D rhesus prophylaxis following a first trimester miscarriage or therapeutic abortion. The group recognised that the comparative studies did not show a statistically significant difference in the rate of sensitisation between women who did and did not receive anti-D rhesus prophylaxis. However, the group believed that the small size of the studies meant that this was unlikely to be a true finding of no effect.

The group was informed that the chance of sensitisation increases when there is a greater likelihood of mixing between the maternal and fetal blood. As a result, there is an increased risk of sensitisation when treating a miscarriage or ectopic pregnancy surgically.

Given the lack of evidence, the GDG did not feel it appropriate to recommend that women with a miscarriage or ectopic pregnancy that resolves spontaneously, without intervention, routinely receive anti-D rhesus prophylaxis. However, recognising the increased risk of sensitisation to women undergoing a surgical intervention, the group felt it appropriate to recommend that these women should receive prophylaxis.

The GDG considered the population of women who will receive medical management for their miscarriage or ectopic pregnancy. From the GDG members' clinical experience and understanding, the effect of misoprostol is to cause the body to mimic the physiological changes that occur during a spontaneously completing miscarriage. They felt that the risk of significant maternal and fetal blood mixing during methotrexate treatment for an ectopic pregnancy was likely to be low. Given this, they did not believe that it would lead to an increased risk of sensitisation, and thus agreed that women receiving medical management for either miscarriage or ectopic pregnancy should not be offered prophylaxis.

The evidence available for the review of the appropriate dose suggested that a 50 microgram dose (250 international units) of prophylaxis was as effective as a larger dose. Given this, and the fact that the 50 microgram dose is cheaper, the GDG agreed that this is the dose which should be provided.

Other considerations

The group noted from the evidence that some of the studies reported the use of a Kleihauer test in which the maternal blood is stained to detect the presence of cells containing fetal haemoglobin and the number of these cells is then manually counted. The group received expert advice that the accuracy of the test decreases at low levels of fetal haemoglobin (less than 1 cell in every 10,000). The group noted that at the time of gestation covered in the guideline, the levels of fetal haemoglobin were likely to be very low, and thus the Kleihauer test was unlikely to give an accurate result. This was supported by the data reported in the included studies, which showed low correlation between the Kleihauer test results and risk of sensitisation. Given this, the group agreed that this specific diagnostic test should not be used for this group of women.

Recommendations

Number	Recommendation
81	Offer anti-D rhesus prophylaxis at a dose of 250 IU (50 micrograms) to all rhesus negative women who have a surgical procedure to manage an ectopic pregnancy or a miscarriage.
82	Do not offer anti-D rhesus prophylaxis to women who: • receive solely medical management for an ectopic pregnancy or miscarriage **or** • have a threatened miscarriage **or** • have a complete miscarriage **or** • have a pregnancy of unknown location.
83	Do not use a Kleihauer test for quantifying feto–maternal haemorrhage.

Number	Research recommendations
RR 9	Does the administration of anti-D rhesus prophylaxis following pain and bleeding in early pregnancy improve outcomes? Outcomes should include rhesus sensitisation in the woman attributable to the early pregnancy event and morbidity related to rhesus disease in subsequent unborn and newborn babies.

10 Health economics

10.1 Introduction

The aims of the health economic input to the guideline were to inform the guideline development group (GDG) of potential economic issues relating to pain and bleeding in early pregnancy and to ensure that its recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits or harms (ideally in terms of quality adjusted life years [QALYs]) and costs of different care options.

The GDG prioritised the clinical questions where it was thought that economic considerations would be particularly important in formulating recommendations. For this guideline the areas prioritised for economic analysis were:

- progesterone for threatened miscarriage (see Section 7.2 for summary and Section 10.2 for full details)
- management of miscarriage (see Section 7.3 for summary and Section 10.3 for full details)
- management of ectopic pregnancy (see Section 8.2 for summary and Section 10.4 for full details).

10.2 Progesterone for threatened miscarriage

Introduction

It has been suggested that a lack of progesterone may be the cause of miscarriage. If it was found that progesterone/progestogen supplementation was effective in preventing miscarriage then given the low cost of this intervention it is also likely to be cost effective.

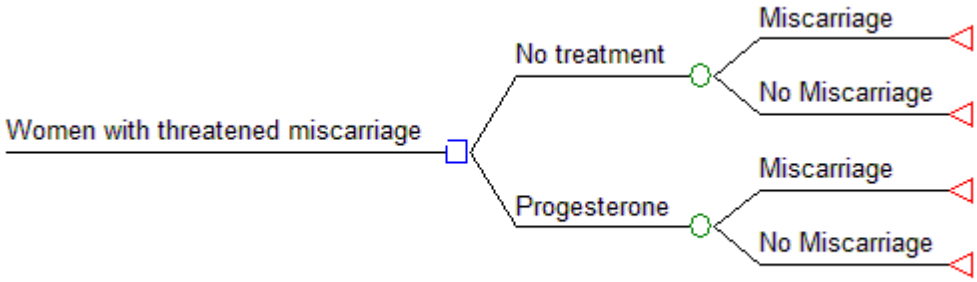
Review of the published health economic evidence

A health economics search of the literature for progesterone for threatened miscarriage identified five articles. The abstracts of these articles were reviewed but none of them were analyses of women with threatened miscarriage. Therefore a new health economic model was developed for the purposes of this guideline. This model is described below.

Method

A simple decision analytic model was developed in Microsoft Excel® to evaluate the cost effectiveness of progesterone/progestogen supplementation in pregnancies with threatened first trimester miscarriage (presence of vaginal bleeding before 12^{+6} weeks of gestation). A schematic of the overall model structure is illustrated in Figure 10.1.

Figure 10.1 Schematic of model decision tree



A number of sensitivity analyses were undertaken to assess the importance of parameter uncertainty within the model.

Model probabilities and treatment effect size

Clinical data was taken from the clinical review undertaken for this guideline. That review considered a number of outcomes:

- term birth
- pre-term birth
- miscarriage
- pregnancy at 20 weeks
- placental abruption
- hypertensive disorders in pregnancy
- gestational diabetes
- intrahepatic cholestasis of pregnancy.

Our model confined itself to miscarriage, the primary focus of the intervention. The model data on miscarriage outcomes is shown in Table 10.1 and was taken from the meta-analysis of four studies (El-Zibdeh et al., 2009; Gerhard et al., 1987; Palagiano et al., 2004; Pandian, 2009) undertaken as part of the clinical review from this guideline. The meta-analysis estimate of the miscarriage rate in no treatment/placebo arms was used as the point estimate of the baseline risk. This value appears similar to other estimates of the miscarriage rate in women with threatened miscarriage (for example Basama & Crosfill, 2004).

Table 10.1 Model **p**robabilities and treatment effect size

Item	Value	Source	Notes
Miscarriage rate with progesterone	13.8%	El-Zibdeh et al., 2009; Gerhard et al., 1987; Palagiano et al., 2004; Pandian, 2009	Guideline meta-analysis
Miscarriage rate no treatment	25.9%	El-Zibdeh et al., 2009; Gerhard et al., 1987; Palagiano et al., 2004; Pandian, 2009	Guideline meta-analysis, assumed to represent baseline risk
Treatment relative risk	0.53	El-Zibdeh et al., 2009; Gerhard et al., 1987; Palagiano et al., 2004; Pandian, 2009	Guideline meta-analysis 95% confidence interval: (0.35 to 0.79)

Costs and resource use

This analysis was undertaken from the perspective of the NHS and personal social services which is in accordance with NICE guidelines methodology (NICE, 2009). Treatment alternatives were compared using standard methods of incremental analysis and costs are based on 2010/11 prices. Discounting was not needed as all model costs fall within a year of the commencement of the intervention.

Table 10.2 shows the cost inputs used in this model.

Table 10.2 Model costs

Item	Value	Source	Notes
Miscarriage	£424	NHS Reference Costs 2010-11	Currency code: MB08Z. Threatened or spontaneous miscarriage Non-elective (short-stay)
Progesterone/progestogen	£2.10	Estimate	Based on a tablet cost of £0.10 and one tablet/day for 21 days

Health economic inputs

There is considerable uncertainty about the QALY loss from miscarriage and none of the studies identified by the search were informative for this parameter. Therefore, the model allows 'what-if' sensitivity analysis to assess the extent to which assumptions with respect to this parameter may affect model conclusions. When generating an incremental cost per QALY it is necessary to have a decision rule regarding the willingness to pay for a QALY to determine whether the benefits are being obtained at an acceptable opportunity cost (the other NHS services that might have to be foregone if the intervention is cost increasing). The base case values for QALY loss associated with miscarriage and willingness to pay for a QALY are shown in Table 10.3.

Table 10.3 Health economic inputs

Item	Value	Source	Notes
QALY loss from miscarriage	0.1	Illustrative	Can be varied as part of a 'what-if' sensitivity analysis
Willingness to pay for a QALY	£20,000	NICE (2009)	Advisory cost effective-ness willingness to pay threshold

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was undertaken using Monte Carlo simulation. The model was run or simulated 10,000 times. In each simulation the value of probabilistic model parameters, shown in Table 10.4 to Tables 10.6 below, are sampled from a probability distribution which reflects sampling uncertainty in the data.

Table 10.4 Parameters for probabilistic sensitivity analysis (baseline probability)

Item	Alpha	Beta	Distribution
Miscarriage rate no treatment	51	146	Beta

Table 10.5 Parameters for probabilistic sensitivity analysis (relative risk [RR])

Item	Log relative risk	Standard error of log RR	Distribution
Relative risk	-0.626	0.2057	Log-normal

Table 10.6 Parameters for probabilistic sensitivity analysis (model costs)

Item	Mean	SE	Distribution
Miscarriage	£424	£15.42	Normal

The distribution to be used for cost estimates and its parameters are derived from a specially designed Microsoft Excel® application. The data from the NHS Reference Costs gives information on the mean cost, the upper and lower quartile range and the number of data submissions on which this is based. It does not give the standard deviation or standard error, measures of dispersion which are required along with the mean to define a distribution for probabilistic sensitivity analysis.

The Microsoft Excel® program in the first instance finds the 'best-fit' distribution for the NHS Reference Cost data from a lognormal, gamma and normal distributions. Gamma and lognormal distributions are commonly applied to costs as the data is often skewed (Thompson et al., 2006). This 'best-fit' is estimated by testing a wide range of possible standard deviations and selecting the one that minimises the sum of the squares of the difference between the lower quartile range of the NHS Reference cost data and the lower quartile range of the distribution (0.25 on the cumulative distribution function) and the upper quartile range of the NHS Reference Cost data and the upper quartile range of the distribution (0.75 on the cumulative distribution function). The 'best-fit' distribution relates to the dispersion of the NHS Reference Cost data submissions but not the dispersion of the sampled mean, the best estimate of the actual cost. Therefore, having obtained a 'best fit' estimate of the standard deviation, the standard error is then calculated using the number of data submissions on which the NHS Reference Cost data was based. It is then assumed, based on the central limit theorem, that sampled means would be normally distributed with the distribution parameters for the probabilistic sensitivity analysis being the mean and calculated standard error.

Results

The base-case results are shown in Table 10.7. This showed progesterone to dominate no treatment, producing cost savings and QALY gains as a result of averted miscarriages.

Table 10.7 Results for base-case analysis

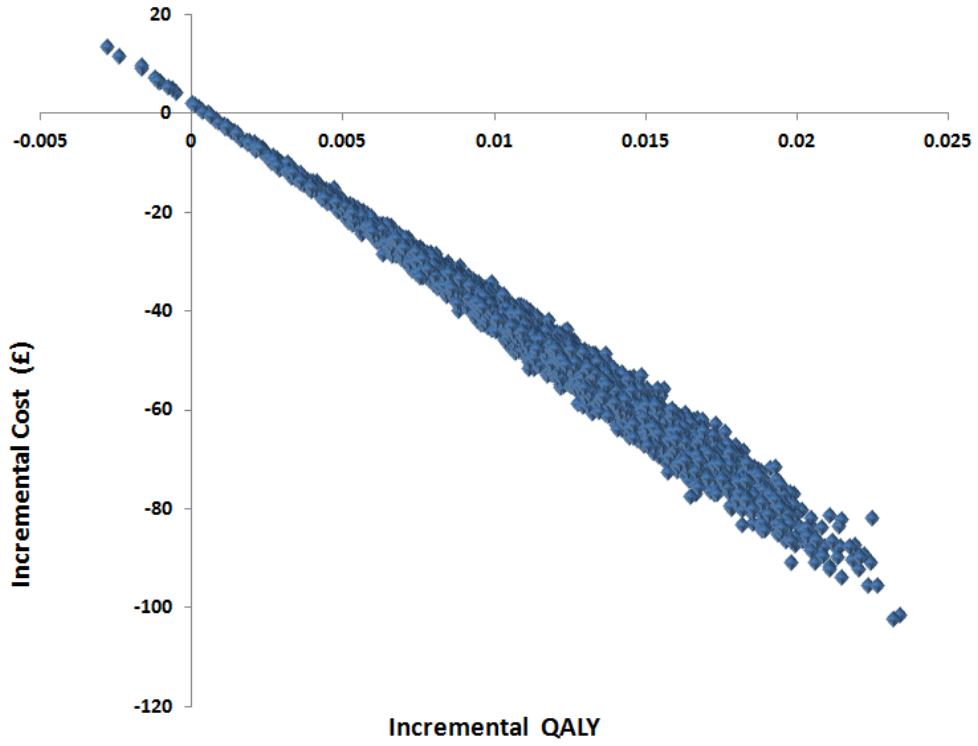
Treatment	Incremental cost	Incremental QALY
Progesterone	-£49	0.012

Sensitivity analysis

Probabilistic sensitivity analysis

The results of a probabilistic sensitivity analysis based on 10,000 simulations are plotted in Figure 10.2. Progesterone treatment was cost effective in 9988 of these simulations (99.88%).

Figure 10.2 Probabilistic sensitivity analysis result of incremental costs and QALYs of progesterone treatment (n = 10,000)



Two-way sensitivity analysis varying the QALY loss associated with miscarriage and the cost of progesterone treatment

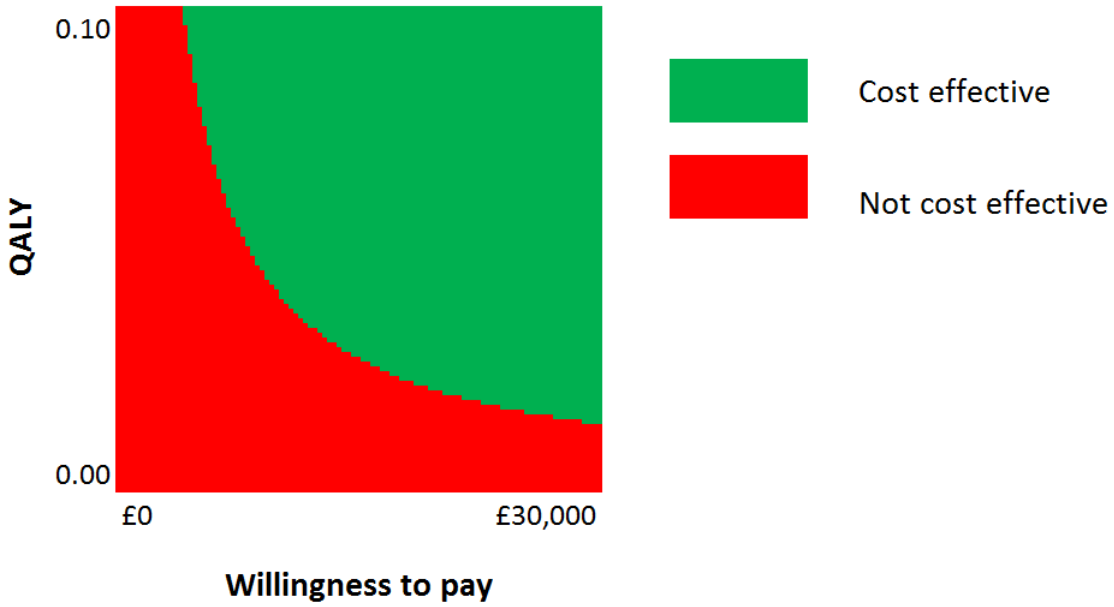
In this sensitivity analysis the cost of treatment is varied from £0 to £250 (the latter being much higher than that used in the base-case analysis). The QALY loss from miscarriage is varied from 0 to 0.1. In Figure 10.3 the results are plotted on a grid which indicates the cost effectiveness threshold across different values of these inputs.

Figure 10.3 Cost effectiveness threshold for various QALY and treatment combinations holding other model inputs constant at their base-case value

Two-way sensitivity analysis varying the QALY loss associated with miscarriage and the willingness to pay for a QALY

With other variables held at their base-case values, the model's conclusions are unaffected by variation in QALY loss associated with miscarriage and the willingness to pay for a QALY. This is because the cost saving from averted miscarriage more than offsets the treatment costs, meaning that the intervention is always cheaper. Therefore, for illustrative purposes in this example, a treatment cost of £100 is assumed because, for example, medical therapy might require increased patient monitoring. The results of this sensitivity analysis are shown in Figure 10.4

Figure 10.4 Cost effectiveness threshold for various QALY and willingness to pay combinations for a treatment cost of £100 and holding other model inputs constant at their base case value



Probabilistic sensitivity analysis but assuming a treatment cost of £200

In this analysis the probabilistic sensitivity analysis is re-run to capture parameter uncertainty relating to treatment effectiveness and miscarriage costs. However, it tests the implications of assuming a treatment cost of £200, almost 100-fold more than in the base-case analysis.

The plot of the 10,000 simulations is shown in Figure 10.5. At a willingness to pay of £20,000 per QALY, progesterone was cost effective in 94.5% of the simulations. A cost effectiveness acceptability curve (CEAC) is displayed in Figure 10.6. This shows the probability of either alternative being cost effective at different willingness to pay values. In this example, with a treatment cost of £200 and a QALY loss of 0.1 from miscarriage, the CEAC suggests that progesterone is likely to be the most cost-effective treatment providing the willingness to pay for a QALY exceeds £13,000. At a willingness to pay of £20,000 per QALY progesterone has an 83% chance of being cost effective.

Figure 10.5 Probabilistic sensitivity analysis result of incremental costs and QALYs of progesterone treatment (n = 10,000) with a treatment cost of £200

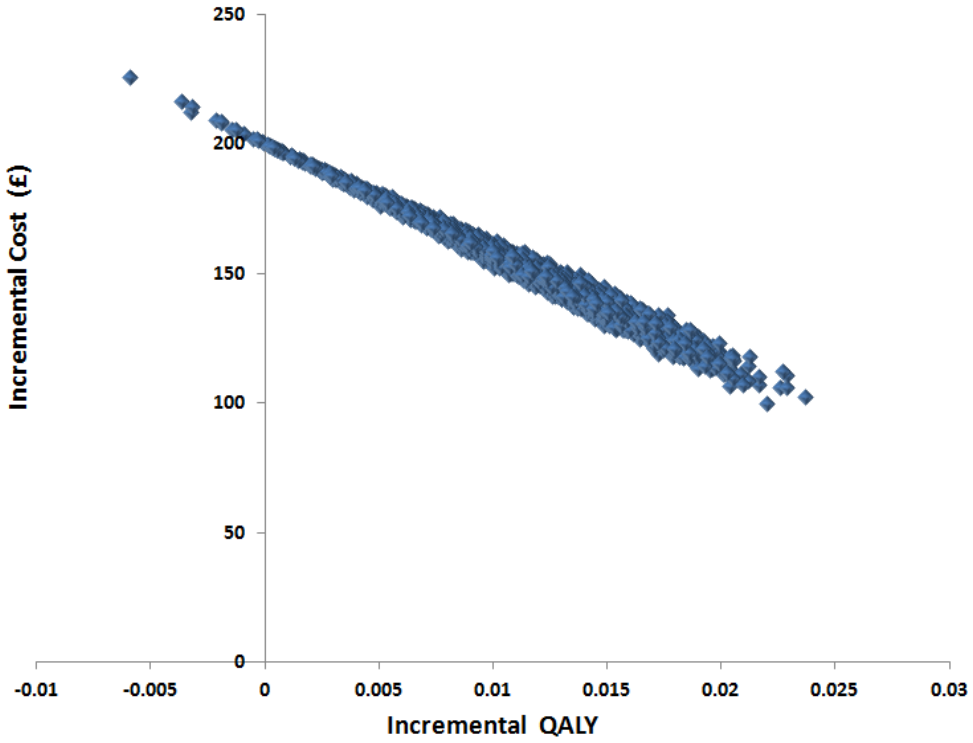
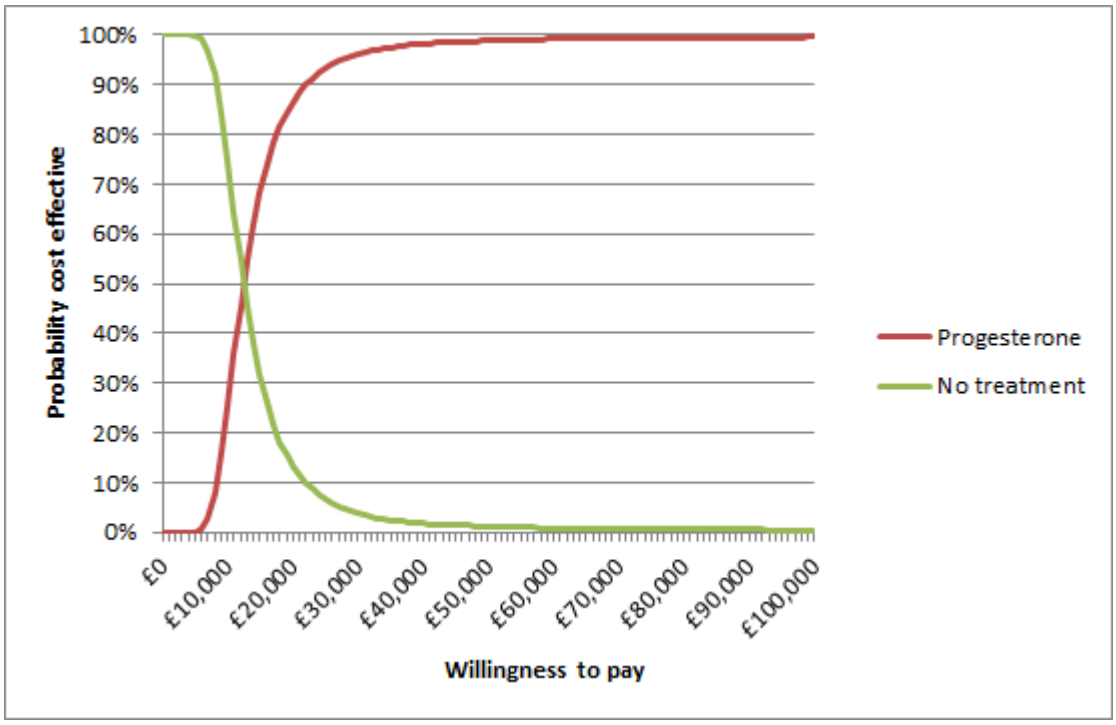


Figure 10.6 Cost effectiveness acceptability curve showing the probability that progesterone is cost-effective treatment for threatened miscarriage at different willingness to pay for a QALY and with a treatment cost of £200



Discussion

This analysis strongly suggests that progesterone is a cost-effective treatment for threatened miscarriage. In the base-case analysis progesterone dominates no treatment, being cheaper and having a lower miscarriage loss which generates a QALY gain. This result is driven by the very cheap cost of the intervention and the large 12.1 percentage point reduction in the absolute risk of miscarriage with progesterone. Given the cost of miscarriage this gives an expected saving of £51.30 per woman, which is well in excess of the cost of treatment. Providing progesterone treatment costs less than £51.30 it will be cost saving with the point estimates of treatment effect size. Progesterone is very cheap and unless medical therapy involves consumption of NHS resources other than the drug itself, then the cost of treatment is unlikely to exceed the saving from averted miscarriage.

The fact that there is such a large saving associated with miscarriage explains the inverse relationship between incremental cost and incremental QALY seen in Figures 10.2 and 10.5. High QALY gains are associated with a large reduction in miscarriage which produces a concomitantly large reduction in net costs (costs of treatment minus 'downstream savings' from reductions in miscarriage). In both Figures 10.2 and 10.5 an overwhelming number of the simulations lie to the right of the vertical axis and their relative frequency gives an estimate of the probability that treatment is effective given the results reported in the meta-analysis. Where the cost of treatment is small relative to the cost saving from averted miscarriage, as in the base-case analysis, then an overwhelming majority of the simulations lie in the south-east quadrant of the cost effectiveness plane, signifying dominance (Figure 10.2). A very small number of simulations do lie in the north-east quadrant where cost effectiveness depends on the willingness to pay for a QALY. That occurs in the base case when the sampled reduction in miscarriage is so small that 'downstream' savings do not offset the small treatment cost. In Figure 10.5 the simulations have been shifted vertically upwards by the £200 increase in treatment costs. In none of the 10,000 simulations does progesterone now produce cost savings, with most simulations concentrated in the north-east quadrant of the cost effectiveness plane. Whether progesterone would hypothetically still be considered cost effective depends on the willingness to pay for a QALY. As the CEAC in Figure 10.6 shows, 85% of these simulations would still be considered to represent a cost-effective trade-off of benefits for increased costs, even at a treatment cost way in excess of what would be realistic. This does, of course, also depend on the QALY gain attributable to an averted QALY.

Considerable uncertainty surrounds the QALY loss attributable to miscarriage. Some short-term effects on the woman seem inevitable, but longer term loss in health related quality of life may depend on whether the woman goes on to have subsequent successful pregnancy outcomes. However, where treatment is very cheap and there are large savings from successful treatment, as in the base-case analysis, then uncertainties about the QALY loss from miscarriage are unimportant because the cost effectiveness of treatment is derived from the intervention being cost saving even in the absence of any QALY benefit. The sensitivity analysis results shown in Figure 10.3 suggest that quantifying the QALY loss from miscarriage is only important for treatment costs of £50 and above. Similarly, as shown in Figure 10.4, the willingness to pay for a QALY only becomes important when the intervention is cost increasing overall.

The model has a number of limitations. The treatment effect size is clearly an important driver of the cost effectiveness conclusions and therefore this data in the model reflects the quality and limitations of the studies on which it was based. Nevertheless, unless there are known biases in these studies in favour of progesterone, this represents the best available evidence to assess cost effectiveness.

As noted earlier, the clinical review for this guideline considered several outcomes but this model focused solely on miscarriage. Modelling always involves some simplification of the real world and the 'art' of modelling often involves knowing when simplification is reasonable. Some of the other outcomes assessed in the clinical review – term birth, pre-term birth and pregnancy rate at 20 weeks – can almost be seen as the other side of the miscarriage 'coin'. If miscarriage occurs then there is a corresponding reduction in those outcomes. As a result of the strong interdependence of these outcomes with miscarriage and the added complexity of modelling, these outcomes were not included in the analysis. While not always statistically significant at the 5% level, the point estimates for these outcomes were generally in favour of progesterone, as would be expected if progesterone reduced miscarriage, and therefore their omission, if anything, biases the model against progesterone. The evidence for hypertensive disorders gave a point estimate for the relative risk of 1.0 (that is, no effect).

Clearly there is uncertainty around this relative risk and it was thought that the inclusion of hypertensive disorders would introduce considerable 'noise' which might mask out the effects of miscarriage, especially given its relative high prevalence. Furthermore, the point estimate of risk for hypertensive disorders ever so slightly favoured progesterone (10.4% versus 11.0%) and therefore its omission does not introduce bias in favour of progesterone into the model.

Placental abruption is a relatively rare event and the evidence indicated large confidence intervals around the point estimate of relative risk. Although the point estimate of relative risk favoured no treatment, this was a long way from achieving statistical significance (relative risk [RR] 95%, confidence interval [CI] 0.53–3.54). Furthermore, the risk for both treatment and no treatment was lower than the 1% risk cited for pregnancy as a whole (http://emedicine.medscape.com/article/252810-overview#a0199 [accessed January 2012]) and therefore it was decided that there was not good evidence that treatment influenced placental abruption. Pain was not included as it contributes directly to health-related quality of life where the preferred measure is the QALY. The review found pain to be significantly lower in women treated with progesterone, which means that progesterone may produce QALY gains over and above those relating to actual miscarriage.

The omission of gestational diabetes and intrahepatic cholestasis of pregnancy is more contentious. Neither of the point estimates of relative risk for these outcomes, which both favoured no treatment, achieved statistical significance at the 5% level. However, the relative risk for gestational diabetes does approach statistical significance (RR 95%, CI 0.94–1.76), so the observed difference may not be down to chance. The point estimates suggested that progesterone carried a number needed to harm of 63 for gestational diabetes.

It has been estimated in a paper on the cost-utility of screening for gestational diabetes that the QALY loss from a serious perinatal complication, an adverse outcome of gestational diabetes, is 2.1 QALYs (Round et al., 2011). That same paper estimated that the risk of a serious perinatal outcome in women with treated gestational diabetes was 0.017. If we accept that progesterone leads to a 1.6 percentage point increase in risk of gestational diabetes, that translates to a 0.000576 average QALY loss for women treated with progesterone for threatened miscarriage due to gestational diabetes.[*] Using point estimates of risk, the QALY loss due to gestational diabetes would only outweigh the QALY gain from averted miscarriage if the loss due to miscarriage was less than 0.0048 QALYs.[†] That same study assumes a treatment cost of gestational diabetes of £162. In addition, there are costs of serious perinatal complications estimated at £1184 to consider. However, in women with treated gestational diabetes the risk of these complications is 0.017 and therefore the expected serious perinatal complication cost per woman with gestational diabetes is £20, making a total cost of gestational diabetes of £182 per woman. Accepting a 1.6 percentage increase in gestational diabetes arising from progesterone for threatened miscarriage would mean that there would be an expected 'downstream' cost of approximately £3 due to gestational diabetes. This is relatively insignificant compared to the expected £50 saving due to averted miscarriage and therefore because of the small expected QALY loss and cost arising from gestational diabetes it is unlikely its omission from this model would change the conclusion.

Conclusion

The model suggests that not only is progesterone likely to be cost effective in the treatment of threatened miscarriage, but that it is also likely to be cost saving because the reduction in miscarriage more than offsets the costs of treatment. Probabilistic sensitivity analysis suggested that this conclusion was robust with respect to parameter uncertainty pertaining to treatment effect size and miscarriage cost. Other sensitivity analysis suggested much higher treatment costs than assumed in the base-case analysis would be needed in order for the cost effectiveness of progesterone to become more equivocal.

[*] Expected QALY loss due to gestational diabetes = 2.1 x 0.017 x 0.016 = 0.000576
[†] Expected QALY loss due to miscarriage = 0.121 x QALY loss from miscarriage 0.121 x 0.0048 ≈ 0.000576

10.3 Management of miscarriage

Introduction

As a result of high rates of gynaecological infection and resulting mortality, surgical management became the routine treatment for first trimester miscarriage (Ankum et al., 2001). However, in recent years there has been an increasing willingness to consider alternatives, such as expectant and medical management (Ankum et al., 2001). Evidence-based medicine requires that consideration be given to the effectiveness of the different treatment alternatives but in any healthcare system where resources are constrained, maximisation of health gain requires that consideration be given additionally to the cost effectiveness of the alternatives. Women's choice is an important determinant of treatment within the NHS, but recommendations in this guideline are also informed by cost effectiveness as is required by the NICE guidelines manual (NICE, 2009).

Overview of the economic evidence

A total of 139 articles were identified by the search strategy. Based on the abstracts, six full papers were obtained, of which five were included in this review (Graziosi et al., 2005c; Hughes et al., 1996; Niinimaki et al., 2009; Rocconi et al., 2005; Petrou et al., 2006). In addition, a further paper (You & Chung, 2005) was identified from the references from one of the included studies (Niinimaki et al., 2009) and was also included within the review.

One UK study compared the costs to the NHS of medical and surgical management for miscarriage (Hughes et al., 1996). The analysis was conducted alongside a partially randomised trial in which enrolled women who expressed a preference were given their treatment of choice (n = 237) with the remainder randomised to either surgical or medical evaluation (n = 200). The precise form of medical treatment varied according to the type of miscarriage. Mifepristone (200 mg) followed by three sequential oral doses of misoprostol 36–48 hours later was used for cases of missed miscarriage and an embryonic pregnancy. Two sequential oral doses of misoprostol were used for women with an incomplete miscarriage confirmed by clinical examination and ultrasound assessment. The study found that the mean cost of medical management was £346 (95% CI £333 to £361) and the mean cost of surgical management was £397 (95% CI £383 to £411). The finding that medical management was cheaper was statistically significant (mean difference [MD] -£51, $P < 0.001$).

A US paper reported a decision analytic model used to compare: observation; medical management; manual vacuum aspiration (MVA); and dilation and curettage (Rocconi et al., 2005). The model's end-point was treatment failure or cure and therefore combined management strategies were not considered. Model inputs for clinical data were derived from a review of the published literature. When literature derived estimates were not available 'local sources were consulted'. Medical management was vaginal misoprostol. In the observation strategy patients were seen weekly and followed for a maximum period of 28 days. Costs were based on the perspective of a third-party payer and were expressed in 2003 US dollars (USD). Sources for cost data were the University of Alabama at Birmingham reimbursement schedules, average wholesale drug costs and using 60% of the charge if a cost was not available for a procedure. The results were as shown in Table 10.8.[*] The authors conclude that, for their baseline analysis, MVA is the most cost effective based on its incremental cost effectiveness ratio (ICER). However, it doesn't automatically follow that the strategy with the lowest ICER is most cost effective, but rather it is the willingness to pay threshold of the decision maker which determines whether the more efficacious strategy is preferred given the increased cost (Drummond et al., 1997).

[*] This presentation of the results is slightly different to that which appears in the paper

Table 10.8 Results from Rocconi et al. (2005)

Strategy	Cost per patient	Cure rate	Incremental cost effectiveness ratio
MVA	$754	95%	$793 per cure
Observation	$804	88%	Dominated
Medical management	$926	81%	Dominated
Dilation & curettage	$2310	99%	$38,900 per cure

A Dutch study undertook a cost analysis alongside a randomised trial of misoprostol versus curettage following expectant management (Graziosi et al., 2005c). The authors stated that a full cost effectiveness analysis was not undertaken because the trial found that both strategies were equally effective. The analysis was undertaken on an intention-to-treat basis. The study enrolled 154 women with early pregnancy failure who had been managed expectantly for a minimum of 1 week. Resource use was prospectively collected for a period of up to 6 weeks. Curettage had to be performed within a week of randomisation. Medical treatment was 4 tablets of 200 micrograms of vaginal misoprostol given in an outpatient setting and repeated 24 hours later if necessary. In the event of failed medical treatment, curettage was planned. Costs were based on a societal perspective. Individual case record data was used to measure resource utilisation. Productivity losses were estimated by self-completed patient questionnaires. Costs relating to trial protocol were excluded from the analysis. The paper reported that the mean direct cost (defined as costs of medical intervention) per woman was €433 for medical management compared to €683 for surgical management (MD €250, 95% CI €184 to €316, $P < 0.001$). The difference in indirect costs (defined as the costs of productivity losses) was not statistically significant at the 5% level (MD €58, 95% CI -€61 to €179, $P = 0.51$). A sensitivity analysis suggested that as long as misoprostol achieved a complete evacuation rate of 31% or more (53% in this study) then medical management was the less costly strategy.

A paper reported a decision analytic cost analysis comparing expectant, medical (misoprostol) and surgical management for uncomplicated miscarriage in the first trimester (You & Chung, 2005). The decision model used clinical inputs sourced from the literature and costs were assessed from the perspective of a public healthcare provider in Hong Kong. In the surgical strategy women received dilation and curettage within one day of inpatient care and one follow-up appointment in an outpatient clinic. The model allowed for the possibility of surgical complications, including the need for further surgical evacuation, although very minor events with little or no resource consequences were not incorporated. In the expectant management and surgical strategies, patient choice was allowed, in that surgery could be chosen as an alternative if the other strategies were deemed unacceptable. In the patients who accepted medical or expectant management it was assumed that patients would be managed within an outpatient setting with two follow-up visits within 2 weeks. The outcomes of these strategies included complications necessitating surgical evacuation. The probabilities for the different branches of the tree emanating from chance nodes were estimated from the literature. A cost per patient was estimated which included primary treatment in the event of a spontaneous miscarriage, the cost of surgical intervention when the primary treatment failed and the cost of other complications. The base-case analysis found that misoprostol was the cheapest strategy with a cost of USD $1000. The expectant and surgical strategy cost USD $1172 and USD $2007 per patient respectively.

A UK economic evaluation, taking a societal perspective and conducted alongside a randomised controlled trial (miscarriage treatment [MIST] trial), compared the cost effectiveness of expectant, medical and surgical in an early pregnancy assessment unit setting (Petrou et al., 2006). Women randomised to expectant management were allowed to go home with no intervention. Women allocated to medical management with incomplete miscarriages were admitted to hospital and given a single dose of 800 micrograms of misoprostol. Medical management for women with incomplete miscarriages were pre-treated with a single oral dose of 200 mg of mifepristone prior to admission 24–48 hours later for a single vaginal dose of 800 micrograms of misoprostol. Surgical management involved admission of women for the surgical evacuation of retained products. Gynaecological infection was the primary outcome of the trial, covering the first 14 days and the first 8 weeks after entry into the trial. Trial data collection forms were used to collect details of resource use by each

study participant. A postal questionnaire was used to collect data on community and social care contacts made by women, as well as childcare support and travel distance to healthcare providers that were attributable to their miscarriage treatment. Unit costs, obtained from a variety of sources, were then used to cost the resource inputs using 2001–02 prices. In total, resource use was collected from 1200 women.

The mean cost of hospital care was £733 (standard deviation [SD] = £845) in the expectant management group, £1008 (SD = £644) in the medical management group and £1210 (SD = £428) in the group allocated to surgical treatment. The authors used non-parametric bootstrapping to determine confidence intervals for the mean difference in costs as the cost data was skewed. They reported that the mean cost of surgical treatment was £200 (95% CI £122 to £278) more expensive than medical treatment and that the mean cost of medical management was £273 (95% £160 to £376) more expensive than expectant management. This finding wasn't affected when broader societal costs were included in the analysis. Both expectant and medical management led to a non-significant reduction in gynaecological infections when compared with surgical management, a result suggesting that surgical management is dominated (more expensive and less effective) than the alternatives. Medical management had the least number of gynaecological infections and the point estimate of the incremental cost effectiveness of medical management relative to expectant management was approximately £63,000 per gynaecological infection avoided. Non-parametric bootstrapping simulation was used to generate 1000 replications of the ICER and derive a concomitant cost effectiveness acceptability curve. With a willingness to pay of £10,000 to avoid a gynaecological infection, there was a 97.8% probability that expectant management was the most cost-effective strategy. Expectant management was found to have the highest probability of being cost effective up to a willingness to pay threshold of £70,000 per gynaecological infection avoided. The authors note that the cost effectiveness of expectant and medical management may have been over-estimated if the higher rate of emergency consultations and admissions observed in those groups led to an increased rate of health care utilisation beyond the study follow-up period (8 weeks post randomisation). The authors also state that a preference based measure of health outcome (such as QALY) would have been better for comparative purposes. They acknowledge that it might have been possible to have mapped the trial outcomes onto a multi-attribute utility measure, such as the SF-6D, and then extrapolate to the QALYs attributable to each management alternative. They suggest that doing so would have added little to the results of the evaluation as none of the eight subscales of the UK Short Form-36 health-related quality of life measure showed any significant difference within the trial with respect to the type of management.

A Finnish cost effectiveness analysis (Niinimaki et al., 2009) evaluated the cost effectiveness of medical and surgical management of miscarriage using data from a previously published randomised study (Niinimaki et al., 2006). In that study 49 women were allocated to medical treatment and 49 women were allocated to surgical treatment. In this 2009 study the cost of both treatment alternatives were compared in terms of the initial allocated procedure and costs arising from treatment complications. The analysis was restricted to the 46 women in each arm who received their allocated treatment in the trial. Resource inputs (such as staffing, drugs and tests) were estimated for surgical and medical treatment with an experienced healthcare professional estimating the staff time involved. Taking the perspective of the healthcare provider, costs were calculated at 2007 prices using institutional prices and charges to the county for outpatient and inpatient visits and procedures. For each study participant the hospital files were used to determine the number, type and length of the hospital visits, which were then costed using these institutional prices. The authors report that the cost for women allocated to medical treatment was €455 compared with €489 for women allocated to surgical treatment. No confidence intervals or standard errors were reported for these point estimates or for the €34 difference they report.[*] An ICER was then calculated using patient satisfaction, pain and successful treatment (defined as no requirement for subsequent intervention) as alternative measures of effect. The results presented by the study authors are shown in Table 10.9.

[*] For medical treatment they report a total cost of €22,282 which for 46 patients would be a cost per patient of €484. For surgical patients they report a total cost of €23,970 which for 46 patients would be a cost per patient of €521 (difference €37)

Table 10.9 Incremental cost effectiveness ratios (Niinimaki et al., 2009)

Measure of effect	Incremental cost of surgery (n = 46)	Incremental gain with surgery (patients)	Incremental cost effectiveness ratio (per woman)
Pain avoidance	€1688	12	€141
Satisfaction	€1688	7	€241
Successful treatment	€1688	5	€338

However, for successful treatment the denominator is based on the women allocated to each treatment arm (n = 49) and clearly an incremental cost based on treating 46 women will be an underestimate of the total incremental cost. Furthermore, for the satisfaction measure the denominator was not identical between the comparators as well as being different from the women on which the total cost was based. In Table 10.10 the ICERs are recalculated using data from the paper but calculating the incremental cost per woman and the incremental gain as the difference in the event rate.

Table 10.10 Recalculated incremental cost effectiveness ratios (Niinimaki et al., 2009)

Measure of effect	Incremental cost per patient	Incremental gain with surgery (event rate)	Incremental cost- effectiveness ratio (per woman)
Pain avoidance	€37	0.26	€142
Satisfaction	€37	0.12	€308
Successful treatment	€37	0.10	€370

It should also be noted that although there is considerable overlap, the women on whom the costs are based are not all the same as the women for whom pain, satisfaction and successful treatment outcomes are based. The authors do not consider the willingness to pay for the benefits attributable to surgery and therefore do not answer the question as to whether the additional costs of surgical treatment represent a cost-effective use of resources. The authors conclude that it would not be ethical to only offer medical treatment based on its lower cost.

Discussion

The main focus of this guideline was to compare the cost effectiveness of expectant, medical and surgical management for first trimester miscarriage. Our quality assessment suggested that study quality varied quite widely across our six included studies. The evidence from these studies and some of its limitations are discussed below.

All the studies included in this review found that surgical management was the most expensive option. In the three studies that considered all three treatment alternatives (Petrou et al., 2006; Rocconi et al., 2005; You & Chung, 2005), two found expectant management to be the cheapest treatment option. One study (You & Chung, 2005) reported that medical management was cheaper than expectant management. However, the decision tree developed for this study allows for patient choice which is not entirely consistent with a comparison of competing alternatives, a key tenet of economic evaluation. In both medical and expectant strategies, patients have the option to reject that management strategy of favour of surgery. The costs of the expectant and medical management strategies therefore become a weighted average of two treatment alternatives with the weights determined by the acceptance rate for the suggested management strategy. The acceptance rates were 64% and 86% for expectant management and medical management respectively. Therefore, their finding that medical management was the lowest cost treatment was an artefact of more of the expectant management patients choosing surgery rather than medical management having intrinsically lower costs. There is a sense that the alternatives are not competing if patients assigned to one management strategy have the option to undergo one of the alternatives being evaluated.

Three of the studies were cost analyses or cost minimisation analyses. This study design is only deemed appropriate in economic evaluation where the alternatives being evaluated are deemed to be equivalent in terms of their benefits and harms. One of the cost studies (Graziosi et al., 2005c) justified this approach on the basis that a recently performed randomised controlled trial (RCT) had found the effectiveness of misoprostol and curettage to be 'equal' (Graziosi et al., 2004). However, the justification for this equivalence is based on a non-statistically significant difference at the 5% level, which is more a case of no strong evidence of a difference rather than evidence of no difference. However, it is argued that the non-statistical significance rationale for cost minimisation analysis is inappropriate and that cost effectiveness analysis with probabilistic sensitivity analysis, utilising the probability distribution of treatment effect, is the preferred approach (Briggs & O'Brien, 2001).

A better rationale for a cost minimisation approach in this case is that a miscarriage is a time limited event and therefore all women are ultimately 'cured'. Furthermore, the morbidity associated with miscarriage is usually only a short-term phenomenon which means that the quality of life gains from earlier resolution are relatively small. Where first-line treatment doesn't achieve a 'cure' further treatment options are available. One study uses cost per cure as its measure of cost effectiveness, with 'cure' being defined as a negative pregnancy test at 28 days after commencement of treatment (Roccini et al, 2005). As a result, this study finds different ICERs for the different strategies, although these are not presented in the paper. However, even correctly calculated, the meaningfulness of these ICERs is questionable. The decision model does not reflect actual clinical practice which may involve the offer of alternative treatment in the event of treatment failure, which has additional resource implications. The value of the measure of effect of 'cure' at 28 days may also be questioned given the time limited nature of the condition. Even if we accept this as a proxy for earlier resolution of symptoms and morbidity the authors offer no guide to the decision makers as to how this benefit is to be valued.

Three of the studies were economic evaluations conducted alongside RCTs (Hughes et al., 1996; Graziosi et al., 2005c, Petrou et al., 2006). However, one of the studies (Hughes et al., 1996) used a partial randomisation approach which allowed women with a strong preference for a particular treatment alternative to be included, although that can clearly dilute the benefits of randomisation if this introduces systematic differences between the treatments in terms of patient characteristics. It may also not reflect treatment options if decisions on treatment are to be determined according to their cost effectiveness.

Another evaluation was based on a previously published trial (Niinimaki et al., 2009). The trial on which patient outcomes were derived had a small number of participants (n = 98). The trial found that surgical management had fewer patients with pain, more satisfied patients and more patients with successful treatment, defined as no requirement for further treatment. Thus it was possible from the data in the paper to calculate ICERs for all these different measures of effect for surgical management and medical management. However, this information is of little use to decision makers without some decision-rule as to what incremental benefit would be sufficient to justify the incremental costs. Also, it can be argued that their definition of success is not the most appropriate as further treatment, while having a resource implication, is likely to erode or eliminate any differences in health-related quality of life. Another major limitation with this study, especially given the small numbers of patients on which it is based, is that no allowance is made for uncertainty. The results are only provided as point estimates and no sensitivity analysis is undertaken.

Most of the included studies have important limitations in terms of their economic methods. However, there was one very good quality economic evaluation (Petrou et al., 2006). This was based on the collection of resource use data alongside a large randomised controlled trial (n = 1,200). Costs were presented from a number of perspectives but they included the health service perspective and the price year is clearly stated (2001–02). The costs of the alternative management strategies were presented as mean values with standard deviations. Comparisons of the costs of different strategies were reported as mean differences with confidence intervals. In addition to a cost comparison, the incremental cost effectiveness was assessed using the cost per gynaecological infection prevented. Uncertainty was taken into account using probabilistic sensitivity analysis by using non-parametric bootstrapping to generate 1000 replications of each of the ICERs. This was made relevant to decision making by the use of cost effectiveness acceptability curves which found that expectant management was likely to be the most cost-effective strategy up to a willingness to pay threshold of £70,000 per

gynaecological infection prevented. Using an advisory willingness to pay threshold of £20,000 per QALY, which is more consistent with NICE methods, expectant management would be most likely to be cost effective as long as the gain from an averted gynaecological infection did not exceed 3.5 QALYs, as seems likely (3.5 QALYs is equivalent to an additional 3.5 years lived in perfect health). The authors acknowledge that the fact that effectiveness has not been measured in a preference based measure of health outcome (such as QALY) is a limitation, but they do note that the MIST trial revealed no significant differences in any of the eight sub-scales of the UK Short Form-36 health-related quality of life measures. This would suggest that the QALY differences between the alternative management strategies are likely to be small and therefore unlikely to change a conclusion that expectant management is likely to be the most cost-effective strategy.

Conclusion

The data from this review suggests that expectant management is the most cost-effective first-line treatment for the management of first trimester miscarriage. The GDG accepted that this evidence was supported by one high quality published economic evaluation which was relevant to an NHS context and which considered the relevant management alternatives (Petrou et al., 2006). Therefore, the GDG was prepared to make recommendations based on this evidence without the requirement for a new guideline model.

10.4 Management of ectopic pregnancy

Introduction

The incidence of ectopic pregnancy in the UK is approximately 1.1% (Lewis, 2007). Ectopic pregnancy can be fatal if left untreated. Technological advances mean that earlier diagnosis is now possible which has helped extend the range of available treatments. However, uncertainty remains as to whether treatment should be medical or surgical and, if the latter, whether surgery should be conservative (salpingotomy) or radical (salpingectomy) and whether the surgical technique should be laparotomic or laparoscopic. Clearly, within a context of trying to maximise health gain from finite resources, the cost effectiveness of these treatment alternatives also has to be considered.

Review of the published health economic evidence

A review of the literature was undertaken based on the three related clinical questions reviewed for this guideline.

Medical compared with surgical management of ectopic pregnancy

A total of 33 articles were found using this search when applying a health economics filter. From reading the abstracts of these papers, 12 full papers were obtained, of which eight were included in this review.

A Canadian study (Yao et al., 1996) undertook a retrospective cost analysis of women treated with methotrexate and women treated with laparoscopy. Treatment decisions were made by doctors with no random allocation of patients. Therefore, it cannot be inferred that the patient groups are comparable. Using direct medical costs they reported that the methotrexate group had a mean cost of 880 Canadian dollars (CAD) (standard error [SE] ± 160) compared to a mean cost of 1840 CAD (SE ± 150) in the laparoscopic group, with the difference statistically significant at the 5% level ($P < 0.001$).

A New Zealand paper (Sowter et al., 2001a) carried out a cost minimisation analysis alongside a small randomised trial (n = 62). In the trial women were randomised to either a single dose of methotrexate or laparoscopic surgery. The study considered both direct and indirect costs (such as productivity losses) but only the former is relevant using NICE methods (NICE, 2009). The authors reported that the direct costs in the methotrexate group were 1613 New Zealand dollars (NZD) (95% CI 1116 NZD to 2061 NZD) lower than the direct costs in the laparoscopy group.

A decision analytic model (Morlock et al., 2000) compared the cost effectiveness of intramuscular methotrexate with laparoscopic salpingotomy for small unruptured ectopic pregnancy. Clinical model inputs were based on a meta-analysis with costs based on local charge data at the authors' US

hospital. With base-case model values, laparoscopic treatment was more than 3000 USD more expensive than methotrexate per resolved ectopic pregnancy. The authors reported a number of sensitivity analyses which continued to find methotrexate to be the cheaper treatment.

A French study (Lecuru et al., 2000) compared the direct costs of single dose methotrexate and laparoscopy in the treatment of unruptured ectopic pregnancy. The study was prospective but women having laparoscopic salpingectomy did so because they either refused methotrexate or because methotrexate was contraindicated. Such studies are vulnerable to selection bias. Methotrexate was found to be significantly cheaper than laparoscopic salpingectomy (€1145 compared with €2442, $P = 0.006$). The authors also noted that the saving with methotrexate was greatest for small unruptured ectopic pregnancy because such cases require less hospitalisation and follow-up.

An earlier but similar French study (Robin et al., 1998) found that mean treatment costs with methotrexate were 1469 USD cheaper than with laparoscopic salpingotomy.

A US study (Alexander et al., 1996) compared the costs of methotrexate and laparoscopic salpingotomy for women with a small unruptured ectopic pregnancy. The authors assumed that both treatments would lead to a resolution of the ectopic pregnancy without maternal morbidity or long-term morbidity, forming their justification for a cost minimisation approach. Clinical outcomes were estimated from a review of the literature. The direct costs of each treatment alternative were estimated using actual reimbursement rates of a third party payer. The authors reported that methotrexate was 2536 USD less expensive in its 'best-case' scenario and 1124 USD less expensive in its 'worst-case' scenario. The authors additionally reported sensitivity analyses showing that methotrexate remained less expensive across a wide range of probability and cost inputs.

A Dutch study (Mol et al., 1999), undertook an economic evaluation alongside a randomised control study to compare systemic methotrexate with laparoscopic salpingotomy in haemodynamically stable women with a confirmed unruptured tubal pregnancy. The authors justified a cost minimisation approach by stating that the clinical outcomes of the trial were the same for the two treatment alternatives. Using direct medical costs methotrexate was 769 USD (95% CI 28 USD to 2384 USD) more expensive than laparoscopic salpingotomy.

A US analysis (Creinin & Washington, 1993) compared the costs of surgery versus methotrexate for the management of ectopic pregnancy. The direct medical costs of surgery were derived from billing statements from all women treated with ectopic pregnancy in 1991. They then estimated what proportion of these women could have been 'eligible' for methotrexate using the following criteria:

- haemodynamically stable
- size of ectopic pregnancy smaller than 35 mm
- the ectopic pregnancy was located in the fallopian tube and not ruptured
- no cardiac activity was present if an ultrasound was performed before the procedure
- no evidence of hepatic dysfunction or renal disease
- a complete blood count did not reveal dyscrasia
- no evidence of poor compliance.

A cost for methotrexate was then estimated using a published protocol for single dose methotrexate (Stovall et al., 1991). The mean surgical cost of the 50 women included in the analysis was 10,509 USD and it was estimated that the cost of methotrexate in 1992 prices would be 1495 USD. Using a methotrexate success rate of 93% in the 30% of 'eligible' women, the authors extrapolated that the use of methotrexate in these women could reduce the mean cost of ectopic pregnancy treatment to 7951 USD per woman.

Laparotomy compared with laparoscopic techniques

The search strategy identified 56 papers of which 10 were obtained in full. Five articles are included in this review.

An Australian study (Lowe at al., 1998) retrospectively analysed 45 consecutive cases of surgically treated ectopic pregnancy in order to compare laparoscopic and laparotomic techniques. Such study

designs are prone to selection bias. Laparoscopic treatment had a mean cost of 2930 USD (95% CI 2458 USD to 3402 USD) compared to 4259 USD (95% CI 3666 USD to 4852 USD). The 1329 USD saving per woman with laparoscopy was statistically significant at the 5% level.

A Swedish cost effectiveness analysis (Gray et al., 1995) compared laparoscopy versus laparotomy for ectopic pregnancy alongside a randomised controlled trial. The authors reported that laparoscopy dominated laparotomy, being equally successful and having lower costs. It was noted that the post-operative inpatient stay for laparotomy was 2.9 days longer and this was an important driver of the increased costs associated with that technique.

A Dutch study (Mol et al., 1997) compared the costs of laparoscopy and open surgery in women with a tubal pregnancy. The analysis was undertaken on a group of consecutive patients having either type of surgery. The authors note that treatment was successful in all 255 women. This study found that laparoscopic salpingectomy was cheaper than laparotomic salpingectomy (1872 USD versus 3,490 USD) and similarly that laparoscopic salpingotomy was cheaper than the open surgery alternative (2125 USD versus 3420 USD).

A US paper (Foulk & Steiger, 1996) reported a retrospective cost analysis of the operative management of ectopic pregnancy within the authors' own hospital. The costs were: laparoscopy alone 4344 USD; laparoscopy converting to laparotomy 6979 USD; laparotomy in haemodynamically stable patients 5333 USD; and laparotomy in haemodynamically unstable patients 7556 USD. The authors note that the cost saving obtained with laparoscopy is reduced when including the 21% of women who convert to laparotomy from an intended laparoscopy. A threshold sensitivity analysis suggested that the costs would be equivalent if the conversion rate reached 37%. In a similar vein it is suggested that costs would be similar if the postoperative length of stay for laparotomy patients was no more than two days.

A non-randomised prospective cohort study in the UK (Baumann et al., 1991) compared the costs of laparotomy and laparoscopy management of ectopic pregnancy in haemodynamically stable women. Costing was based on 20 randomly selected women from each treatment group and found that laparoscopy produced an overall saving of £701.47 ($P < 0.001$), primarily as a consequence of a shorter length of stay.

Salpingectomy compared with salpingotomy

The search strategy identified 60 papers. However, the abstracts were reviewed and none were relevant for this question.

Notwithstanding the findings of this review of the literature, much of which is quite dated and prone to selection bias, the GDG felt it would be useful to develop a new model for this guideline reflecting the best available clinical evidence, based on the reviews undertaken for this guideline, and relevant for an NHS context. This model is described below. The GDG thought that it was not useful to consider laparotomic techniques, as this is rarely thought appropriate as a first-line treatment and because the health economic evidence, limited as it is, suggests that laparoscopic techniques are likely to be more cost effective as well as preferable to women.

Method

A decision analytic model was developed in Microsoft Excel® to compare the cost effectiveness of the following treatment alternatives in women diagnosed with an ectopic pregnancy but not requiring urgent surgical intervention as, by definition, medical intervention could not be considered as a treatment alternative in such women.

Laparoscopic salpingotomy

Here women are assigned to laparoscopic salpingotomy although it is assumed that a proportion of these will convert to an open procedure. The women having an open salpingotomy will incur a different procedure cost but it assumed that there are no costs incurred from conversion in itself. The surgery is assumed to have a complication and blood transfusion rate which differs according to whether laparoscopic or open surgery is undertaken. It is assumed that the surgical complication and blood transfusion rates are independent of 'success' or 'failure' (when further intervention is required to treat the ectopic pregnancy). There is a risk of emergency admission in women in whom the initial procedure fails. Some women have salpingectomy as the second-line treatment subsequent to failure

of the initial surgery. The remaining women in whom first-line treatment fails then receive methotrexate as second-line treatment. In patients failing with second-line methotrexate, salpingectomy will be undertaken as a third-line treatment. Salpingectomy, whether offered as a second-line or third-line treatment, will usually be performed laparoscopically but a proportion will convert to open salpingectomy. As for the initial surgery, complication and blood transfusion rates will differ according to whether surgery is laparoscopic or open. Second-line or third-line surgery is assumed to be 100% successful. There is not assumed to be any further risk of emergency admission following second-line treatment.

Laparoscopic salpingectomy

As with salpingotomy it is assumed that a proportion of laparoscopic salpingectomy patients will convert to an open salpingectomy with a different procedure cost but no costs of conversion. Where salpingectomy 'fails' some women will have a second-line salpingectomy, which would normally be laparoscopic but with some conversion to open surgery. Other patients 'failing' with initial salpingectomy receive methotrexate as the second-line treatment. The assumptions, with respect to surgical complications and blood transfusion, are the same as for salpingotomy. It is assumed that there are no emergency admissions with this strategy.

Methotrexate

Women are initially treated with methotrexate. In a proportion of cases, the treatment will fail in which instance there is a risk of rupture which is assumed to lead to an emergency admission. A proportion of women who rupture will require a blood transfusion. There will also be some women in whom first-line treatment with methotrexate fails who require an emergency admission without a rupture. It is assumed that a proportion of those in whom methotrexate fails will have further methotrexate as a second-line treatment. The remaining women in whom methotrexate fails as a first-line treatment will have laparoscopic salpingectomy, with a proportion converting to open salpingectomy. Those in whom methotrexate fails as a second-line treatment will then have laparoscopic salpingectomy with some converting to open salpingectomy as third-line treatment. As with first-line methotrexate treatment failure, women in whom methotrexate fails as a second–line treatment have a risk of rupture, blood transfusion and emergency admission. Of these a proportion will have an emergency admission as a result of rupture. Surgery carries the same risk of complication and blood transfusion as in the previous strategies.

A schematic of the overall model structure is illustrated in Figure 10.7 with greater detail of the individual treatment tree being shown in Figures 10.8 to 10.10.

Figure 10.7 Schematic of model decision tree

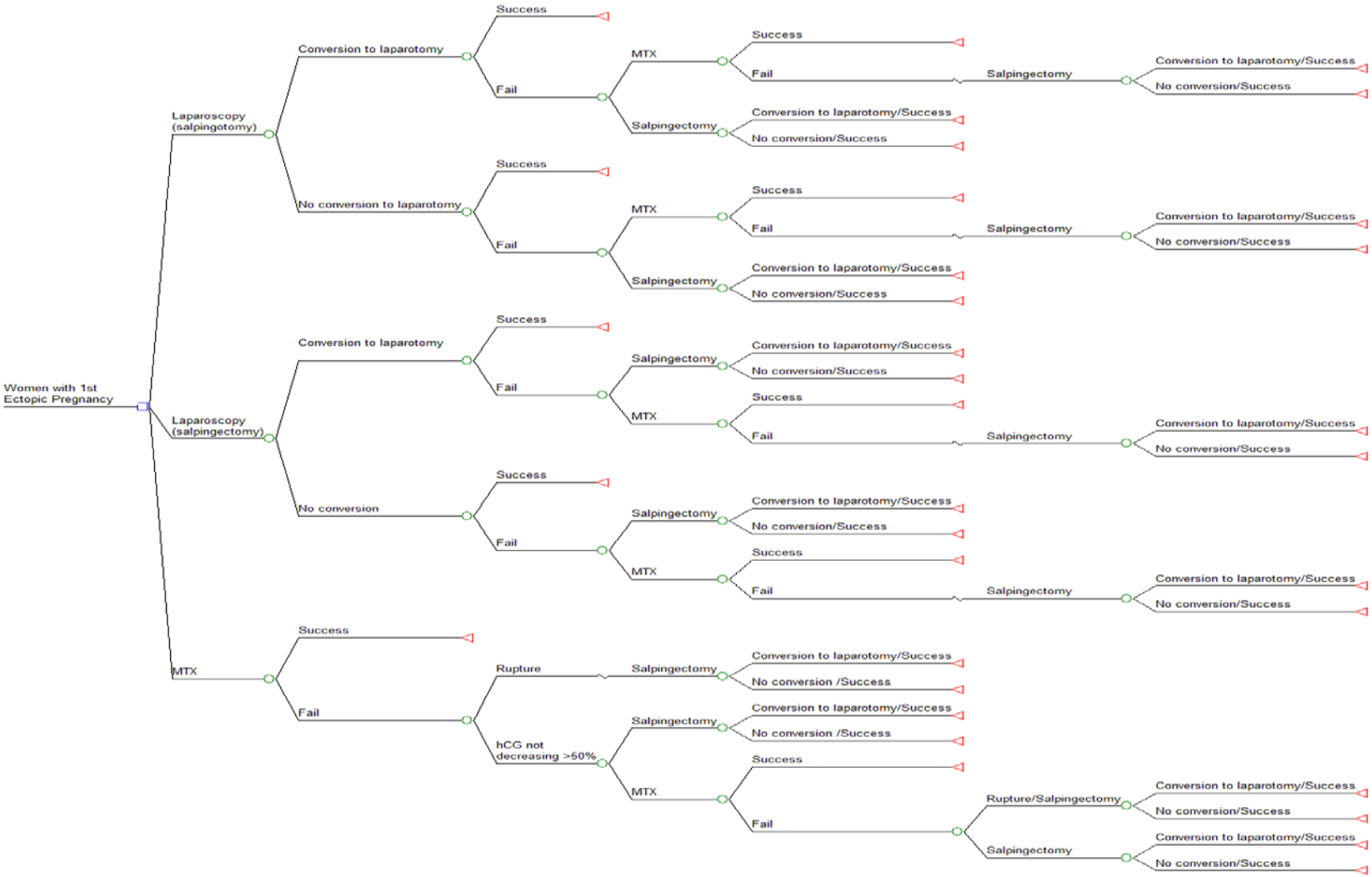


Figure 10.8 Salpingotomy decision tree

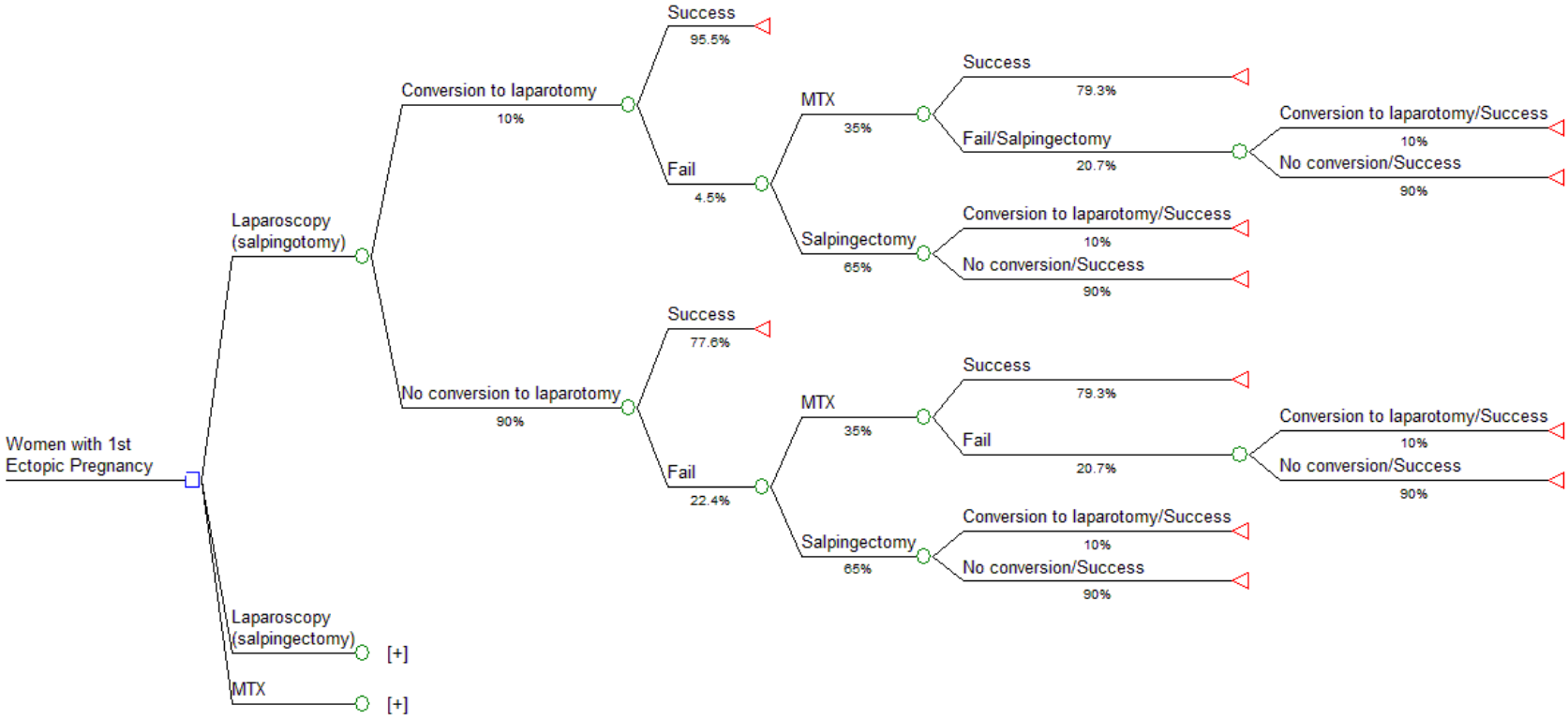


Figure 10.9 Salpingectomy decision tree

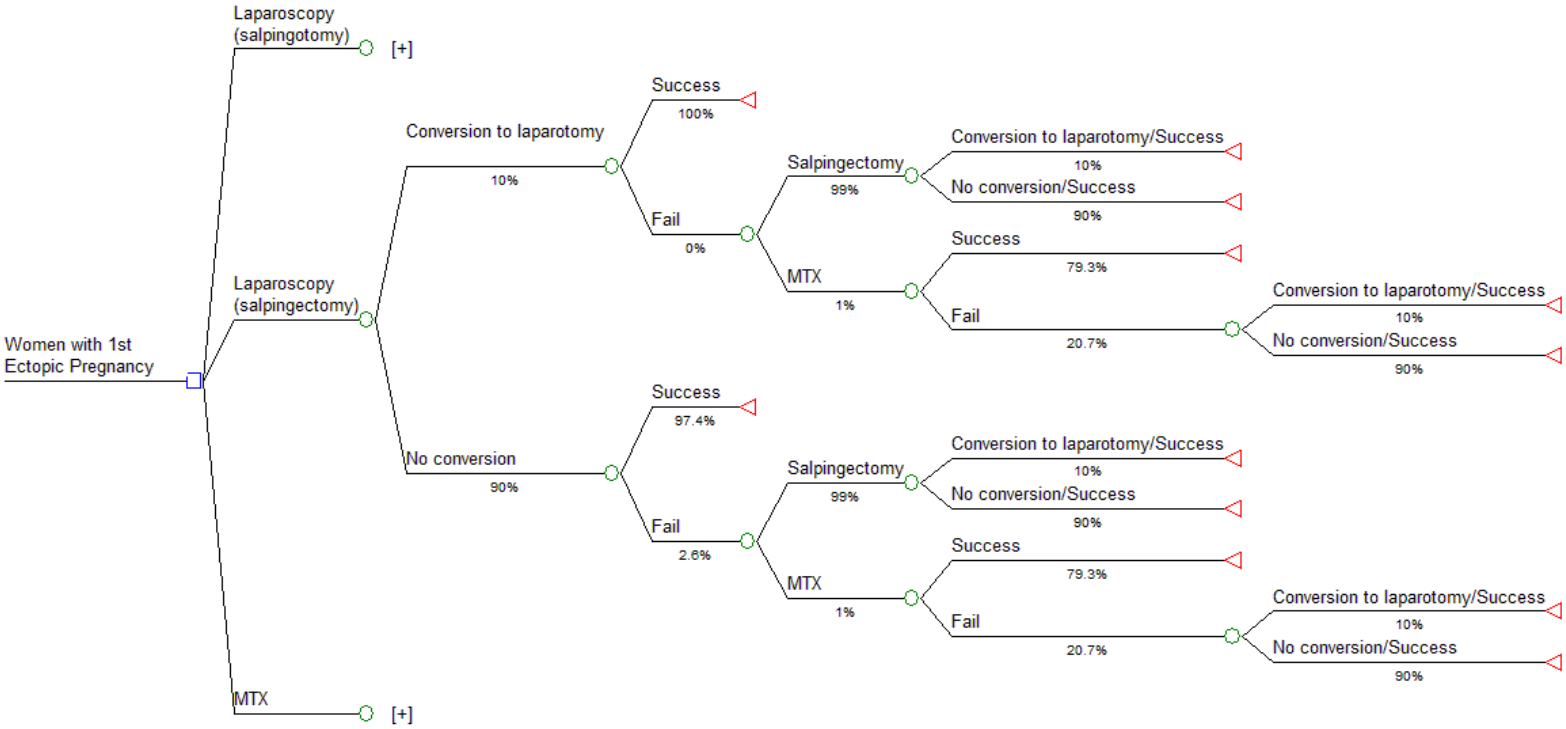
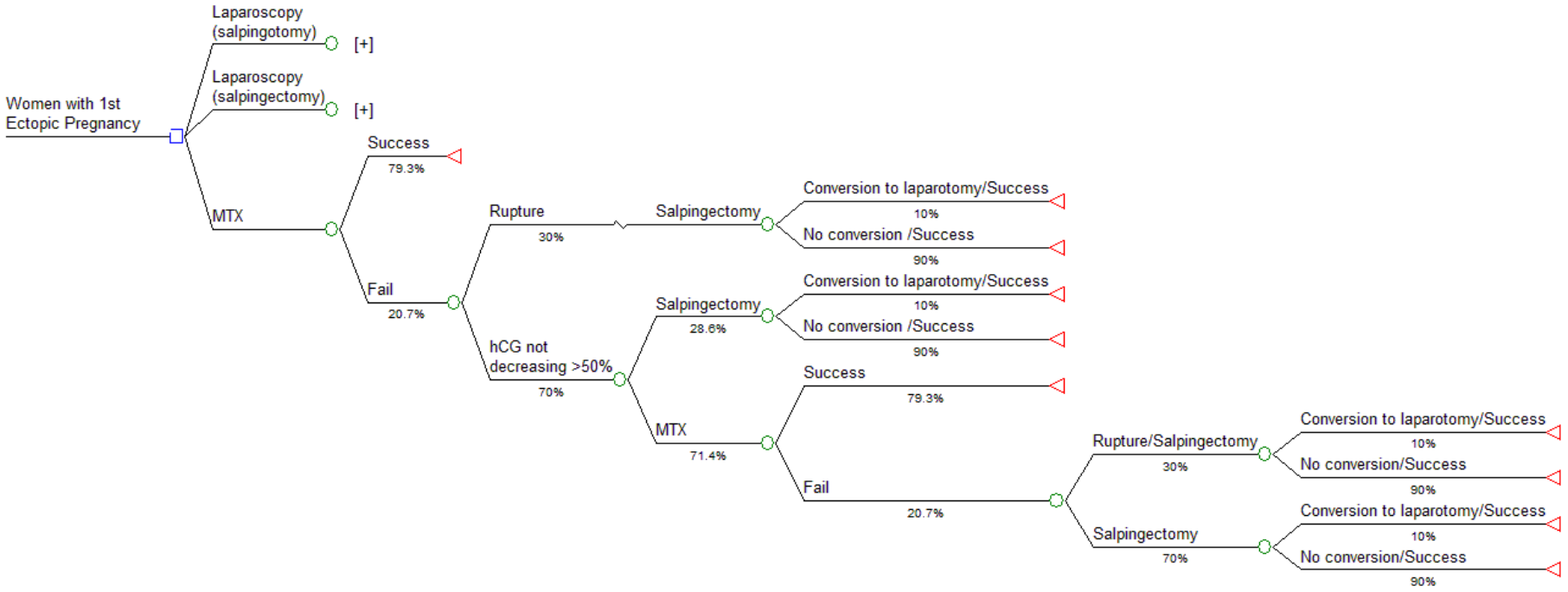


Figure 10.10 Methotrexate decision tree



The structure of the decision tree was agreed by the GDG as being appropriate in an NHS context to the population of interest, namely women with a diagnostically confirmed first ectopic pregnancy and without emergency presentation.

The base case assessment of cost effectiveness is undertaken using a cost minimisation approach, where the optimal strategy is that which is the cheapest. Such an approach may be considered valid when the effectiveness of all treatment alternatives is considered identical. Historically, this approach has sometimes been used when the clinical data fails to reject a null hypothesis of no difference at the 5% level. However, the 5% cut-off for statistical significance is an arbitrary one and a failure to reject the null hypothesis does not imply that treatment effectiveness is identical and the cost minimisation approach in such cases has been criticised (Briggs & O'Brien, 2001). Nevertheless, the GDG considered that a cost minimisation approach was reasonable in this context. The rationale was that all women are ultimately 'cured' and that this occurs within a fairly short time frame so that any QALY differences between treatment alternatives would be small.

Probabilistic sensitivity analyses and other sensitivity analyses were undertaken to assess the importance of parameter uncertainty within the model. A QALY loss variable for methotrexate treatment was incorporated into the model so that its impact could be assessed as part of a 'what-if' sensitivity analysis. Methotrexate typically has a longer duration to resolution of symptoms than surgery (see Tables 7.1 and 7.2) as well as a risk of rupture which, although rare, can lead to death (http://www.nlm.nih.gov/medlineplus/ency/article/000895.htm [accessed January 2012]).

Model probabilities

Where possible the probabilities were taken from the relevant clinical reviews undertaken for the guideline. Data in the reviews related to treatment offered as first-line and therefore, where additional treatment was provided subsequent to first-line treatment, it was assumed that efficacy would not be different from that achieved first-line. Where data was not available from the reviews to populate model parameters, estimates taken from the literature or the GDG were used.

The model probabilities are shown in Table 10.11.

Table 10.11 Model probabilities

Item	Value	Source	Notes
Methotrexate first-line success	79.3%	Hajenius (1997), Moeller (2009), Fernandez (1998), Saraj (1998), Sowter (2001b)	Systemic methotrexate. Guideline meta-analysis
Methotrexate second-line success	79.3%	Hajenius (1997), Moeller (2009), Fernandez (1998), Saraj (1998), Sowter (2001b	Assumed to be the same as for first-line treatment but this assumption can be relaxed as part of a sensitivity analysis
Laparoscopic salpingectomy success	97.4%	Mol (1997)	
Open salpingectomy success	100%	Mol (1997)	
Laparoscopic salpingotomy success	77.6%	Mol (1997)	
Open salpingotomy success	95.5%	Mol (1997)	
Laparoscopic blood transfusion risk	0.4%	Mol (1997)	Assumed that this would not differ between salpingectomy and salpingotomy and combined data from both procedures (1/39 + 0/76)

Item	Value	Source	Notes
Open surgery blood transfusion risk	7.1%	Mol (1997)	Assumed that this would not differ between salpingectomy and salpingotomy and combined data from both procedures (9/118 + 1/22)
Methotrexate blood transfusion risk | Rupture	50.0%	GDG estimate	
Emergency admission | MTX fail (no rupture)	10.0%	GDG estimate	
Emergency admission | salpingotomy fail	10.0%	GDG estimate	
Laparoscopic surgical complications	0.4%	Mol (1997)	There were 0/115 complications in laparoscopic group. It is not possible to calculate the standard error (SE) for a proportion if there are zero events. Without a SE it is not possible to sample from a distribution. Therefore, a common fix for this problem is to add 0.5 to the events and non-events (continuity correction)
Open surgery complications	3.6%	Mol (1997)	5/140 in the study had surgical complications (2/118 with open salpingectomy open and 3/22 with salpingotomy open)
MTX | Salpingectomy fail	50.0%	GDG estimate	
MTX | Salpingotomy fail	35.0%	GDG estimate	
Rupture | MTX fail first-line	15.0%	GDG estimate	
Rupture | MTX fail second-line	30.0%	GDG estimate	
Salpingectomy | MTX fail	50.0%	GDG estimate	
Conversion to open salpingectomy	10.0%	GDG estimate	
Conversion to open salpingotomy	10.0%	GDG estimate	

The '|' symbol should be read as meaning the first item, given the second item

Model costs and resource use

This analysis was undertaken from the perspective of the NHS and personal social services which is in accordance with NICE guidelines methodology (NICE, 2009). Treatment alternatives were compared using standard methods of incremental analysis and costs are based on 2010/11 prices. Discounting was not needed as all model costs fall within a few weeks of the ectopic pregnancy diagnosis.

Table 10.12 shows the unit cost for resource use inputs in the model and Table 10.13 shows the assumptions, based on GDG estimates, about resource use associated with monitoring and follow-up for each treatment alternative.

Table 10.12 Model costs

Item	Value	Source	Notes
Methotrexate	£425	NHS Reference Costs 2010-11	Currency Code: MA18C Medical termination of pregnancy – less than 14 weeks of gestation Day case
Salpingectomy (laparoscopy)	£1392	NHS Reference Costs 2010-11	Currency Code: MA09Z Upper Genital Tract Laparoscopic / Endoscopic Intermediate Procedures, Day case
Salpingectomy (laparotomy)	£1474	NHS Reference Costs 2010-11	Currency Code: MA11Z Upper Genital Tract Intermediate Procedures, Elective
Salpingotomy (laparoscopy)	£1392	NHS Reference Costs 2010-11	See Salpingectomy (laparoscopy)
Salpingotomy (laparotomy)	£1474	NHS Reference Costs 2010-11	See Salpingectomy (laparoscopy)
Emergency admission	£789	NHS Reference Costs 2010-11	Calculated as the difference in cost between an elective and non-elective (long stay) 'Upper Genital Tract Intermediate Procedure' (Currency Code: MA11Z)
Blood transfusion	£297	http://www.hta.ac.uk/fullmono/mon1044.pdf	Unit of blood £111.16 x 2 Matching £23.24 Updated to 2010 prices using Hospital and Community Health Service (HCHS) index
Surgical complications	£1333	Mol (1997), NHS Reference Costs 2010-11, Plowman (1999), Park (2011)	From Mol (1997) surgical complications were as follows: UTI 40%, Pneumonia 40%, Thromboembolism 20%. The following units costs were used: Thromboembolism £786, Pneumonia £941 UTI £1997 These costs were then weighted using the proportions from Mol (1997). The cost of Thromboembolism was estimated from the NHS Reference Cost for DVT. UTI was estimated from a study on hospital acquired infection in the UK (Plowman et al., 1999) and updated to 2010 prices using the HCHS index. Pneumonia was estimated from a US study (Park et al., 2011). The study value in USD was converted to UK pounds. (http://www.xe.com/ucc/convert/?Amount=1&From=USD&To=GBP [accessed January 2012]) and updated to 2010 prices using the HCHS index.
GP visit	£36	Unit Costs of Health and Social Care, Curtis (2010)	Based on surgery consultation lasting 11.7 minutes and including qualification and direct care staff costs

Item	Value	Source	Notes
Clinic visit	£141	NHS Reference Costs 2010-11	Consultant led first attendance: Face to face non-admitted
Full Blood Count	£3.94	Liverpool Women's Hospital (2011)	Obtained by GDG member
hCG	£3.94	Liverpool Women's Hospital (2011)	Obtained by GDG member
Kidney function	£3.60	Liverpool Women's Hospital (2011)	Obtained by GDG member
Liver function	£4.72	Liverpool Women's Hospital (2011)	Obtained by GDG member
Urine pregnancy test	£1	Estimate	

DVT deep vein thrombosis, hCG β-human chorionic gonadotrophin, USD US dollars, UTI urinary tract infection

Table 10.13 Quantity of **r**esource use by treatment

Item	**1st line**	**MTX**	**Salpin-gectomy**	**Salpin-gotomy**	**Salpin-gotomy**	**Salpin-gotomy**	**Salpin-gotomy**	**Salpin-gectomy**	**MTX**
	2nd line				**Salpin-gectomy**	**MTX**	**MTX**	**MTX**	**Salpin-gectomy**
	3rd line					**Salpin-gectomy**			
Full blood Count		1	0	0	0	1	1	1	1
Serum hCG		5	0	3	2	3	5	5	4
Kidney function		1	0	0	0	1	1	1	1
Liver function		2	0	0	0	2	2	2	2
Urine preg-nancy test		1	1	1	1	1	1	1	1
GP visit		0	0.5	0	0.5	0.5	0	0	0.5
Clinic visit		5	0.5	1	2.5	3.5	5	5	4

hCG β-human chorionic gonadotrophin, MTX methotrexate

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis takes into account sampling uncertainty in the data inputs in the same way that sampling uncertainty is taken into account when generating confidence intervals for point estimates of an effect size. A probability distribution for the parameter point estimate can be established based on its point estimate, sampling variability and sample size. Probability sensitivity analysis then involves Monte Carlo simulations where model parameters are repeatedly sampled from their distribution to generate simulation results. The results of the simulation then provide quantitative

information on the extent to which the cost effectiveness conclusion is sensitive to parameter uncertainty.

The probabilistic parameters for the model inputs based on data obtained from the clinical review are shown in Table 10.14. The probabilistic sensitivity analysis assumed that the methotrexate would always have the same effectiveness when used after first-line treatment as it would when used as a first-line treatment. The probabilistic parameters for the treatment costs are shown in Table 10.15.

Table 10.14 Parameters for probabilistic sensitivity analysis (model probabilities)

Item	Alpha	Beta	Distribution
Methotrexate success	157	41	Beta
Laparoscopic salpingectomy success	38	1	Beta
Open salpingectomy success	21	1	Beta
Laparoscopic salpingotomy success	59	17	Beta
Blood transfusion | laparoscopy	1	114	Beta
Blood transfusion | open surgery	10	130	Beta
Surgical complications | laparoscopy	0.5	114.5	Beta
Surgical complications | open surgery	5	135	Beta

The '|' symbol should be read as meaning the first item, given the second item

Table 10.15 Parameters for probabilistic sensitivity analysis (model costs)

Item	Mean	SE	Distribution
Methotrexate	£425	£22.66	Normal
Laparoscopic salpingectomy/salpingotomy	£1392	£40.61	Normal
Open salpingectomy/salpingotomy	£2218	£58.86	Normal
Surgical complications | open surgery	£789	£91.38	Normal

The '|' symbol should be read as meaning the first item, given the second item

See Section 10.2 for the method used to obtain the probabilistic costs parameters listed in Table 10.15.

Results

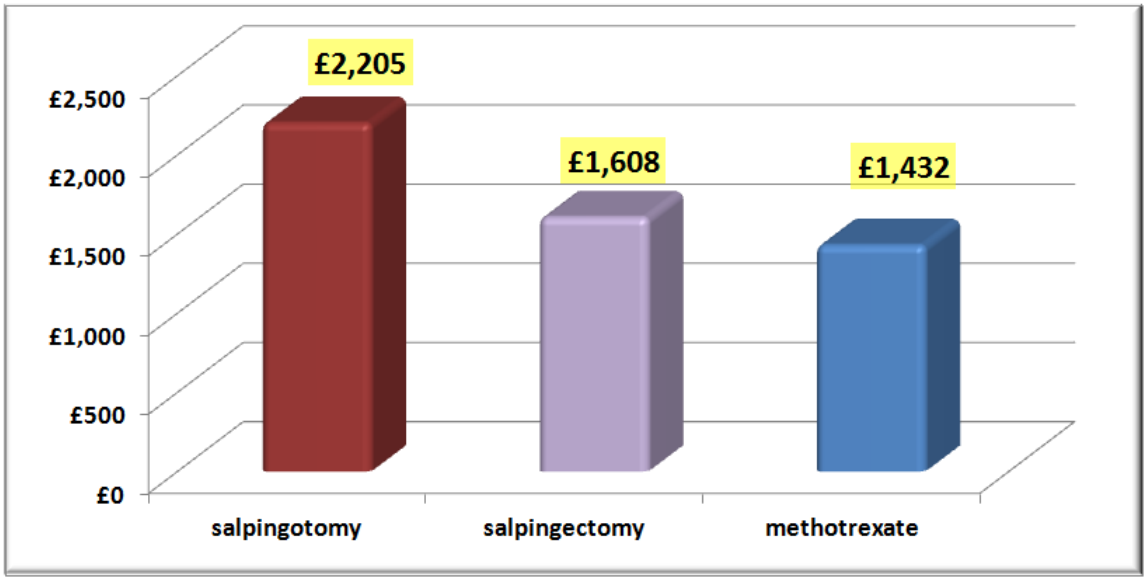
The base-case results are shown in Table 10.16 and Figure 10.11. Using a cost minimisation approach this suggests that methotrexate is the preferred strategy with a cost of £176 less than the next cheapest alternative.

It is likely that there may be some small QALY differences between the different treatments and the final two columns in Table 10.16 are used to illustrate the QALY gain that would be needed for the more expensive option to be considered cost effective relative to the next cheapest alternative. Where no strategy is dominated, that is, the QALY gain from salpingectomy is not less than the QALY gain from methotrexate, then an incremental QALY gain of 0.0088 or greater would be needed for salpingectomy to be considered cost effective relative to methotrexate. This is equivalent to health state utility gain of 1.0 (the gain that is achieved in going from death to a life lived in perfect health) sustained over approximately 77 hours. Alternatively, it would be equivalent to a health state utility gain of 0.40 sustained over approximately 8 days.

Table 10.16 Results for base-case analysis

Treatment	Cost	Incremental cost	Incremental QALY needed (no dominance)
Methotrexate	£1432	-	-
Salpingectomy	£1608	£176	0.0088
Salpingotomy	£2205	£597	0.0298

Figure 10.11 Results for base-case analysis



Calculations

The calculations below show how the results for each treatment alternative are derived.*

Salpingotomy

First-line

90% Laparoscopic salpingotomy first-line	£1392 x 0.9 = £1252.80
Of which:	
Surgical complications	£1333 x 0.9 x 0.004 = £4.80
Blood transfusion	£297 x 0.9 x 0.009 = £2.41
10% Open salpingotomy first-line	£2218 x 0.1 = £221.80
Of which:	
Surgical complications	£1333 x 0.1 x 0.036 = £4.80
Blood transfusion	£297 x 0.1 x 0.071 = £2.11
20.61% fail salpingotomy first-line	
Of which:	
Emergency admission	£789 x 0.2061 x 0.1 = £16.26

* Calculated answers may not exactly match those reported in the results above due to rounding

Second-line

7.21% Methotrexate second-line £425 x 0.0721 = £30.64

12.06% Laparoscopic salpingectomy second-line £1,392 x 0.1206 = £167.88

Of which:

Surgical complications £1333 x 0.1206 x 0.004 = £0.64

Blood transfusion £297 x 0.1206 x 0.009 = £0.32

1.34% Open salpingectomy second-line £2218 x 0.0134 = £29.72

Of which:

Surgical complications £1333 x 0.0134 x 0.036 = £0.64

Blood transfusion £297 x 0.0134 x 0.071 = £0.28

1.49% fail methotrexate second-line

Of which:

1.34% Laparoscopic salpingectomy third-line £1,392 x 0.0134 = £18.65

Of which:

Surgical complications £1333 x 0.0134 x 0.004 = £0.07

Blood transfusion £297 x 0.0134 x 0.009 = £0.04

0.15% Open salpingectomy third-line £2,218 x 0.0015 = £3.33

Of which:

Surgical complications £1333 x 0.0015 x 0.036 = £0.07

Blood transfusion £297 x 0.0015 x 0.071 = £0.03

Follow-up

79.4% Salpingotomy follow-up

Full blood count £3.94 x 0 x 0.794 = £0

Serum hCG £3.94 x 3 x 0.794 = £9.39

Kidney function £3.60 x 0 x 0.794 = £0

Liver function £4.72 x 0 x 0.794 = £0

Urine pregnancy test £1 x 1 x 0.794 = £0.79

GP visit £36 x 0 x 0.794 = £0

Clinic visit £141 x 3 x 0.794 = £335.86

5.7% Salpingotomy/methotrexate follow-up

Full blood count £3.94 x 1 x 0.057 = £0.22

Serum hCG £3.94 x 5 x 0.057 = £1.12

Kidney function £3.60 x 1 x 0.057 = £0.21

Liver function £4.72 x 2 x 0.057 = £0.54

Urine pregnancy test £1 x 1 x 0.057 = £0.06

GP visit £36 x 0 x 0.057 = £0

Clinic visit £141 x 5 x 0.057 = £40.19

13.4% Salpingotomy/salpingectomy follow-up

Full blood count	£3.94 x 0 x 0.134 = £0
Serum hCG	£3.94 x 2 x 0.134 = £1.06
Kidney function	£3.60 x 0 x 0.134 = £0
Liver function	£4.72 x 0 x 0.134 = £0
Urine pregnancy test	£1 x 1 x 0.134 = £0.13
GP visit	£36 x 0.5 x 0.134 = £2.41
Clinic visit	£141 x 2.5 x 0.134 = £47.24

1.5% Salpingotomy/methotrexate/salpingectomy follow-up

Full blood count	£3.94 x 1 x 0.015 = £0.06
Serum hCG	£3.94 x 3 x 0.015 = £0.18
Kidney function	£3.60 x 1 x 0.015 = £0.05
Liver function	£4.72 x 2 x 0.015 = £0.14
Urine pregnancy test	£1 x 1 x 0.015 = £0.02
GP visit	£36 x 0.5 x 0.015 = £0.27
Clinic visit	£141 x 3.5 x 0.015 = £7.40

Average weighted cost of salpingotomy = £2205

Salpingectomy

First-line

90% Laparoscopic salpingectomy first-line	£1392 x 0.9 = £1,252.80
Of which:	
Surgical complications	£1333 x 0.9 x 0.004 = £4.80
Blood transfusion	£297 x 0.9 x 0.009 = £2.41
10% Open salpingectomy first-line	£2218 x 0.1 = £221.80
Of which:	
Surgical complications	£1333 x 0.1 x 0.036 = £4.80
Blood transfusion	£297 x 0.1 x 0.071 = £2.11

Second-line

1.04% Laparoscopic salpingectomy second-line	£1392 x 0.0104 = £14.48
Of which:	
Surgical complications	£1333 x 0.0104 x 0.004 = £0.06
Blood transfusion	£297 x 0.0104 x 0.009 = £0.03

0.115% Open salpingectomy second-line	£2218 x 0.00115 = £2.55
Of which:	
Surgical complications	£1333 x 0.00115 x 0.036 = £0.06
Blood transfusion	£297 x 0.00115 x 0.071 = £0.02
1.15% Methotrexate second-line	£425 x 0.015 = £6.38

Follow-up

98.5% Salpingectomy follow-up

Full blood count	£3.94 x 0 x 0.985 = £0
Serum hCG	£3.94 x 0 x 0.985 = £0
Kidney function	£3.60 x 0 x 0.985 = £0
Liver function	£4.72 x 0 x 0.985 = £0
Urine pregnancy test	£1 x 1 x 0.985 = £0.99
GP visit	£36 x 0.5 x 0.985 = £17.73
Clinic visit	£141 x 0.5 x 0.985 = £69.44

1.15% Salpingectomy/methotrexate follow-up

Full blood count	£3.94 x 1 x 0.0115 = £0.05
Serum hCG	£3.94 x 5 x 0.0115 = £0.23
Kidney function	£3.60 x 1 x 0.0115 = £0.04
Liver function	£4.72 x 2 x 0.0115 = £0.11
Urine pregnancy test	£1 x 1 x 0.0115 = £0.01
GP visit	£36 x 0 x 0.0115 = £0
Clinic visit	£141 x 5 x 0.0115 = £8.11

Average weighted cost of salpingectomy = £1609

Methotrexate

First-line

100% Methotrexate first-line	£425 x 1 = £425

20.7% fail methotrexate first-line

Of which:	
15% rupture	£789 x 0.207 x 0.15 = £24.50
Of which:	
Blood transfusion	£297 x 0.207 x 0.15 x 0.5 = £4.61
85% no rupture	
Of which:	
10% emergency admission	£789 x 0.207 x 0.85 x 0.1 = £13.88

Second-line

Methotrexate second-line	£425 x 0.207 x 0.5 = £43.99
Laparoscopic salpingectomy second-line	£1392 x 0.207 x 0.5 x 0.9 = £129.66
Of which:	
Surgical complications	£1333 x 0.207 x 0.5 x 0.9 x 0.004 = £0.50
Blood transfusion	£297 x 0.207 x 0.5 x 0.9 x 0.009 = £0.25
Open salpingectomy second-line	£2218 x 0.207 x 0.5 x 0.1 = £22.96
Of which:	
Surgical complications	£1333 x 0.207 x 0.5 x 0.1 x 0.036 = £0.50
Blood transfusion	£297 x 0.207 x 0.5 x 0.1 x 0.071 = £0.22
2.14% fail methotrexate second-line	
Of which:	
30% rupture	£789 x 0.0214 x 0.30 = £5.07
Of which:	
Blood transfusion	£297 x 0.0214 x 0.30 x 0.5 = £0.95
70% no rupture	
Of which:	
10% emergency admission	£789 x 0.0214 x 0.70 x 0.1 = £1.18

Third-line

Laparoscopic salpingectomy third-line	£1392 x 0.0214 x 0.9 = £26.81
Of which:	
Surgical complications	£1333 x 0.0214 x 0.9 x 0.004 = £0.10
Blood transfusion	£297 x 0.0214 x 0.9 x 0.009 = £0.05
Open salpingectomy third-line	£2218 x 0.0214 x 0.1 = £4.75
Of which:	
Surgical complications	£1333 x 0.0214 x 0.1 x 0.036 = £0.10
Blood transfusion	£297 x 0.0214 x 0.1 x 0.071 = £0.05

Follow-up

87.5% Methotrexate follow-up	
Full blood count	£3.94 x 1 x 0.875 = £3.45
Serum hCG	£3.94 x 5 x 0.875 = £17.24
Kidney function	£3.60 x 1 x 0.875 = £3.15
Liver function	£4.72 x 2 x 0.875 = £8.26
Urine pregnancy test	£1 x 1 x 0.875 = £0.88
GP visit	£36 x 0 x 0.875 = £0
Clinic visit	£141 x 5 x 0.875 = £616.88

12.5% Methotrexate/salpingectomy follow-up

Full blood count	£3.94 x 1 x 0.125 = £0.49
Serum hCG	£3.94 x 4 x 0.125 = £1.97
Kidney function	£3.60 x 1 x 0.125 = £0.45
Liver function	£4.72 x 2 x 0.125 = £1.18
Urine pregnancy test	£1 x 1 x 0.125 = £0.13
GP visit	£36 x 0.5 x 0.125 = £2.25
Clinic visit	£141 x 4 x 0.125 = £70.50

Average weighted cost of methotrexate = £1432

Sensitivity analysis

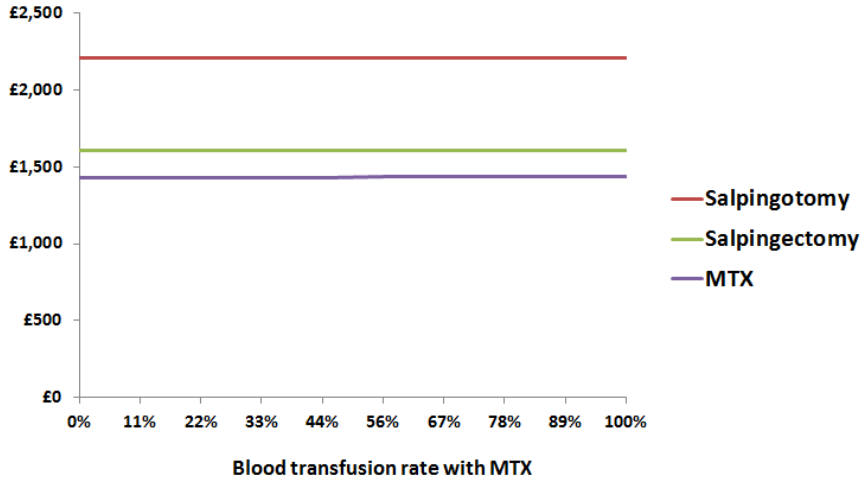
Probabilistic sensitivity analysis

A probabilistic sensitivity analysis based on one million simulations found that methotrexate had a 99.65% probability of being the cheapest treatment. Salpingectomy had a 0.35% probability of being the cheapest treatment but salpingotomy was never the lowest cost option in any of the simulations.

Varying the blood transfusion rate with methotrexate rupture

In this analysis the proportion of women who need blood transfusion after rupture is varied from 0% to 100%. The results are shown in Figure 10.12.

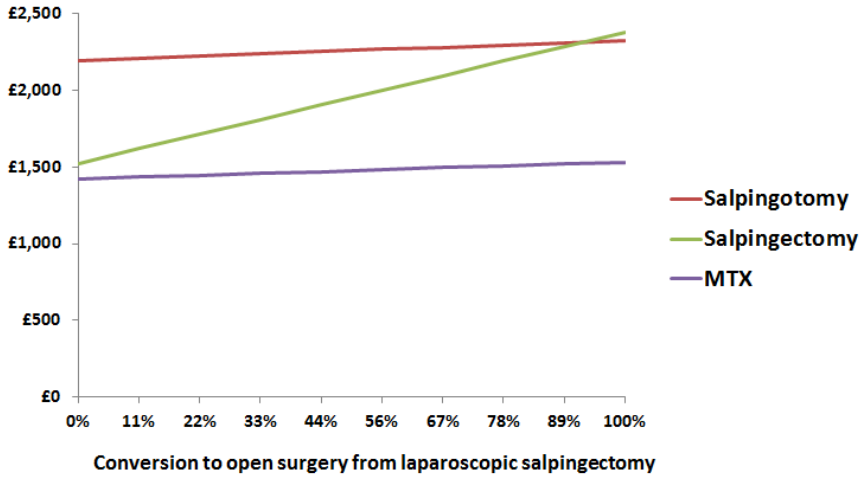
Figure 10.12 Sensitivity analysis varying the blood transfusion rate with methotrexate rupture



Varying the conversion from laparoscopic salpingectomy to open surgery

In this analysis the proportion of patients having laparoscopic salpingectomy converting to open salpingectomy is varied from 0% to 100%: see Figure 10.13.

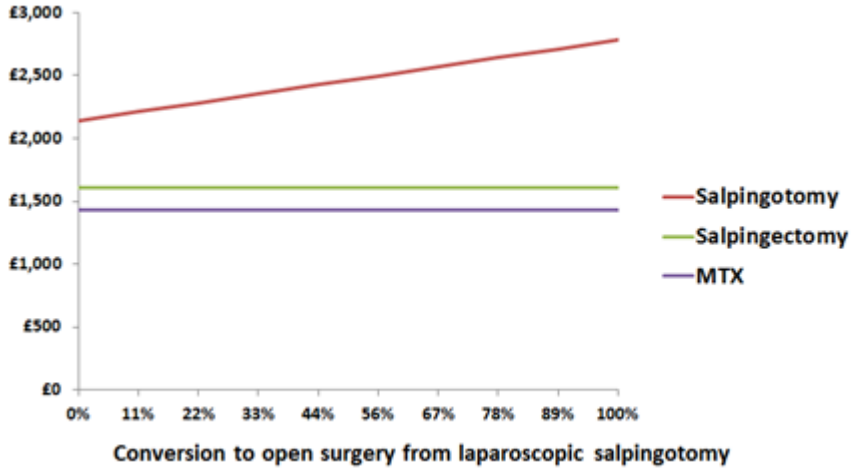
Figure 10.13 Sensitivity analysis varying the proportion converting from laparoscopic to open salpingectomy



Varying the conversion from laparoscopic salpingotomy to open surgery

Here the proportion of patients converting to open salpingotomy after laparoscopic salpingotomy is varied from 0% to 100% with the results shown in Figure 10.14.

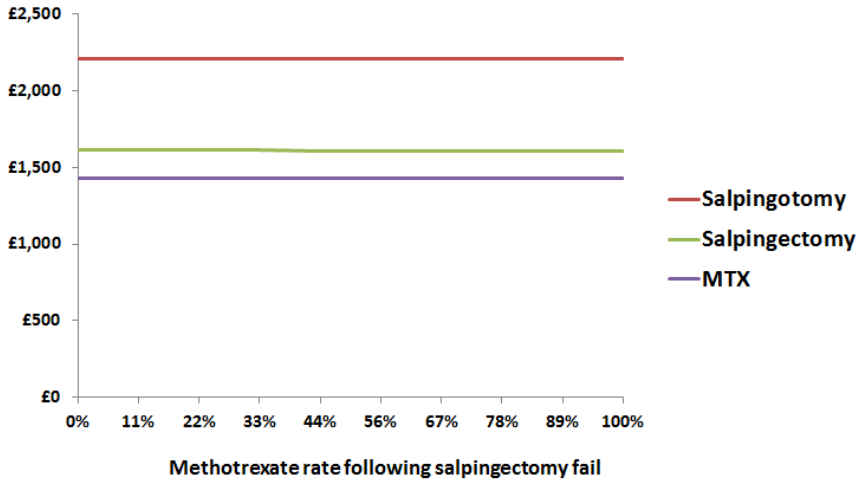
Figure 10.14 Sensitivity analysis varying the proportion converting from laparoscopic to open salpingotomy



Varying methotrexate rate if salpingectomy fails first-line

In this sensitivity analysis the proportion of the patients having methotrexate after failed salpingectomy is varied from 0% to 100% and is shown in Figure 10.15.

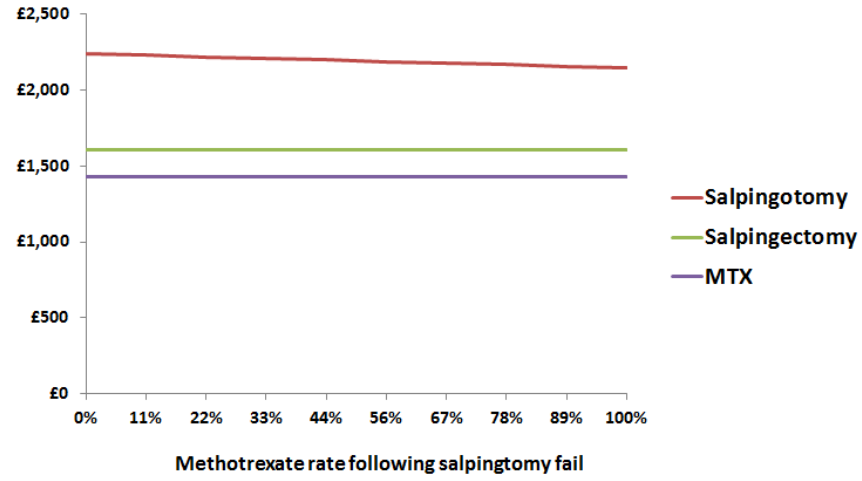
Figure 10.15 Sensitivity analysis varying the proportion having methotrexate after salpingectomy fails



Varying methotrexate rate if salpingotomy fails first-line

Here the proportion of failed salpingotomy patients having methotrexate as second-line treatment is varied from 0% to 100%. The results are displayed in Figure 10.16.

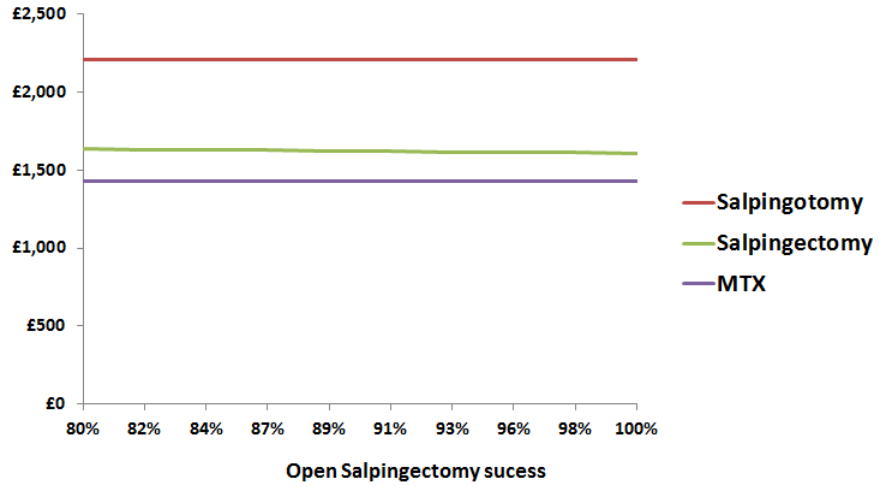
Figure 10.16 Sensitivity analysis varying the proportion having methotrexate after salpingotomy fails



Varying success rate of open salpingectomy

In the base-case analysis it is assumed that open salpingectomy has no failure rate. Here that assumption is relaxed and the effects are shown in Figure 10.17.

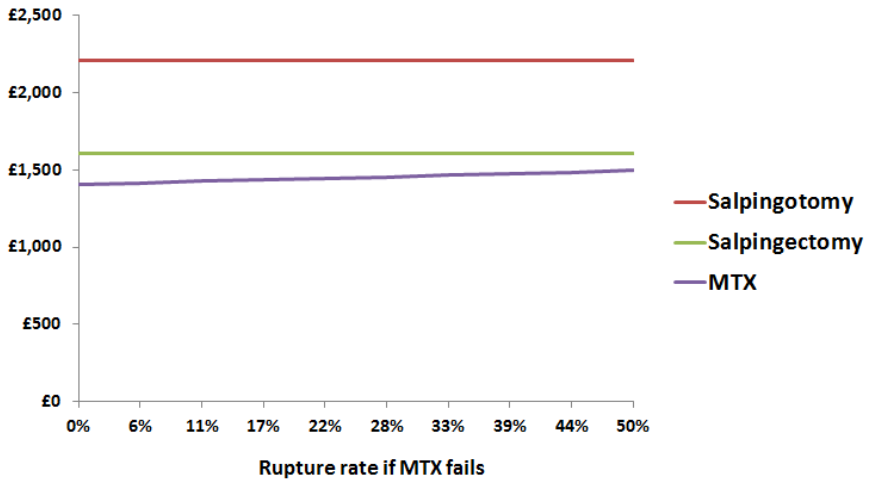
Figure 10.17 Sensitivity analysis varying the success rate of open salpingectomy



Varying rupture rate if methotrexate fails first-line

Rupture is an important outcome in the event of treatment failure and Figure 10.18 shows the consequences of varying this from 0% to 50%.

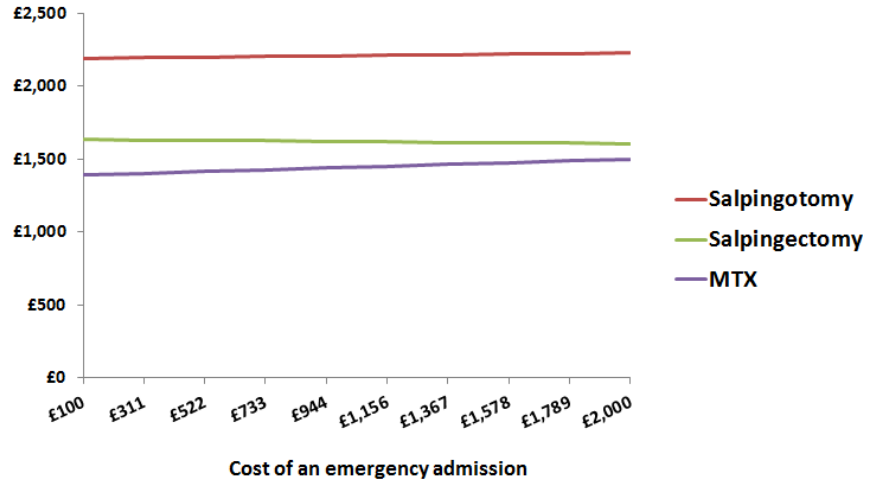
Figure 10.18 Varying the proportion with rupture after first-line methotrexate treatment failure



Varying cost of an emergency admission

In this analysis, shown in Figure 10.19, the cost of an emergency admission is varied from £100 to £2,000.

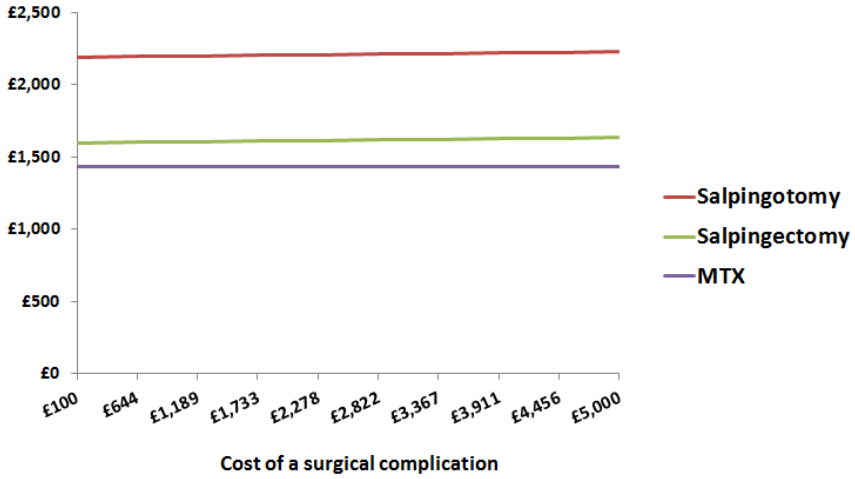
Figure 10.19 Varying the cost of an emergency admission



Varying the cost of surgical complications

Here the cost of a surgical complication is varied from £100 to £5,000 with the results illustrated in Figure 10.20.

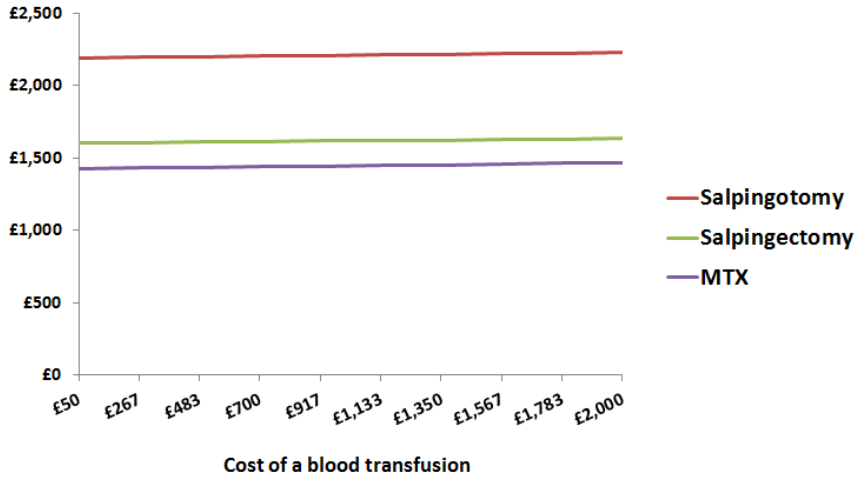
Figure 10.20 Varying the cost of surgical complications



Varying the cost of blood transfusion

The graph in Figure 10.21 shows the impact of varying the cost of a blood transfusion from £50 to £2,000.

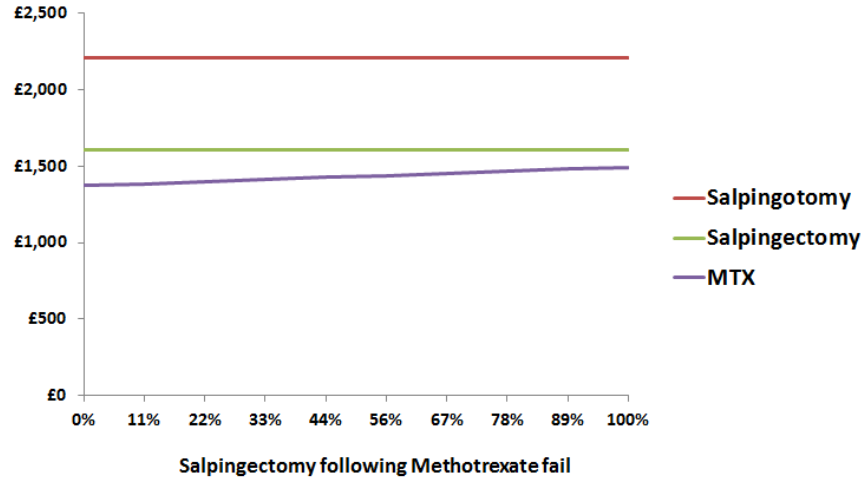
Figure 10.21 Varying the cost of blood transfusion



Varying the proportion of women having second-line salpingectomy following first-line methotrexate treatment failure

Here the proportion of women having failed first-line treatment with methotrexate then having surgery as second-line treatment is varied from none to all, as shown in Figure 10.22.

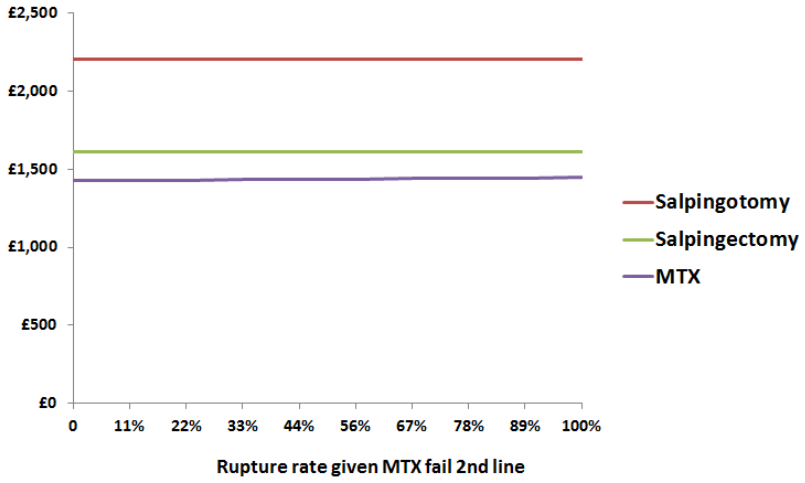
Figure 10.22 Varying the proportion having salpingectomy after first-line methotrexate failure



Varying the proportion of ruptures in women failing methotrexate second-line

The effects of varying the proportion of women who rupture after second-line methotrexate treatment failure from 0% to 100% is shown in Figure 10.23.

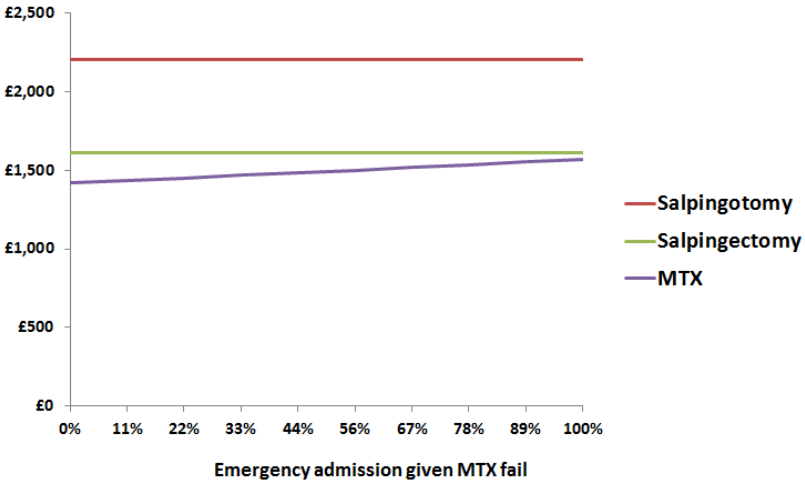
Figure 10.23 Varying the proportion with rupture following second-line methotrexate treatment failure



Varying the emergency admission rate after methotrexate treatment failure

In this analysis the proportion of women who will require emergency admission after methotrexate treatment failure is varied from 0% to 100% with the results displayed in Figure 10.24.

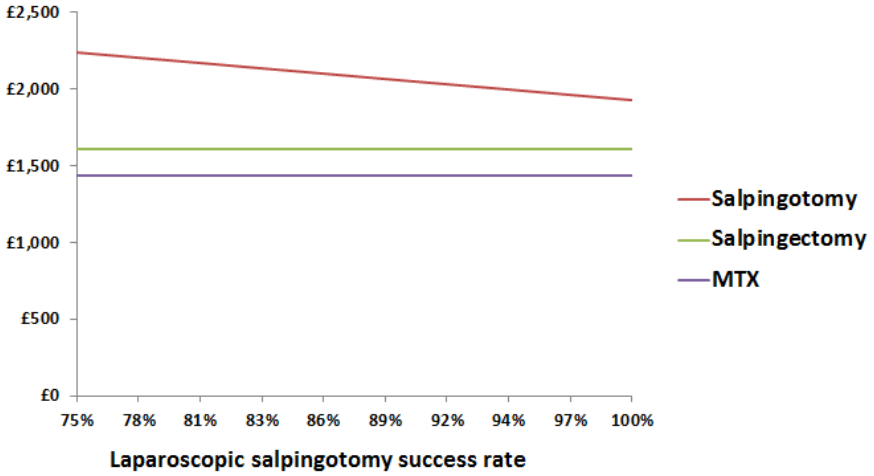
Figure 10.24 Varying the rate of emergency admission in women having methotrexate treatment failure



Varying the success rate of salpingotomy

The impact of varying the success rate of salpingotomy from 75% to 100% was explored in this sensitivity analysis and the results are shown in Figure 10.25.

Figure 10.25 Varying the success rate of laparoscopic salpingotomy



Introducing a QALY loss for methotrexate

The base-case analysis took a cost minimisation approach on the assumption that all interventions lead to cure. However, all of the interventions have associated and different complications, some of which may carry a small risk of long-term morbidity or even mortality. Also, the clinical review undertaken for this guideline suggested that the resolution time was almost 9 days longer with medical treatment than with surgery, which could result in a short-term reduction in health related quality of life. The base-case analysis found that methotrexate was the cheapest option and by assumption cost effective. In sensitivity analysis it is often useful to 'bias' the model against the apparently preferred option to assess how robust the conclusion is to different assumptions.

One of the disadvantages of methotrexate compared to surgical alternatives is the risk of rupture. Apart from the resource implications of rupture (which is addressed in the base-case analysis and other sensitivity analyses) the event is traumatic for the women and carries a small mortality risk. It is estimated that in the UK there are 0.26 deaths per 100,000 pregnancies due to a rupture in ectopic pregnancy (Cantwell et al., 2011). Using a QALY loss of 24.80 per death (National Collaborating Centre for Women's and Children's Health, 2011) that would represent a QALY loss of 0.000064 per woman with medically treated ectopic pregnancy due to the risk of death from rupture.[*] Let us also assume that methotrexate carries a QALY loss due to a 9 day longer resolution of the ectopic pregnancy. The maximum QALY loss if an ectopic pregnancy was equivalent to death in terms of health related quality of life is 9 ÷ 365 = 0.025. However, this doesn't seem realistic for our model population who are women who are not initially presenting as an emergency. One study (Sonneberg et al; 2004) estimated a short-term disutility due to ectopic pregnancy of 0.08333 which for a duration of 9 days would amount to a QALY loss of 0.0021. If we add that to the QALY loss due to the risk of death we have a total QALY loss of 0.0021 attributable to methotrexate treatment.[†] The results of this are shown in Table 10.17. It is assumed that the surgical alternatives give identical QALYs.

[*] 0.26 ÷ 100,000 x 24.8 = 0.000064
[†] For this sensitivity analysis we assume surgery has no long term QALY loss due adverse events

Table 10.17 Results assuming that methotrexate has a QALY loss of 0.0021

Treatment	Cost	Incremental cost	Incremental QALY	ICER
Methotrexate	£1432	-	n/a	n/a
Salpingectomy	£1608	£176	0.0021	£83,805
Salpingotomy	£2205	£597	0	Dominated

ICER incremental cost effectiveness ratio, QALY quality adjusted life year

In this analysis methotrexate would still be considered the cost-effective option because although salpingectomy is more efficacious, the increased benefits are not deemed to be worth the additional cost using a £20,000–£30,000 willingness to pay for a QALY threshold.

If the loss in health state utility due to ectopic pregnancy was assumed to be 0.5 for the additional 9 days duration then the total QALY loss due to methotrexate would be 0.0110. Using this would give the results shown in Table 10.18. In this scenario salpingectomy would be considered cost effective, falling within an incremental cost effectiveness ratio of £20,000 per QALY.

Table 10.18 Results assuming that methotrexate has a QALY loss of 0.0110

Treatment	Cost	Incremental cost	Incremental QALY	ICER
Methotrexate	£1432	-	n/a	n/a
Salpingectomy	£1608	£176	0.0110	£15,999
Salpingotomy	£2205	£597	0	Dominated

ICER incremental cost effectiveness ratio, QALY quality adjusted life year

Discussion

The results of this model suggest that methotrexate was the cheapest of the three treatment alternatives for women with an ectopic pregnancy but who are not presenting at the point of decision with a need for urgent surgical intervention. As shown in Table 10.12 the lower cost of methotrexate is driven by its low cost compared with surgical alternatives. This means that, although it has higher rates of re-intervention than salpingectomy and greater follow-up costs, this is not enough to offset the initial treatment saving. Salpingotomy was considerably more expensive than salpingectomy despite identical initial procedural cost. This is because salpingotomy has higher rates of failure and more follow-up costs.

A probabilistic sensitivity analysis suggested that this finding was not sensitive to uncertainty in parameters with well defined distributions derived by sampling methods, such as NHS treatment costs and treatment success rates.

A limitation of this analysis was that data on treatment effectiveness was not derived from comparative randomised studies. The success of methotrexate first-line treatment was estimated as a weighted average of the studies included in the guideline clinical review meta-analysis and the GDG members considered this to be reasonable based on their opinion and experience. For the probabilistic sensitivity analysis methotrexate success was sampled from a beta distribution using cases and non-cases as the alpha and beta parameters respectively. However, this meta-analysis was based on studies which compared methotrexate with surgery and this analysis was required to consider different surgical approaches (salpingotomy and salpingectomy). Therefore, the relative risk calculated from the meta-analysis was not used in the model as the basis for treatment effect size. No relevant RCTs were found in the clinical evidence review which compared salpingectomy with salpingotomy and it was considered that the best source of data for salpingotomy/salpingectomy success was a non-randomised study by Mol et al (1997), as this included a breakdown into success by open and laparoscopic surgery. Although the model focused on laparoscopic surgery it is recognised that in clinical practice a proportion of patients convert from a laparoscopic procedure to an open one and so the model required success rates for both. One-way sensitivity analysis was used to assess the extent to which different treatment success rates would alter the model's conclusions.

Furthermore, a number of parameters were estimated using the clinical opinion of the GDG and important uncertainty may remain with respect to these values. Nevertheless, many of these estimates were subjected to one-way sensitivity analysis (Figures 10.12 to Figures 10.24) and shown to have a negligible impact on total costs. The upper and lower values used in the sensitivity analysis were not intended to represent plausible extremes for these parameters but to highlight the variation, or lack of it, across the entire range of theoretical values. Often the small impact of these one-way sensitivity analyses was a consequence of the very small number of patients affected, which itself was a function of the clinical estimates of treatment success. So, for example, varying the cost of blood transfusions between £100 and £2000 will only have a minimal impact on total costs because this cost is only relevant to a small minority of patients. The ordinal ranking of the treatment costs only changed in one of the sensitivity analyses (see Figure 10.13) which were predicated on nearly every patient having laparoscopic salpingectomy converting to an open procedure, which does not reflect the clinical reality.

If it was deemed that, for all practical purposes, these treatments were equivalent in terms of their effectiveness and impact on health-related quality of life, then this model strongly suggests that methotrexate is the preferred cost-effective option. However, if this is not thought to be the case then the issue is whether the more expensive alternatives produce sufficient additional benefit to be commensurate with their additional cost.

Given the point estimates of the costs of the different treatment strategies it was suggested that salpingectomy would have to produce an average QALY gain of at least 0.0088 QALYs compared with methotrexate to be considered cost effective. While this may not seem very much, it needs to be seen in the context of the time-limited nature of ectopic pregnancy and the limited difference between treatments in terms of long-term adverse outcomes. Indeed, the mortality risk discussed in the final sensitivity analysis relates to the entire population of ectopic pregnancies and it is likely to be even lower in the model population where there is not initially a need for urgent surgical intervention. Using an estimate of health state utility from one published study (Sonneberg et al.; 2004) it was suggested that methotrexate would still be considered cost effective. Uncertainty surrounds that estimate, but the loss in health state utility required to make salpingectomy cost effective would have to be comparable to the loss reported in, for example, stable advanced non-small cell lung cancer with no additional symptoms (Doyle at al., 2008) .

In the clinical review undertaken for this guideline comparing salpingectomy with salpingotomy the evidence did not generally indicate better outcomes for salpingotomy. Therefore, in the light of the proceeding discussion it is most unlikely that salpingotomy can be considered a cost-effective treatment given its considerably higher costs.

The studies on which the clinical inputs in this model are based did not all restrict their population on the basis of their hCG levels. However, from the reporting of the median values it is likely that most of the women in the studies would have had an hCG of less than 5000 IU/l. The GDG is strongly of the view that such patients are an important sub-group with a much higher risk of rupture and therefore it is not thought that this analysis should inform recommendations for such patients.

Conclusion

This model suggests that methotrexate is almost £200 cheaper than salpingectomy and almost £800 cheaper than salpingotomy. Under a cost minimisation approach this would make methotrexate the preferred alternative. Even if it is accepted that there are QALY differences between the treatment alternatives, it is far from clear that surgery offers sufficient additional benefits to make the additional cost worthwhile. In particular, the higher costs of salpingotomy relative to salpingectomy in the absence of any clear clinical benefit makes it reasonable to reject this as a treatment option on cost effectiveness grounds.

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12 Abbreviations and glossary

Please also see the NICE glossary for abbreviations and definitions of terms used in this guideline.

12.1 Abbreviations

A&E	accident and emergency unit
AEPU	Association of Early Pregnancy Units
AGU	acute gynaecology unit
CEAC	cost effectiveness acceptability curve
CES-D	Center for Epidemiological Studies-Depression scale
CI	confidence interval
CRL	crown–rump length
D&C	dilation and curettage
DASS	Depression Anxiety Stress Scales
ED	emergency department
EDIS	emergency department information system
EP	ectopic pregnancy
EPAC	early pregnancy assessment clinic
EPAS	early pregnancy assessment service
EP(A)U	early pregnancy (assessment) unit
EPPS	early pregnancy problem service
ER	emergency room
ERPC	evacuation of retained products of conception
EUP	extra-uterine pregnancy
EVA	electric vacuum aspiration
FMH	feto–maternal haemorrhage
GP	general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
hCG	β-human chorionic gonadotrophin
HCP	healthcare professional
HSG	hysterosalpingography
ICER	incremental cost effectiveness ratio

ICSI	intracytoplasmic sperm injection
ICT	Indirect Coombs' test
IM	intramuscular
IMI	intramuscular injection
IPUV	intrauterine pregnancy of uncertain viability
IU	international unit(s)
IUCD	intrauterine contraceptive device
IUGR	Intrauterine growth restriction
IUP	intrauterine pregnancy
IV	intravenous
IVF	in-vitro fertilisation
LR+ / LR-	likelihood ratios for positive and negative test results
MAC	monitored anaesthesia care
MD	mean difference
Mf	mifepristone
Ms	misoprostol
MSD	mean gestational sac diameter
MTX	methotrexate
MVA(C)	manual vacuum aspiration (curettage)
NC	not calculable
NPV	negative predictive value
NR	not reported
NS	not significant
OR	odds ratio
PFC	plaque-forming cells
PID	pelvic inflammatory disease
PPV	positive predictive value
PUL	pregnancy of unknown location
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy
RBC	red blood cells
RCOG	Royal College of Obstetricians and Gynaecologists
Rh / Rh-	rhesus/ rhesus negative
RPOC	retained products of conception
RR	risk ratio
SC	suction curettage
SD	standard deviation
SEM	standard error of the mean
SF-36	Short Form-36

SHO	senior house officer
STAI	State-Trait Anxiety Inventory
STI	sexually transmitted infection
TAS	transabdominal scan
TAU	transabdominal ultrasound
TB	tuberculosis
TVS	transvaginal scan
TVU	transvaginal ultrasound
US	ultrasound
VAS	visual analogue scale
WHO	World Health Organization

12.2 Glossary

Active treatment/management	Intervention to manage a condition, usually in the form of surgery or management with drugs
Anti-D	Immunoglobulin that binds to, and causes the removal of, any Rhesus D positive red blood cells that have passed from the fetus into the maternal circulation
Early pregnancy	Pregnancy in the first trimester; that is, up to 13 completed weeks of pregnancy
Ectopic pregnancy	A pregnancy located outside of the uterine cavity, usually in the fallopian tube
Electric vacuum aspiration	The use of suction, generated using an electric pump, to remove the contents of the uterus through the cervix
Expectant management	A management approach in which treatment is not administered, with the aim of seeing whether the condition will resolve naturally
hCG ratio	A measure of the pattern of increase or decrease in hCG levels, calculated by dividing one hCG measurement by the previous measurement
Hospital Anxiety and Depression scale	A 10-point scale used to determine levels of anxiety and depression experienced by patients. A score of 1 indicates a potential need for psychiatric treatment, whereas a score of 10 represents clinical stability.
Human chorionic gonadotrophin	Glycoprotein hormone produced during pregnancy by the embryo and later the placenta. It can be detected using blood tests or urine pregnancy tests.
Incomplete miscarriage	A diagnosed non-viable pregnancy in which bleeding has begun, but pregnancy tissue remains in the uterus
Indirect Coombs' test	A test to detect antibodies against red blood cell antigens; it can be used, for example, to detect antibodies against Rhesus D
Inevitable miscarriage	A diagnosed non-viable pregnancy in which bleeding has begun and the cervical os is open, but pregnancy tissue remains in the uterus
Intrauterine pregnancy of uncertain viability	A pregnancy that is located within the uterus, without a visible heartbeat and which cannot be diagnosed as a confirmed miscarriage following an ultrasound scan
Kleihauer test	A method of quantifying the amount of fetal haemoglobin that has passed into the maternal bloodstream

Laparoscopy	Surgical operation performed within the abdomen or pelvis using cameras and instruments inserted through small incisions
Laparotomy	Open surgical procedure involving a surgical incision into the abdomen
Manual vacuum aspiration	The use of suction, generated using a manual pump, to remove the contents of the uterus through the cervix
Methotrexate	Anti-metabolite drug which can stop the development of a pregnancy and therefore has been used in the medical management of ectopic pregnancy. Methotrexate can be administered systemically or locally at the site of the pregnancy (either ultrasound guided or using laparoscopic injection).
Missed miscarriage	A non-viable pregnancy identified on ultrasound scan, without associated pain and bleeding (also known as early fetal demise, delayed miscarriage or silent miscarriage)
Os	The opening of the cervix
Pregnancy of unknown location	A descriptive term used to classify a pregnancy when a woman has a positive pregnancy test but no pregnancy can be seen on an ultrasound scan
Recurrent miscarriage	The loss of three or more pregnancies before 23^{+6} weeks of gestation
RhoGAM®	Brand of rhesus D immune globulin
Salpingectomy	Surgical removal of the Fallopian tube
Salpingo-oophorectomy	Surgical removal of the Fallopian tube and ovary
Salpingostomy	Surgical formation of an opening of Fallopian tube where the fimbrial end (the end closest to the ovaries) has been closed by infection or chronic inflammation
Salpingotomy	Surgical incision of a Fallopian tube to remove an ectopic pregnancy
Sensitisation	Development of antibodies against antigens found on fetal red blood cells
Short Form-36 scale	A survey of patient health, consisting of eight scales: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. The scores are summed and transformed into a scale of 0-100. The scale can also be divided into two aggregate measures, the Physical Component Summary and the Mental Component Summary.
State-Trait Anxiety Inventory	A questionnaire containing two 20-item scales covering both current (state) and background (trait) anxiety. Items are rated on a 4-point scale with total scores ranging from 20 to 80 where higher scores represent higher levels of anxiety.
Surgical completion of miscarriage	Treatment of a miscarriage using a surgical procedure (for example dilation and curettage, vacuum aspiration); also known as evacuation of retained products of conception
Threatened miscarriage	Vaginal bleeding in the presence of a viable pregnancy in the first 23^{+6} weeks of pregnancy