National Institute for Health and Care Excellence

Final

Ectopic pregnancy and miscarriage: diagnosis and initial management

[C] Progestogens for preventing miscarriage

NICE guideline NG126 (update)

Evidence review underpinning recommendations 1.9.2 and 1.9.3, and recommendations for research in the NICE guideline

November 2021

Final

This evidence review was developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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ISBN: 978-1-4731-3380-8

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Evidence review for progestogens for preventing miscarriage

Review question

What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

Introduction

Miscarriage is a common complication of early pregnancy, affecting about 20% of all pregnancies. It can have serious consequences for women, including psychological harm and mental health complications such as anxiety, depression and post-traumatic stress disorder. 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' gestation. Low levels of circulating progesterone have been linked to impending miscarriage and the presence of associated early pregnancy bleeding. It has been postulated that a lack of progesterone is a cause of miscarriage rather than a secondary signal of failing pregnancy, and that augmenting levels of progesterone may prevent miscarriage of euploid (without any genetic abnormalities) fetuses. The aim of this review is to assess the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women at risk of miscarriage, for example: • Women with threatened miscarriage (defined as early vaginal bleeding during the first trimester of pregnancy) • Women with a history of recurrent miscarriage (defined by the investigators).
Intervention	Progestogens: • Oral dydrogesterone • Oral micronised progesterone • Vaginal micronised progesterone • Intramuscular 17-OH progesterone
Comparison	• Any of the above progestogens compared to another • No treatment • Placebo
Outcome	**Critical** • Live birth **Important** • Miscarriage (birth before 24 weeks' gestation) • Preterm birth (birth before 37 weeks' gestation) • Stillbirth • Ectopic pregnancy • Congenital abnormalities • Adverse drug effects

OH: hydroxy

For further details see the review protocol in appendix A.

Methods and process

During the development of this guideline, a registered Cochrane protocol was identified which matched the committee's intended protocol. The Cochrane review team completed their review (Devall 2021) and presented their results to the committee which used them to make recommendations. Cochrane's methods are closely aligned to standard NICE methods and minor deviations (the use of the original Cochrane risk of bias tool and defining primary and secondary outcomes as opposed to critical and important) relevant to the topic area were highlighted to the committee and taken into account in discussions of the evidence.

See differences between the final Cochrane review (Devall 2021) and the Cochrane review protocol (Devall 2020) in https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

One Cochrane review (Devall 2021) including 7 randomised controlled trials (RCTs) (Chan 2020, Coomarasamy 2015, Coomarasamy 2019, Gerhard 1987, MacDonald 1972, Shearman 1963, Siew 2018) was considered in this report. This review was used for recommendation making by the committee as it was considered sufficiently relevant, high quality and up to date.

The Cochrane review is summarised in Table 2 and the results of the review are provided in the summary of the evidence in this report, however full details of the Cochrane review including methods are available here: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full

See the Cochrane review for the literature search strategy, study selection flowchart, forest plots and GRADE summary of findings tables.

Excluded studies

See the Cochrane review for the list of excluded studies with reasons for their exclusions

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Comparisons	Outcomes
Devall 2021 Systematic review	Number of studies= 7 RCTs Number of women = 5682	**Women with threatened miscarriage** <u>Vaginal micronised progesterone versus placebo</u> 2 RCTs, N=4090, UK, Germany, Coomarasany 2019, Gerhard 1987 <u>Dydrogesterone versus placebo</u> 1 RCT, N= 406, Hong Kong, Chan 2020 <u>Oral micronised progesterone versus dydrogesterone</u> 1 RCT, N=118, Singapore, Siew 2018 **Women with recurrent miscarriage** <u>Vaginal micronised progesterone versus placebo</u> 1 RCT, N=826, UK, Coomarasany 2015 <u>Dydrogesterone versus placebo</u> 1 RCT, N=40, UK, MacDonald 1972 <u>17- hydroxyprogesterone versus placebo</u> 1 RCT, N=50, Australia, Shearman 1963	• Live birth • Miscarriage (birth before 24 weeks gestational age) • Preterm birth (birth before 37 weeks gestational age) • Stillbirth • Ectopic pregnancy • Congenital abnormalities • Adverse drug effects

RCT(s): randomised controlled trial(s)

See the Cochrane review for full evidence tables.

Summary of the evidence

<u>Women with threatened miscarriage</u>

Across all the comparisons identified in this Cochrane review, the majority showed no important difference for any outcomes between the interventions compared (for example, vaginal micronised progesterone versus placebo, dydrogesterone versus placebo, oral micronised progesterone versus dydrogesterone) for women with threatened miscarriage.

Evidence from pre-specified subgroups showed that there was no important benefit for vaginal micronised progesterone versus placebo in women with no previous miscarriages and early pregnancy bleeding in terms of the outcome of live birth. However, for this same

comparison, vaginal micronised progesterone showed an important benefit in terms of the outcome of live birth for the subgroup of women with one or more previous miscarriages and early pregnancy bleeding.

Typically, the outcomes for which no difference between interventions was found included few studies and had seriously imprecise findings, therefore they should not be taken as definitive evidence of no difference between the interventions. For the comparison vaginal micronised progesterone versus placebo and dydrogesterone versus placebo, the outcome miscarriage was precise and of high to moderate quality evidence, therefore this is indicative that the true effect is similar to the estimated effect.

Women with recurrent miscarriage

Overall, vaginal micronised progesterone, dydrogesterone and 17-hydroxyprogesterone appeared to have no important benefit over placebo for the outcomes assessed in women with recurrent miscarriage.

The outcomes reported for the comparison vaginal micronised progesterone versus placebo were generally of high quality, indicating that the true effect may be similar to the estimated effect.

The outcomes reported for the comparison dydrogesterone and 17-hydroxyprogesterone versus placebo were generally of low to very low quality evidence, indicating that the true effect might be markedly different from the estimated effect.

Quality of the Cochrane review

Based on the methodological limitations assessed with the ROBIS tool to assess risk of bias in systematic reviews and the modified PRISMA-NMA checklist, the Cochrane review was deemed to be high quality. It was conducted following methodologically robust methods, and a prospectively registered protocol. There were not important differences between the included studies; all were conducted in the same setting and included women with similar baseline characteristics in terms of age, gestational age and findings on ultrasonography. The authors conducted pre-planned subgroup analyses for the factors that could have interacted with treatment effects, such as age, number of previous miscarriages, regimen, dosage and route of drug administration. As women with threatened miscarriage and women with recurrent miscarriage are two very distinct populations, analyses were conducted separately from the outset. There were no particular concerns for risk of bias in any of the trials included, and the Cochrane review authors conducted a scientific integrity/trustworthiness check, following the criteria agreed by the Cochrane Pregnancy and Childbirth criteria, which provides an additional layer of quality assessment for the trials included in the Cochrane review. Publication bias could not be fully ruled out, although it was not possible to assess it formally in the Cochrane review.

The Cochrane review identified a gap in the evidence based. The authors had intended to conduct a NMA, however interventions did not form a connected network, therefore only indirect comparisons and pairwise analyses were performed. The authors defined in advance the methods to conduct a NMA, which were considered to be appropriate.

For further details see the methodological limitations of the review in appendix L.

Economic evidence

Included studies

Two economic studies (reporting on results from the same randomised controlled trial) were identified which were relevant to this question (Ogwulu 2019, Coomarasamy 2020).

As this review was based on a published Cochrane systematic review, no formal economic literature search was undertaken but the included studies reported on an economic evaluation that was undertaken alongside the PRISM RCT which was by far the biggest study contributing to the clinical evidence in the Cochrane review.

Summary of included economic evidence

See Table 3, Table 4 and Table 5 for the economic evidence profile of the included studies.

Table 3: Economic evidence profile of progesterone for preventing miscarriage for women with bleeding in early pregnancy and ultrasound evidence of an intrauterine sac

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Coomarasamy 2020 Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT	Minor limitations	Directly applicable[1]	**Type of economic analysis**: Cost-effectiveness analysis – economic evaluation conducted alongside a RCT **Time horizon:** < 1-year Trial duration **Primary measure of outcome:** Live births ≥ 34 weeks gestation	£79[2]	0.022	£3,612 per live birth[2]	Probabilistic sensitivity analysis using non-parametric bootstrapping to generate 5000 paired estimates of costs and outcomes suggested that there was a greater than 90% probability that progesterone was cost-effective for a cost-effectiveness threshold of £30,000 per live birth Deterministic sensitivity analysis was undertaken to assess: • Fixed progesterone costs until a gestational age of 16 weeks

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
							• Imputation of missing primary care costs • Varying costs of inpatient night admissions • Varying cost of miscarriage management • Removing birth costs The ICERs for these sensitivity analyses ranged from £3,282 per live birth to £4,977 per live birth

[1] QALYs are not used as an outcome measure but the results can still be benchmarked using a cost per QALY approach as a live birth is likely to be valued much more highly than a QALY
[2] Costs from a 2017-18 price year were updated for inflation to 2019/20 using an inflator of 1.05 derived from the hospital & community health services (HCHS) index and NHS Cost Inflation Index (NHSCII).

Table 4: Economic evidence profile of progesterone for preventing miscarriage for women with bleeding in early pregnancy and ultrasound evidence of an intrauterine sac and at least 1 previous miscarriage

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Ogwulu 2019 The cost-effectiveness of progesterone in preventing	Minor limitations	Directly applicable[1]	**Type of economic analysis**: Cost-effectiveness analysis – economic evaluation	-£337[2]	0.055	Progesterone dominant	Probabilistic sensitivity analysis using non-parametric bootstrapping to generate 5000

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
miscarriages in women with early pregnancy bleeding: an economic evaluation based on the PRISM trial			conducted alongside a RCT **Time horizon:** < 1-year Trial duration **Primary measure of outcome:** Live births ≥ 34 weeks gestation				paired estimates of costs and outcomes suggested that there was a greater than 90% probability that progesterone was cost-effective for a cost-effectiveness threshold of £20,000 per live birth

[1] QALYs are not used as an outcome measure but as the results showed dominance they can easily be interpreted for the purposed of decision making
[2] Costs from a 2017-18 price year were updated for inflation to 2019/20 using an inflator of 1.05 derived from the hospital & community health services (HCHS) index and NHS Cost Inflation Index (NHSCII).

Table 5: Economic evidence profile of progesterone for preventing miscarriage for women with bleeding in early pregnancy and ultrasound evidence of an intrauterine sac and 3 or more previous miscarriages

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Ogwulu 2019 The cost-effectiveness of progesterone in preventing miscarriages in women with early pregnancy bleeding: an economic	Minor limitations	Directly applicable[1]	**Type of economic analysis**: Cost-effectiveness analysis – economic evaluation conducted alongside a RCT **Time horizon:** < 1-year	£1,834[2]	0.15	£12,137 per live birth[2]	Probabilistic sensitivity analysis using non-parametric bootstrapping to generate 5000 paired estimates of costs and outcomes suggested that there was a greater than 90%

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
evaluation based on the PRISM trial			Trial duration **Primary measure of outcome:** Live births ≥ 34 weeks gestation				probability that progesterone was cost-effective for a cost-effectiveness threshold of £20,000 per live birth

[1] QALYs are not used as an outcome measure but the results can still be benchmarked using a cost per QALY approach as a live birth is likely to be valued much more highly than a QALY
[2] Costs from a 2017-18 price year were updated for inflation to 2019/20 using an inflator of 1.05 derived from the hospital & community health services (HCHS) index and NHS Cost Inflation Index (NHSCII).

Economic model

No economic modelling was undertaken for this review because there was a recently published UK economic evaluation alongside an RCT, which was considered sufficiently high quality to support the committee in making recommendations.

Evidence statements

Economic evidence statements

One cost effectiveness analysis undertaken in the UK found that progesterone to prevent miscarriage in early pregnancy had an incremental cost-effectiveness ratio of £3,612 per live birth (price year 2019-20) relative to placebo. There was a greater than 90% probability that progesterone was cost-effective at a cost-effectiveness threshold of £30,000 per live birth. The economic analysis is directly applicable to the NICE decision-making context, and is characterised by minor limitations.

One cost effectiveness analysis undertaken in the UK found that progesterone to prevent miscarriage in early pregnancy in women with previous miscarriage dominated placebo. There was a greater than 90% probability that progesterone was cost-effective at a cost-effectiveness threshold of £20,000 per live birth. The economic analysis is directly applicable to the NICE decision-making context, and is characterised by minor limitations.

One cost effectiveness analysis undertaken in the UK found that progesterone to prevent miscarriage in early pregnancy in women with 3 or more previous miscarriages had an incremental cost-effectiveness ratio of £12,137 per live birth (price year 2019-20) relative to placebo. There was a greater than 90% probability that progesterone was cost-effective at a cost-effectiveness threshold of £20,000 per live birth. The economic analysis is directly applicable to the NICE decision-making context, and is characterised by minor limitations.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

As the aim of this review was to determine if progestogens can prevent miscarriage, the primary outcome was live birth, and the secondary outcomes were miscarriage (defined as delivery before 24 weeks of gestation) and preterm birth (defined as birth before 37 weeks of gestation). Other secondary outcomes to determine if the use of progestogens in early pregnancy led to any adverse effects were stillbirth, ectopic pregnancy, congenital abnormalities and adverse drug events.

The quality of the evidence

The quality or the evidence was high to very low, and it was typically downgraded due to imprecision (small sample size and the 95% confidence intervals spanned possible benefit and possible harm) and due to limitations in the study designs. The methodological limitations of the Cochrane review were assessed using the ROBIS tool to assess risk of bias in systematic reviews and the modified PRISMA-NMA checklist. The overall quality of the Cochrane review was considered to be high (see appendix L for further details).

The Cochrane authors reported that there were 13 studies awaiting classification following assessment with their scientific integrity and trustworthiness checks (where the Cochrane authors contact the primary study authors and request further details about the study). The authors of the Cochrane review concluded that when all the studies awaiting classification were included, the benefit of vaginal micronised progesterone in the sub-group of women with early pregnancy bleeding and a previous miscarriage remained (data not shown).

Benefits and harms

There was high quality evidence that in women with one or more previous miscarriages and early pregnancy bleeding, 400 mg twice a day of vaginal micronised progesterone increased the live birth rate compared to placebo, therefore the committee based their recommendation on the use of progesterone in women with threatened miscarriage on this evidence. The committee noted that there was no evidence of harms for women or babies following the use of vaginal micronised progesterone in this way, with no increase in risk of stillbirth, ectopic pregnancy, congenital abnormalities or adverse drug reactions. However, they also noted that the trials were not powered to detect very rare events and so the possibility of these cannot be excluded.

The committee noted that the effect size observed in the subgroup of women with one or more previous miscarriages and early pregnancy bleeding was larger than that observed in the subgroup of women with no previous miscarriages and early pregnancy bleeding. Therefore, the committee agreed that vaginal micronised progesterone in women with no previous miscarriages and early pregnancy bleeding would be of little or no benefit, however, according to this evidence, progesterone would be beneficial in women with one or more previous miscarriages and early pregnancy bleeding. This conclusion was further reinforced by the biological rationale by which euploid miscarriages (that is, loss of chromosomally normal pregnancies) are more likely to occur with increasing number of previous miscarriages. Euploid miscarriages are associated with luteal phase defect, which is caused by low progesterone levels and associated with vaginal bleeding, therefore it is biologically plausible that the benefit of vaginal micronised progesterone is greater as the number of previous miscarriages increases.

The committee noted that the evidence for the effectiveness of vaginal micronised progesterone was in women with an ultrasound-confirmed intra-uterine pregnancy and a confirmed fetal heartbeat. This was also the case for the population of women included in the trial providing the highest weight (98.8%) to the meta-analysis for vaginal micronised progesterone versus placebo reporting on the live birth outcome, the Progesterone In Spontaneous Miscarriage (PRISM) trial (Coomarasamy 2019), in which women had an intrauterine gestational sac visible on ultrasonography.

The committee discussed the relative merits of starting vaginal micronised progesterone as early as possible (for example, after a positive home pregnancy test) in women with a previous miscarriage and early pregnancy bleeding, compared to starting after an ultrasound scan. The committee noted that there was no evidence about the effectiveness and safety of progesterone started prior to ultrasound confirmation of an intra-uterine pregnancy as no controlled trials had been conducted to date on women with only a positive pregnancy test. Furthermore, there were also concerns that recommending progesterone be commenced based only a pregnancy confirmed using a pregnancy test, may lead to potential over-prescription of vaginal micronised progesterone. As women in this early stage of their pregnancy would usually present to their GP first, there would also be pressure on GPs to prescribe it immediately, rather than referring women for an early pregnancy scan.

The committee discussed the fact that an intrauterine pregnancy can be detected on an ultrasound scan as early as 4 weeks + 4 days of gestation, whereas the fetal heartbeat may not be detected until about 5 weeks + 5 days of gestation. Therefore, to avoid any potential delays in the commencement of vaginal micronised progesterone in women with early pregnancy bleeding, the committee agreed to recommend that it should be started once there is confirmation of an intra-uterine pregnancy, and then if the fetal heartbeat is seen, the progesterone can be continued up to 16 weeks. The committee noted that if heartbeat is not seen on an initial scan, women are always offered a repeat scan in a maximum timeframe of 2 weeks.

The committee discussed that the recommendation to use vaginal micronised progesterone would not be generalizable to women with a pregnancy of unknown location or ectopic pregnancy as the evidence had excluded these pregnancies, but that the use of ultrasound confirmation of pregnancy would enable these women to be identified before the progesterone was prescribed.

The committee discussed that the progesterone should initially be prescribed in secondary care (usually by the Early Pregnancy Unit who had conducted the scan), but after the initial prescription it would be easier for the woman if the prescription could be continued by her GP. The committee agreed that this may also remove the pressure on GPs to prescribe progesterone prior to a scan. However, the committee were aware that shared care prescribing arrangements are usually agreed locally and so did not include this detail in their recommendations.

The committee noted that threatened miscarriage can be very stressful and upsetting regardless of the prognosis and type of pregnancy the woman has, and emphasised that healthcare professionals providing care for these women will need to provide accurate information about what to expect, as well as providing details of support and advice available from relevant organisations. However, they agreed it was not necessary to make a separate recommendation about this as it is already covered in the support and information giving section of the guideline.

The committee discussed that the risk of miscarriage increases with maternal age and whether the age of the woman could have a role on the effectiveness of vaginal micronised progesterone, however no age effect was observed when data was split between those above and below 35 years on prespecified subgroup analysis.

The committee noted that there are 4 types of progesterone preparations available in the UK: micronised oral progesterone, micronised vaginal progesterone, progesterone vaginal tablets and pessaries, and a progesterone vaginal gel. These are indicated in women for supplementation of the luteal phase, for luteal phase support and pre-menstrual syndrome or postnatal depression but are not approved for the prevention of miscarriage.

The authors of the PRISM trial emphasised that the conclusions obtained about the effectiveness of 400 mg twice a day of vaginal micronised progesterone cannot be extrapolated to other progesterone preparations, doses or routes and it cannot be assumed that non-micronised preparations would behave in the same way as micronised progesterone as this preparation has an identical molecular structure to natural progesterone. The committee also noted that the 2 main trials contributing to the evidence (PRISM and Gerhard 1987) both used vaginal micronised progesterone. Therefore, although vaginal micronised progesterone is not licenced in the UK for the prevention of miscarriage, the committee agreed that it was necessary to be specific about this formulation in their recommendations, and they also adopted the dose used in the PRISM study. The review found no evidence of harm for the prespecified outcomes, namely stillbirth, ectopic pregnancy, congenital abnormalities

or adverse drug reactions, however this should not be taken as definitive evidence as the trials were not powered to detect very rare events.

The committee noted that progesterone pessaries (not micronised) are commonly used in clinical practice for the prevention of miscarriage and were aware that there is no available evidence to support their effectiveness, or evidence for any of the other available preparations. As there was so little evidence for other progesterone preparations the committee made a research recommendation to determine the comparative effectiveness of other progesterone preparations for the prevention of miscarriage.

The committee also discussed the duration of therapy and noted that the PRISM study had continued therapy until 16 completed weeks of pregnancy. This decision to use this duration in the PRISM study had been based on a consensus of a national body of UK clinicians, and reflected that the progesterone was being used to treat an assumed deficit in the pregnant woman's own endogenous progesterone production. The committee discussed that in a normal pregnancy, the predominant source of progesterone in the first 12 weeks of pregnancy is the corpus luteum and after that the placenta is the main source of progesterone. So, if progesterone therapy was intended to correct only a corpus luteal defect, then treatment for the first 12 weeks of gestation would have been sufficient, but as placental production of progesterone may also be sub-optimal it was felt necessary to continue the treatment to 16 weeks.

The PRISM trial is a well-powered multi-center randomised placebo-controlled trial, conducted with methodological rigour, following a prespecified protocol. However, it is worth noting that the primary analysis in the trial did not find any important difference between groups, and that the only clinically important finding was found in a prespecified subgroup analyses, which was not adjusted for multiplicity. Therefore, this may raise concerns about a possible false positive result. Given the biological rationale presented above, the small but important effect size the PRISM trial showed, and the critical evaluation following guidelines for the interpretation of subgroup analysis with which the trial has been assessed (Coomarasamy 2020), the committee agreed that the evidence was a robust enough base for their recommendation.

The committee discussed the evidence for women with unexplained recurrent miscarriage (but no early pregnancy bleeding). Three studies had been included in the Cochrane analysis for this population of women using three different progestogens. The PROgesterone in recurrent MIScarriagE (PROMISE) trial (Coomarasamy 2015) used vaginal micronised progesterone and is the largest published in the field. However, it did not result in a significantly higher rate of live births. The other studies used dydrogesterone and 17OH-progesterone and provided little or no evidence for the outcome of live birth. The committee agreed that further research is needed to assess the role of progestogens in women with unexplained recurrent miscarriage, therefore the committee made a research recommendation to this effect.

Cost effectiveness and resource use

An economic evaluation of the PRISM trial was reported in 2 papers (Ogwulu 2019, Coomarasamy 2020). The primary analysis was in a population of women with early pregnancy bleeding and an ultrasound confirmed intrauterine sac. The evaluation assessed the cost-effectiveness of progesterone compared with placebo in preventing pregnancy loss.

As part of the trial, maternal and neonatal hospital resource use was recorded from randomisation to hospital discharge for each pregnancy. Health services self-completed questionnaires were used to measure other resource use provided in primary care and the community during the same period. The adjusted mean difference in costs of £76 was not statistically significant with the intervention cost of £204 partly offset by a non-significant reduction in hospital costs in the intervention group. The intervention resulted in 2.2 (95% CI –0.4% to 5.0%; p = 0.08) additional live births at ≥ 34 weeks' gestational age per 100 pregnancies. The incremental cost-effectiveness ratio (ICER) was £3,305 per live birth. If a live birth was assumed to be equivalent to approximately 25 discounted Quality Adjusted Life Years (QALYs) then the ICER would be around £138 per QALY, which the committee noted would easily fall within a £20,000 per QALY cost-effectiveness threshold often used to inform recommendations for NICE guidelines. Probabilistic sensitivity analysis based on 5,000 simulations using non-parametric bootstrapping found that there was a greater than 90% probability that progesterone would be considered cost-effective at a cost-effectiveness threshold of £30,000 per live birth.

However, the committee noted that the analysis was based on a population that included some women with a history of previous miscarriage for whom the evidence of treatment benefit was clearer and therefore they did not consider there was sufficient evidence to recommend progesterone for women without a history of previous miscarriage.

A sub-group analysis in the PRISM trial suggested that progesterone was dominant in women with a history of previous miscarriage, leading to a cost saving of £322 and 5.5 more live births per 100 pregnancies. Probabilistic sensitivity analysis indicated that there was more than a 90% probability that this would be cost-effective at a cost-effectiveness threshold of £20,000 per live birth. Therefore, the committee agreed there was strong evidence to support a recommendation for progesterone to prevent miscarriage in women with early pregnancy bleeding who have a history of previous miscarriage.

A further sub-group analysis considered progesterone in the smaller sub-group of women who had a history of 3 or more previous miscarriages. In this analysis progesterone led to higher costs although, as in the other analyses, the difference was not statistically significant and, reflecting the smaller sample, the confidence intervals were much wider than for the other analyses. However, the committee noted that the authors tentatively suggested that the higher costs of the progesterone intervention in this group could be a result of its success with greater neonatal intensive care costs because of averted miscarriage driving the increase in costs. Despite the higher costs probabilistic sensitivity analysis indicated that progesterone was likely to be cost-effective. However, the committee did not consider that the results of this sub-group analysis warranted any additional recommendations for women with a history of 3 or more miscarriages.

The committee noted that recommending progesterone for women with a history of previous miscarriage would represent a change in practice for the NHS. However, they did not consider that this change would have a significant resource impact. Although the effect is likely to be small, successfully averted miscarriages are likely to result in a reduction in subsequent conceptions, which would offset treatment costs to some extent. Furthermore, although subject to considerable uncertainty as to the precise effect, the subgroup analysis in women with a history of previous miscarriage had suggested that the intervention may generate cost savings.

Other factors the committee took into account

The committee were made aware by stakeholders that progesterone may be prescribed for women who have taken mifepristone as part of an abortion process, but then have changed their mind, and wish to reverse the effects of the mifepristone. Although this population of women had not been included in the original evidence review, the committee were concerned about this practice, and were not aware of any evidence that suggested that the use of progesterone would be safe and effective in this situation. The committee therefore added this information to the rationale and impact section of the guideline.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.9.2 to 1.9.3 and the research recommendations on the use of progesterone in recurrent miscarriage and the effectiveness of other progesterone preparations at preventing miscarriage.

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

See Cochrane review
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792/epdf/full

Appendix B Literature search strategies

Literature search strategies for review question: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

See Cochrane review
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full

Appendix C Effectiveness

Study selection for: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

See Cochrane review
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full

Appendix D Evidence tables

Evidence tables for review question: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

See Cochrane review
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full

Appendix E Forest plots

Forest plots for review question: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

See Cochrane review
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full

Appendix F GRADE tables

GRADE tables for review question: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

See Cochrane review
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full

Appendix G Economic evidence study selection

Study selection for: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

See NIHR technology appraisal and associated article in the British Journal of Obstetrics and Gynaecology (BJOG)

https://www.journalslibrary.nihr.ac.uk/hta/hta24330#/abstract

https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.16068

Appendix H Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

Table 6: Economic evidence tables

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Coomarasamy 2020 UK Ogwulu 2019 UK **Study type:** Cost-effectiveness analysis **Source of funding:** UK National Institute for Health Research (NIHR) Health Technology Assessment programme	**Intervention:** 400 mg of progesterone (Twice daily vaginal 200 mg pessaries for the duration of treatment – treatment began as soon as possible after confirmation of an intrauterine pregnancy sac and within 4 days of vaginal bleeding and continued until a gestational age of 16 weeks **Comparator:** Placebo pessaries :	Women with bleeding in early pregnancy bleeding, with an intrauterine gestation sac visible on ultrasonography, aged 16–39 years at randomisation **Modelling approach:** Economic evaluation alongside PRISM RCT **Source of baseline data:** Control group in RCT **Source of effectiveness data:** RCT **Source of resource use data:**	**Primary analysis** **Mean cost per participant:** **Intervention:** £7,655 **Control:** £7,572 Difference: £76 **Primary measure of outcome:** Live birth at ≥ 34 weeks gestation **Mean outcome per participant** **Intervention:** 0.0747	**Primary analysis** **ICERs:** £3,305 per live birth **Probability of being cost effective:** >80% probability of being cost-effective as a cost-effectiveness threshold of £15,000 per live birth >90% probability of being cost-effective as a cost-effectiveness threshold of £30,000 per live birth **Sensitivity analysis:**	**Currency:** GBP **Cost year:** 2017-18 **Time horizon:** Duration of trial **Discounting:** None (N/A) **Applicability:** Directly applicable **Limitations:** Minor limitations **Other comments:** The results were presented in 2 papers

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		RCT – data on hospital resource use from randomisation to discharge was collected using researcher completed data forms. Data on services provided in the community was collected retrospectively using health services self-completed questionnaires. **Source of unit cost data:** • NHS Reference Costs 2016/17 • PSSRU • BNF	**Control:** 0.0725 **Difference:** 0.022 **<u>Sub-group analysis (Women with at least 1 previous miscarriage)</u>** **Mean cost per participant** **Difference:** -£322	Fixed progesterone costs until 16 weeks: £4,977 per live birth Imputation of primary care costs: £4,321 per live birth Varying costs of inpatient night admissions: £3,356 per live birth Varying costs of miscarriage management: £3,282 per live birth Removing birth costs: £3,743 per live birth **<u>Sub-group analysis (Women with at least 1 previous miscarriage)</u>** Progesterone dominates >90% probability of being cost-effective as a cost-effectiveness	but were based on the same PRISM RCT. Costs difference are adjusted means based on bootstrapped difference

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			Mean outcome per participant **Difference:** 0.055 **<u>Sub-group analysis (Women with at 3 or more previous miscarriages)</u>** **Mean cost per participant** **Difference:** £1,754 **Mean outcome per participant** **Difference:** 0.15	threshold of £20,000 per live birth **<u>Sub-group analysis (Women with at 3 or more previous miscarriages)</u>** £11,606 per live birth >90% probability of being cost-effective as a cost-effectiveness threshold of £20,000 per live birth	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments

BNF = British National Formulary; ICER = incremental cost-effectiveness ratio; PSSRU = Personal Social Services Research Unit; RCT = randomised controlled trial

Appendix I Economic model

Economic model for review question: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

Excluded effectiveness studies

See Cochrane review
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full

Appendix K Research recommendations – full details

Research recommendations for review question: What is the clinical and cost-effectiveness of progestogens in improving outcomes in women at risk of miscarriage?

K.1.1 Research recommendation

What is the clinical and cost-effectiveness of progesterone in improving outcomes in women with unexplained recurrent miscarriage?

K.1.2 Why this is important

Women with previous pregnancy losses have an increased risk of miscarriage in subsequent pregnancies. Progesterone is essential for maintaining a healthy pregnancy, and there is evidence that it is safe for both women and fetuses.

A recent randomised controlled trial assessed the effectiveness of micronised vaginal progesterone supplementation in women with 3 or more first-trimester losses and did not show a benefit with progesterone therapy use during the first trimester, concluding that there is not enough evidence to support its use in women with unexplained recurrent miscarriage. However, this trial was designed to look for a 10% difference in live birth outcomes in those who received progesterone versus those who did not receive it. A larger randomised controlled trial is required to determine if there is a smaller difference (for example 2.5% to 5%) which would still lead to a meaningful increase live births and reduce the trauma of a further miscarriage for a number of women.

K.1.3 Rationale for research recommendation

Table 7: Research recommendation rationale

Importance to 'patients' or the population	Miscarriage can have significant long-lasting negative effects on women, their partners and families. Progestogen supplementation may increase the opportunity to maintain a healthy pregnancy in some women.
Relevance to NICE guidance	The committee were unable to make recommendations on women with unexplained recurrent miscarriage as current evidence base does not show a benefit with progesterone use. A high-quality clinical trial with a large number of participants is needed to study small effect size. This would allow recommendations to be made in future guideline updates.
Relevance to the NHS	The management of miscarriage and its complications poses a significant burden to the NHS. Ensuring women at high risk of miscarriage are able to maintain a healthy pregnancy will lead to better outcomes for women and support the NHS goal to improve the care of women with unexplained recurrent miscarriage.
National priorities	High
Current evidence base	A number of small trials which have found a benefit and the PROMISE study which did not find a benefit.
Equality considerations	None known

PROMISE: PROgesterone in recurrent MIScarriagE

K.1.4 Modified PICO table

Table 8: Research recommendation modified PICO table

Population	Women with 3 or more unexplained previous miscarriages
Intervention	Progestogens: • Dydrogesterone • Micronised oral progesterone • Micronised vaginal progesterone • Non-micronised vaginal progesterone • 17-OH progesterone
Comparator	• Any of the above progestogens compared to another • No treatment • Placebo
Outcome	• Live birth • Miscarriage (birth before 24 weeks' gestation) • Preterm birth (birth before 37 weeks' gestation) • Stillbirth • Ectopic pregnancy • Congenital abnormalities • Adverse drug effects
Study design	Randomised, double-blind placebo controlled trial
Timeframe	36 months
Additional information	None

OH: hydroxy

K.1.5 Research recommendation

What is the clinical and cost-effectiveness of vaginal micronised progesterone versus other progesterone preparations in improving outcomes in women at risk of miscarriage?

K.1.6 Why this is important

Evidence from a recent randomised controlled trial showed a small but important benefit for the outcome of live birth when vaginal micronised progesterone was given to women with early pregnancy bleeding and a history of one or more previous miscarriages. However, there was not enough evidence available to assess whether other formulations of progesterone would lead to other beneficial outcomes in this group of women. Research is needed to identify whether there is a difference in the effectiveness of micronised versus non-micronised progesterone therapy in women with early pregnancy bleeding and a history of one or more previous miscarriages.

K.1.7 Rationale for research recommendation

Table 9: Research recommendation rationale

Importance to 'patients' or the population	Miscarriage can have a significant emotional and physical impact on women, their partners and families. The specific type of progesterone used may have a role in the attainment and maintenance of a healthy pregnancy.

Relevance to NICE guidance	A high-quality clinical trial will allow recommendations for a range of progestogen preparations to be made in future guideline updates.
Relevance to the NHS	The management of miscarriage and its complications poses a significant burden to the NHS. Ensuring women at high risk of miscarriage are able to maintain a healthy pregnancy will lead to better outcomes for women and support the NHS goal to improve the care of women with threatened miscarriage.
National priorities	High
Current evidence base	Minimal
Equality considerations	None known

K.1.8 Modified PICO table

Table 10: Research recommendation modified PICO table

Population	Women with early pregnancy bleeding and a history of one or more previous miscarriages
Intervention	• Vaginal micronised progesterone
Comparator	• Vaginal non-micronised progesterone preparations • Oral/subcutaneous/rectal progesterone preparations
Outcome	• Live birth • Miscarriage (birth before 24 weeks' gestation) • Preterm birth (birth before 37 weeks' gestation) • Stillbirth • Ectopic pregnancy • Congenital abnormalities • Adverse drug effects
Study design	Randomised, double-blind placebo controlled trial
Timeframe	36 months
Additional information	None

Appendix L Methodological limitations

The methodological limitations of the Cochrane review (Devall 2021) have been assessed using the ROBIS tool to assess risk of bias in systematic reviews and the modified PRISMA-NMA checklist

L.1.1 ROBIS tool to assess risk of bias in systematic reviews

Domain 1: Study eligibility criteria

1.1 Did the review adhere to pre-defined objectives and eligibility criteria? Y
1.2 Were the eligibility criteria appropriate for the review question? Y
1.3 Were eligibility criteria unambiguous? Y
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (for example, date, sample size, study quality, outcomes measured? N
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (for example, publication status or format, language, availability of data)? Y
Concerns regarding specification of study eligibility criteria: LOW

Domain 2: Identification and selection of studies

2.1 Did the search include an appropriate range of databased/electronic sources for published and unpublished reports? Y
2.2 Were methods additional to database searching used to identify relevant reports? Y
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Y
2.4 Were restrictions based on date, publication format, or language appropriate? Y
2.5 Were efforts made to minimise error in selection of studies? Y
Concerns regarding methods used to identify and/or select studies: LOW

Domain 3: Data collection and study appraisal

3.1 Were efforts made to minimise error in data collection? Y
3.2 Were sufficient study characteristics available for both review authors and reader to be able to interpret the results? Y
3.3 Were all relevant study results collected for use in the synthesis? Y
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?
3.5 Were efforts made to minimised error in risk of bias assessment? Y
Concerns regarding methods used to collect data or appraise studies: LOW

Domain 4: synthesis and findings

4.1 Did the synthesis include all studies that it should? Y
4.2 Were all pre-defined analyses reported or departures explained? Y
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? Y
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis? Y
4.5 Were the findings robust, for example, as demonstrated through funnel plot or sensitivity analyses? Y
4.6 Were biases in primary studies minimal or addressed in the synthesis? Y
Concerns regarding the synthesis and findings: LOW

Risk of bias in the review

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?
B. Was the relevance of identified studies to the review's research question appropriately considered?
C. Did the reviewers avoid emphasising results on the basis of statistical significance? Y
Risk of bias in the review: LOW

L.1.2 Modified PRISMA-NMA checklist

1. Describe the reasons for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted

   Not applicable

2. Specify study characteristics (for example, PICOS, length of follow-up) and report characteristics (for example, years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).

   Not applicable

3. Describe methods used to explore the geometry of the treatment network and potential biases related to it. This should include how the evidence base has been graphically summarised for presentation, and what characteristics were compiled and used to describe the evidence base to readers

   Authors included a network diagram for each outcome and a qualitative description of the treatment network, which represented the available comparisons, number of trials, number of participants included, and the grading of the direct evidence.

   The size of the nodes and the limited number of edges indicated a gap in the evidence base and the graphical representation of all comparisons showed that a NMA was not feasible (because the interventions did not form a connected network).

   See Cochrane review
   https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full

   Quantitative metrics assessing features of the network geometry were not mentioned.

4. State the principal summary measures (for example, risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses

   The principal summary measure of relative treatment effect of dichotomous outcomes for direct comparisons were risk ratios (RRs). The authors planned to rank and obtain a hierarchy of the treatments according to their SUCRA values and to evaluate each outcome to determine the confidence of the NMA output. The treatment hierarchy was going to be presented along with summary effect measures and 95% CIs, however, it was not possible to do this due to the paucity of evidence. As a result, modified approaches to represent the summary findings, such as additional graphical or tabular approaches, were not included.

5. Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: a) Handling of multi-

arm trials; b) Selection of variance structure; c) Selection of prior distributions in Bayesian analyses; d) Assessment of model fit.

Methods for handling data:

a) Cluster randomised trials were planned to be included and to use appropriate methods for adjusting sample size, combining results with individually randomised trials and exploring heterogeneity. However, no cluster randomised trials were included in the review.
b) Multi-arm trials were planned to be included and treated as multiple independent comparisons. For global analyses, authors planned to combine different dosage, regimen and route of drug administration and to explore these in separate subgroup analyses. However, no multi-arm trials were included in the review.
c) Missing data: authors planned to note levels of attrition and to explore high levels of missing data in sensitivity analyses. Intention-to-treat (ITT) analysis were prioritised.
d) Statistical heterogeneity: this was planned to be estimated from the multivariate meta-analysis model, based on the magnitude of the heterogeneity variance parameter (T2) and compared to empirical distributions for dichotomous variables.
e) Clinical homogeneity was explored by describing the study population characteristics across trials. The appropriateness of the transitivity assumption was met for both direct and indirect comparisons.
f) Inconsistency: this was planned to be done following local (such as node-splitting) and global (such as 'design by treatment' interaction model) approaches, along with the evaluation of clinical homogeneity described above.

Methods for combining results:

g) Indirect treatment comparisons: data was extracted and set up using the augmented format by comparing all treatments with a reference treatment, and those studies without a treatment have one created. Network diagrams were created to verity if a NMA was feasible. NMAs would have been performed under a frequentist framework using multivariate random effect meta-analyses estimated using maximum likelihood estimation. NMAs were planned to be carried using Stata® statistical software. Indirect comparisons were produced where possible and estimated using Microsoft Excel®.

6. Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address inconsistency when found.

   As a NMA could not be conducted, the authors did not evaluate the agreement of direct and indirect evidence in the treatment networks, however they noted in their protocol that their final step for assessing the quality of the NMA would include the consideration of coherence between direct and indirect effect estimates.

7. Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: e) Sensitivity or subgroup analyses; f) Meta-regression analyses; g) Alternative formulations of the treatment network; h) Use of alternative prior distributions for Bayesian analyses (if applicable).

   As a NMA could not be conducted, the authors did not describe additional methods of analyses. However, in the protocol they describe that sensitivity analyses were

planned by evaluating model fit for: overall quality of the studies, randomisation unit and use of placebo.

No additional methods of additional analyses were described.

8. Provide a network graph of the included studies to enable visualisation of the geometry of the treatment network.

   See Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013792.pub2/epdf/full

9. Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomised patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure (for example, publication bias).

   Due to the paucity of evidence, the network of interventions was not connected and it did not contain closed loops. For this same reason, it was not possible to assess bias formally.

10. Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (for example, placebo or standard care). League tables and forest plots may be considered to summarise pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.

    Not applicable as NMA was not feasible.

11. Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.

    As a NMA could not be conducted, the authors did not investigate inconsistency. However, in the protocol, they described that sensitivity analyses were planned by evaluating model fit for overall quality of the studies, randomisation unit and use of placebo.

12. Give results of additional analyses, if done (for example, sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).

    Apart from the sensitivity analyses outlined above, no additional methods of additional analyses were described.

13. Discuss limitations at study and outcome level (for example, risk of bias), and at review level (for example, incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (for example, avoidance of certain comparisons).

    All 7 studies were judged to be at low risk of bias. In addition to the risk of bias assessment per study, authors also conducted a scientific integrity/trustworthiness check, which ensures that only studies deemed to be sufficiently trustworthy are included in the analysis. Publication bias could not be assessed formally due to the paucity of evidence, however if this was investigated informally it was not reported.

The results of the analysis may have been impacted by publication bias, for example where results had not been published because results were unfavourable to progestogen treatment. The source of funding was not reported for 2 of the studies and the remaining studies were funded by public bodies. As non-publication is more common in trials that received industry funding, publication bias cannot be completely ruled out, although the Cochrane review authors did attempt to minimise it by identifying all relevant studies regardless of language and publication status. This approach also minimises the risk of incomplete retrieval of identified research. Some of the Cochrane review authors were also authors of the largest trial including women with threatened miscarriage, however they did not participate in any decisions regarding the assessment for inclusion/exclusion of trials, risk of bias assessment or data extraction, and there were not conflicts of interest reported, so it is not anticipated that this would have introduced bias in the reviewing process.

The assumption of transitivity was considered to be valid as the different progesterone preparations are administered in a similar way across trials. Trials were also similar in terms of design and characteristics. The treatment network showed that there were not enough trials available to conduct a NMA, indicating potential gaps of evidence. For example, most trials compared an active treatment with placebo, but there was only 1 study providing evidence for a type of progesterone compared to another. Indirect treatments were possible, but network interventions were not connected, limiting the ability to compare multiple treatments simultaneously in a single analysis. For this reason, the committee made a research recommendation to assess the clinical and cost-effectiveness of vaginal micronised progesterone versus other progesterone preparations in women at risk of miscarriage.

Overall, no significant limitations were identified, and it was considered that the statistical methods planned for the NMA were appropriate.