

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive

Clinical guideline

CG156: Fertility

Publication date

February 2013

Surveillance report for GE

April 2015

Surveillance recommendation

The Evidence Update on CG156: Fertility identified 2 potential impacts on the guideline.

An additional 2 potential impacts were identified from external correspondence with NICE and identification of related new evidence.

Following further discussion of the impacts at a Triage Panel, GE is asked to consider the proposal to:

- Update the following question in CG156 using a Standing Committee for Updates via the Clinical Guidelines Update Team:
 - What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?

GE is asked to note that this 'yes to update' proposal will not be consulted on.

Key findings

			Potential impact on guidance	
			Yes	No
Evidence identified from Evidence Update			✓	
Anti-discrimination and equalities considerations				✓
Feedback from Triage Panel meeting			✓	
No update	CGUT update	Standard update	Transfer to static list	Change review cycle
	✓			

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Centre for Clinical Practice – Surveillance Programme

Surveillance review of CG156: Fertility

Recommendation for Guidance Executive

Background information

Guideline issue date: 2013

2-year review: 2015

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

2-year Evidence Update

1. The Evidence Update on CG156: Fertility was used as a source of evidence for this surveillance review and considered new evidence since the guideline was published. The search dates of the Evidence Update were 01 December 2011 to 17 September 2014. A summary of the evidence is provided in the Evidence Update.
2. The Evidence Update identified 2 areas in which there may be an impact on current guideline recommendations:
 - Use of gonadotrophin-releasing hormone (GnRH) agonists in the luteal support protocol.
 - The choice or composition of embryo culture media.These areas would be considered for a standard update at the next surveillance review point.

Triage Panel

3. The new evidence that may potentially impact on guideline recommendations was considered by the Triage Panel.

4. **Clinical question: What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?**
5. NICE received a query about the formulation of the recommendations on IUI. Additionally, a further RCT⁴ on IUI was highlighted by the Chair of the Evidence Update Advisory Group during sign-off of the completed Evidence Update. This study suggested that IUI is non-inferior to in-vitro fertilisation (IVF). The panel felt that the new study provided new evidence that should be considered in an update and felt that this question should be updated with more urgency than the other questions under consideration.

Decision: NICE to update this clinical question using Standing Committee for Updates via the Clinical Guidelines Update Team.

6. **Clinical question: What is the effectiveness of luteal phase support as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?**
7. The Evidence Update included a systematic review⁹ suggesting that addition of gonadotrophin releasing hormone (GnRH) agonists to the luteal support protocol was associated with a higher probability of live birth compared with standard luteal support. The panel agreed that the new evidence is not ground-breaking and that adding GnRH agonist treatment in the luteal phase is not routine practice currently. However, the panel recommended on the basis of the new evidence that this question is considered as part of a standard update of the guideline. Updating this question was not thought to be urgent and would be carried forward to the next surveillance review for consideration.

Decision: NICE to consider this clinical question to be included in a standard update at the next review point.

8. **Clinical question: What are the effects of culture media on outcomes of IVF?**
9. The Evidence Update included 2 studies relevant to this question. A Cochrane review¹² found that adding high levels of hyaluronic acid to culture media was associated with increases in live births. An additional quasi-randomised study¹³ found significant differences in height and weight of children at 2 years depending on which of 2 branded culture media was used during IVF. The panel discussed whether culture media were covered by the scope of the guideline and whether widening the scope would necessitate looking at other environmental factors not currently covered by guidance. The panel felt strongly that culture media could have an important effect on the outcomes of IVF but the exact composition of culture media is not known to clinicians. Updating this question was not considered to be urgent.

10. **Decision:** NICE to consider this clinical question to be included in a standard update at the next surveillance review point..

11. During discussions with topic experts at the triage panel it was noted that a number of the areas of the guideline not updated in 2013 were now out of date and that a larger standard update would probably be required. However, no key evidence in these areas was picked up by the Evidence Update process on which this surveillance review was based. It was agreed that this would be considered at the next full surveillance review in 2017, which would consider the totality of the guideline and any new evidence, including those areas identified above.

Ongoing research

12. No ongoing research was identified.

Anti-discrimination and equalities considerations

13. None identified.

Implications for other NICE programmes

14. This guideline relates to a quality standard, QS73: fertility problems.
- a. None of the quality statements are likely to be affected by the proposed area for update by the CGUT team.

Conclusion

15. Through the Evidence Update of CG156, new evidence that may potentially impact guideline recommendations was identified in the following areas of the guideline and discussed at the Triage Panel:
- a. Effectiveness of IUI
 - i. This area was considered by the Triage Panel, where it was decided that this update could be achieved by updating the following question in the guideline:
 - ii. What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?
 - b. GnRH agonists for luteal support
 - i. This area was considered by the Triage Panel where it was decided that the new evidence should be considered in a standard update of the guideline and would be carried forward to the next surveillance review.
 - c. Choice of culture media
 - i. This area was considered by the Triage Panel where it was decided that the new evidence should be considered in a standard update of the guideline and would be carried forward to the next surveillance review.

16. For all other areas of the guideline no evidence was identified which would impact on recommendations.

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Appendix 1 Decision matrix

Surveillance and identification of triggers for updating CG156. The table below provides summaries of the evidence that were identified and included in the Evidence Update.

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
156-01 Providing information			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-02 Psychological effects of fertility problems			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-03 Specialist and generalist care			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-04 Chance of conception			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-05 Frequency and timing of sexual intercourse or artificial insemination			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-06 Alcohol			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-07 Smoking			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-08 Caffeinated beverages			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
156-09 Body weight			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-10 Tight underwear			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-11 Occupation			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-12 Prescribed, over-the-counter and recreational drug use			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-13 Complementary therapy			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-14 Folic acid supplementation			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-15 Defining infertility			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-16 Investigation of suspected male factor infertility			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-17 Investigation of suspected ovulation disorders How accurate are tests of ovarian reserve in predicting pregnancy and its outcomes for women with infertility undergoing ovulation induction or ovarian stimulation treatment assisted reproduction (including unexplained infertility and IVF)			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
156-18 Investigation of suspected tubal and uterine abnormalities			
The Evidence Update included a systematic review ¹ and meta-analysis of 30 studies to compare ultrasound hysterosalpingography (HSG) with laparoscopy for diagnosis of tubal occlusion in women with fertility problems. Ultrasound HSG had sensitivity of 92% for diagnosing tubal occlusion and specificity of 95%. In studies comparing both ultrasound HSG and standard HSG with laparoscopy as the reference standard, no significant differences were noted between ultrasound HSG and standard HSG.	Not applicable	Not applicable	Evidence suggests that ultrasound HSG may be as effective as standard HSG for diagnosing fallopian tube occlusion, and both appear to have high sensitivity and specificity compared with laparoscopy. The Evidence Update concluded that no impact on NICE CG156 was expected because ultrasound HSG is already recommended as an alternative to standard HSG for women who are not known to have comorbidities and where appropriate expertise is available.
156-19 Additional investigations for viral infection and cancer - What is the effectiveness and safety of sperm washing to reduce the risk of viral transmission? - What is the risk of transmission by vaginal intercourse when HIV positive male partners are on treatment? - What is the risk of transmission by vaginal intercourse when HIV positive male partners have a low viral load? - What is the risk of transmission by vaginal intercourse when HIV negative women use pre-exposure anti-retroviral prophylaxis?			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-20 Strategies for management of fertility problems			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-21 Medical management of male factor fertility problems			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
156-22 Surgical management of male factor fertility problems			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-23 Management of ejaculatory failure			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-24 WHO Group I ovulation disorders What is the effectiveness and safety of ovulation induction strategies in women with WHO Group I Ovulation Disorders?			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-25 WHO Group II ovulation disorders What is the effectiveness and safety of ovulation induction strategies in women with WHO Group II Ovulation Disorders?			
The Evidence Update included a Cochrane review ² of 26 RCTs (n=5560) of aromatase inhibitors in women with anovulatory polycystic ovary syndrome and infertility. Letrozole significantly increased live birth rate compared with clomifene citrate (OR=1.64) with no difference in rates of ovarian hyperstimulation syndrome (OHSS; RR=0.00) and lower rates of multiple pregnancy.	Not applicable	Not applicable	Evidence suggests that in women with polycystic ovary syndrome, letrozole appears to be associated with a higher live birth rate, lower rates of multiple pregnancy and lower incidence of OHSS than clomifene citrate. However, the Evidence Update concluded that because of the low quality of the evidence base, no impact on NICE CG156 is expected.
The Evidence Update included a systematic review and meta-analysis ³ of 7 RCTs (n=334) of metformin compared with placebo or no treatment in women with polycystic ovary syndrome treated with gonadotrophins. Metformin plus gonadotrophins was associated with a significantly higher live birth rate compared with gonadotrophins alone	Not applicable	Not applicable	Evidence suggests that in women with polycystic ovary syndrome who are known to be resistant to clomifene citrate, metformin plus gonadotrophins may be associated with higher live birth rates than

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
(OR=1.94). Adding metformin to gonadotrophins also significantly increased the pregnancy rate (OR=2.25). No significant effect of metformin was seen on multiple pregnancies, miscarriages or OHSS.			gonadotrophins alone, without affecting rates of multiple pregnancies or OHSS. This evidence was considered unlikely to have impact on NICE CG156, because of the low quality of the included studies.
156-26 Hyperprolactinaemic amenorrhoea – dopamine agonists			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-27 Monitoring ovulation induction during gonadotrophin therapy			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-28 Tubal microsurgery and laparoscopic tubal surgery			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-29 Tubal catheterisation or cannulation			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-30 Surgery for hydrosalpinges before in vitro fertilisation treatment			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-31 Uterine surgery			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-32 Medical management (ovarian suppression) of endometriosis			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
156-33 Surgical ablation of endometriosis			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-34 Ovarian stimulation for unexplained infertility What is the effectiveness and safety of ovarian stimulation agents in women with unexplained infertility?			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-35 Intrauterine insemination What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?			
No new key evidence was included in the Evidence Update. A further RCT ⁴ on IUI was highlighted by the Chair of the Evidence Update Advisory Group during sign-off of the completed Evidence Update. The RCT (n=602 couples) compared in-vitro fertilisation (IVF) using single embryo transfer with IVF in a modified natural cycle, and with IUI using controlled ovarian hyperstimulation. Birth of a healthy child occurred in: 52% of couples in the IVF using single embryo transfer group; 43% of those in the IVF in a modified natural cycle group; and 47% of those in the IUI using controlled ovarian hyperstimulation group. Both IVF in modified natural cycle and IUI using controlled ovarian hyperstimulation were non-inferior to IVF using single embryo transfer. Multiple pregnancies did not differ significantly between groups.	Not applicable	Not applicable	Evidence suggests that IUI may be comparable to IVF in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility. This may be a potential impact on NICE CG156, which currently has a 'do not do' recommendation around routine use of IUI, although IUI is recommended for certain populations.
156-36 Prediction of IVF success What are the factors which predict the success of IVF?			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
156-37 Procedures used during in vitro fertilisation treatment			
The Evidence Update included a Cochrane review⁵ of reviews that summarised 58 published Cochrane reviews on assisted reproduction procedures. Interventions that significantly improved live birth rates were: • Endometrial injury performed in the month before ovulation induction • Embryo culture in low oxygen concentrations. • Hyaluronic acid in embryo culture media. • Use of growth hormone in women who respond poorly to IVF.	Not applicable	Not applicable	The available evidence suggests that several interventions may improve the outcome of assisted reproduction procedures. The Evidence Update included several of the individual Cochrane reviews and considered potential impacts of each individual review.
156-38 Pre-treatment for IVF			
• What is the effectiveness of pre-treatment as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-39 Down-regulation or other regimens to avoid premature luteinising hormone surges			
• What is the effectiveness of down-regulation as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-40 Controlled ovarian stimulation in IVF			
• What is the effectiveness of the following strategies as part of an ovarian stimulation protocol in women undergoing IVF or ICSI treatment: – stimulation with gonadotrophins – ‘milder’ stimulation – adjuvant growth hormone and di-hydro-epi-androsterone (DHEA) treatment for women with a previous poor response?			
The Evidence Update included a systematic review ⁶ and meta-analysis of 10 RCTs (n=900) of metformin in women with polycystic ovary syndrome undergoing IVF or intracytoplasmic sperm injection (ICSI). Gonadotrophins plus	Not applicable	Not applicable	This evidence suggests that in women with polycystic ovary syndrome who are undergoing IVF, adding metformin to

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
metformin was not associated with significantly different live birth rates or pregnancy rates compared with gonadotrophins plus placebo or no treatment. The rate of OHSS was significantly lower with metformin.			gonadotrophins may not increase live birth rate compared with gonadotrophins alone, although incidence of OHSS may be reduced. This evidence was considered unlikely to affect NICE CG156 because of limitations of the evidence and the absence of an increase in live birth rate.
156-41 Triggering ovulation in IVF Which is the most effective ovulation trigger to use as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?			
The Evidence Update included a Cochrane review ⁷ of 2 RCTs (n=248) investigating the dopamine agonist cabergoline for preventing moderate or severe OHSS in women undergoing assisted reproduction procedures. Cabergoline was associated with an overall reduction in moderate or severe OHSS. However in subgroup analysis, moderate OHSS was significantly lower in women who received cabergoline, but severe OHSS was not. No significant effect on clinical pregnancy rate or multiple pregnancies was seen.	Not applicable	Not applicable	Evidence suggests that cabergoline may be associated with a reduction in OHSS without affecting rates of pregnancies or multiple pregnancies. This evidence was considered unlikely to have an impact on NICE CG156, because no significant effect was seen on severe OHSS, which is of greater clinical concern than moderate OHSS.
156-42 Oocyte and sperm retrieval in IVF			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
156-43 Embryo transfer strategies - What is the effectiveness and safety of different embryo/blastocyst transfer strategies in relation to both: - number of embryos (comparing single with double) - timing of transfer (comparing cleavage with blastocyst stage).			
The Evidence Update included a systematic review and meta-analysis⁸ of 8 studies to compare embryo transfer at blastocyst stage with transfer at cleavage stage. Blastocyst-stage transfer was associated with higher risk of very preterm delivery, defined as delivery before 32 weeks (RR=1.22). Preterm delivery, defined as delivery before 37 weeks, was also significantly more likely after blastocyst-stage transfer. However, blastocyst-stage transfer was associated with a lower likelihood of delivery of a baby that was small for gestational age.	Not applicable	Not applicable	This evidence suggests that embryo transfer at the blastocyst stage may be associated with higher rate of preterm and very preterm birth than transfer at the cleavage stage, but may be associated with lower frequency of babies born small for gestational age. However, the Evidence Update concluded that limitations in the evidence base mean no impact on NICE CG156 is expected.
156-44 Luteal phase support after IVF What is the effectiveness of luteal phase support as part of an ovarian stimulation strategy for women undergoing IVF or ICSI treatment?			
The Evidence Update included a systematic review and meta-analysis⁹ of 6 RCTs (n=2012), which investigated the effects of adding GnRH agonist treatment in the luteal phase on live birth rates after IVF or ICSI. Overall, addition of GnRH agonists to the luteal support protocol was associated with a higher probability of live birth compared with standard luteal support (risk difference=0.16). Results were similar when analysed separately depending on whether ovarian stimulation was performed with GnRH agonists or antagonists.	Not applicable	Not applicable	This evidence suggests that addition of GnRH agonists to the luteal support protocol may be associated with increases in live birth rate after IVF. This evidence was considered to have a potential impact on NICE CG156.

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
156-45 Gamete intrafallopian transfer and zygote intrafallopian transfer			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-46 Indications for intracytoplasmic sperm injection			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-47 Genetic issues and counselling			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-48 Intracytoplasmic sperm injection versus IVF			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-49 Cost effectiveness of intracytoplasmic sperm injection			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-50 Clinical indications for donor insemination			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-51 Information and counselling			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-52 Screening of sperm donors			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-53 Assessment of the woman			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-54 Intrauterine insemination versus intracervical insemination			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
156-55 Unstimulated versus stimulated donor insemination			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-56 Indications for oocyte donation			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-57 Screening of oocyte donors			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-58 Oocyte donation and 'egg sharing'			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-59 Cryopreservation of semen, oocytes, embryos and ovarian tissue What is the effectiveness of cryopreservation (including vitrification) in fertility preservation strategies?			
No new key evidence was found for this section	Not applicable	Not applicable	Not applicable
156-60 Long-term safety of ovulation induction and ovarian stimulation What is the long-term safety of ovulation induction and ovarian stimulation strategies in women with infertility and their children?			
The Evidence Update included a cross-sectional study ¹⁰ investigating the risk of venous thromboembolism and pulmonary embolism in pregnant women who conceived after IVF (n=23,498) compared with matched women with natural pregnancies (n=116,960). The proportion of women with IVF pregnancies who were diagnosed with venous thromboembolism was 4.2 in 1000 compared with 2.5 in 1000 for women with natural pregnancies. Pulmonary embolism occurred in 8.1 per 10,000 women in the IVF group compared with 6.0 per 10,000 women who had natural pregnancies. The heightened risk was mainly in the first	Not applicable	Not applicable	This evidence suggests that women with pregnancies conceived with IVF appear to be at greater risk of venous thromboembolism and pulmonary embolism, particularly in the first 3 months, than women with pregnancies conceived naturally. The Evidence Update concluded that this evidence is not expected to impact NICE CG156, which

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
trimester after IVF, and may be due to the proximity in time to the IVF procedure.			does not include recommendations about risks associated with IVF treatment.
156-61 Long-term safety of IVF • What is the long-term safety of IVF in women with infertility and their children?			
The Evidence Update included a population-based study ¹¹ in Australia to determine hospital use in the first 5 years of life for children born after assisted reproduction procedures. Frequency, duration and costs of hospital admissions were compared for singleton children born after assisted reproduction procedures (n=2199) and singleton children born after natural conception (n=224,425). Children conceived by assisted reproduction procedures were more likely to be delivered by emergency caesarean section and to be born prematurely. Children born after assisted reproduction procedures were significantly more likely to be admitted to hospital in the first 5 years of life.	Not applicable	Not applicable	This evidence suggests that children born after use of assisted reproduction procedures, to mothers who are wealthier and healthier but older, appear to have a greater likelihood of admission to hospital in the first 5 years of life than children born after natural conception. This evidence was considered unlikely to affect NICE CG156 because the absolute increase in admissions to hospital was small.
156-62 New question – what are the effects of culture media on outcomes of IVF?			
The Evidence Update included a Cochrane review ¹² of 17 RCTs (n=3898) to determine the effects of using embryo transfer media containing adherence compounds on live birth and pregnancy rates in assisted reproduction. Overall, high-dose hyaluronic acid was associated with an increase in live births compared with low-dose or no hyaluronic acid. In another study of culture media, ¹³ 2 types of culture medium were compared to assess postnatal growth in the first 2 years of life. At 2 years of age, children born after Vitrolife	Not applicable	Not applicable	These studies suggest that the choice or composition of culture media may affect live birth rates and the growth of children up to 2 years after birth. The Evidence Update concluded that this evidence may have a potential impact on NICE CG156, which does not contain recommendations

Main findings and conclusion of the 2-year Evidence Update (March 2015)	Is there any new evidence/intelligence identified during this 2-year surveillance review (2015) that may change this conclusion?	Clinical feedback from the GDG	Impact of findings of this 2-year Evidence Update on guideline recommendations
culture were 188 g heavier and 4.9 mm taller than those born after Cook culture.			about choice of culture media.
156-63 New question – what are the effects of oxygen concentration during embryo culture			
The Evidence Update included a Cochrane review ¹⁴ of 7 RCTs (n=2422) comparing embryo culture at low oxygen concentrations (about 5%) with atmospheric oxygen concentrations (about 20%). Low oxygen concentrations during embryo culture were associated with a significantly higher live birth rate than atmospheric oxygen concentrations (OR=1.39).	Not applicable	Not applicable	This evidence suggests that culturing embryos in low oxygen concentration (about 5%) may result in higher live birth rates than culturing at atmospheric oxygen concentration. However, the Evidence Update concluded that no impact on NICE CG156 is expected because the guideline does not specify laboratory conditions for culturing embryos.
156-64 New question – what is the efficacy and safety of endometrial injury to improve outcomes of assisted reproduction procedures?			
The Evidence Update included a Cochrane review ¹⁵ of 5 RCTs (n=591) of endometrial injury performed up to 6 months before treatment with assisted reproduction procedures. Endometrial injury in the month before starting ovulation induction was associated with a significant increase in live birth rate compared with control. Another systematic review and meta-analysis ¹⁶ assessed the effects of local endometrial injury reported in 8 studies. Across all studies the clinical pregnancy rate in the endometrial injury group ranged from 27% to 69% and in the control groups ranged from 9% to 44%. In randomised studies the clinical pregnancy rate in the endometrial injury group was more than twice that in the control groups.	Not applicable	Not applicable	These studies suggest that intentional endometrial injury in the month before embryo implantation may be associated with higher rates of live birth than control. However, the Evidence Update concluded that limitations of the evidence base, particularly the need to fully evaluate adverse events after a procedure that causes intentional injury, mean that no impact on NICE CG156 is expected.

References

1. Maheux-Lacroix S, Boutin A, Moore L et al. (2014) Hysterosalpingosonography for diagnosing tubal occlusion in subfertile women: a systematic review with meta-analysis. *Human Reproduction* 29: 953–63
2. Franik S, Kremer JA, Nelen WL et al. (2014) Aromatase inhibitors for subfertile women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* issue 2: CD010287
3. Palomba S, Falbo A, La Sala GB (2014) Metformin and gonadotropins for ovulation induction in patients with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Reproductive Biology and Endocrinology* 12: 3
4. Bendsdorp AJ, Tjon-Kon-Fat RI, Bossuyt PM et al. (2015) Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. *BMJ* 350: g7771
5. Farquhar C, Rishworth JR, Brown J et al. (2014) Assisted reproductive technology: an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* issue 12: CD010537
6. Palomba S, Falbo A, La Sala GB (2012) Effects of metformin in women with polycystic ovary syndrome treated with gonadotrophins for in vitro fertilisation and intracytoplasmic sperm injection cycles: a systematic review and meta-analysis of randomised controlled trials. *BJOG* 120: 267–76
7. Tang H, Hunter T, Hu Y et al. (2012) Cabergoline for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* issue 2: CD008605
8. Maheshwari A, Kalampokas T, Davidson J et al. (2013) Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of blastocyst-stage versus cleavage stage embryos generated through in vitro fertilisation treatment: a systematic review and meta-analysis. *Fertility and Sterility* 100: 1615–21
9. Kyrrou D, Kolibianakis EM, Fatemi HM et al. (2011) Increased live birth rates with GnRH agonist addition for luteal support in ICSI/IVF cycles: a systematic review and meta-analysis. *Human Reproduction Update* 17: 734–40
10. Henriksson P, Westerlund E, Wallen H et al. (2013) Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: cross sectional study. *BMJ* 346: e8632
11. Chambers GM, Lee E, Hoang VP et al. (2014) Hospital utilization, costs and mortality rates during the first 5 years of life: a population study of ART and non-ART singletons. *Human Reproduction* 29: 601– 10
12. Bontekoe S, Heineman MJ, Johnson N et al. (2014). Adherence compounds in embryo transfer media for assisted reproductive technologies. *Cochrane Database of Systematic Reviews* issue 2:CD007421
13. Kleijkers SH, van Montfoort AP, Smits LJ et al. (2014) IVF culture medium affects post-natal weight in humans during the first 2 years of life. *Human Reproduction* 29: 661–9

14. Bontekoe S, Mantikou E, van Wely M et al. (2012). Low oxygen concentrations for embryo culture in assisted reproductive technologies.
Cochrane Database of Systematic Reviews issue 7: CD008950
15. Nastri CO, Gibreel A, Raine-Fenning N et al. (2012) Endometrial injury in women undergoing assisted reproductive techniques.
Cochrane Database of Systematic Reviews issue 7: CD009517
16. El-Toukhy T, Sunkara S, Khalaf Y et al. (2012) Local endometrial injury and IVF outcome: a systematic review and meta-analysis.
Reproductive BioMedicine Online 25: 345–54