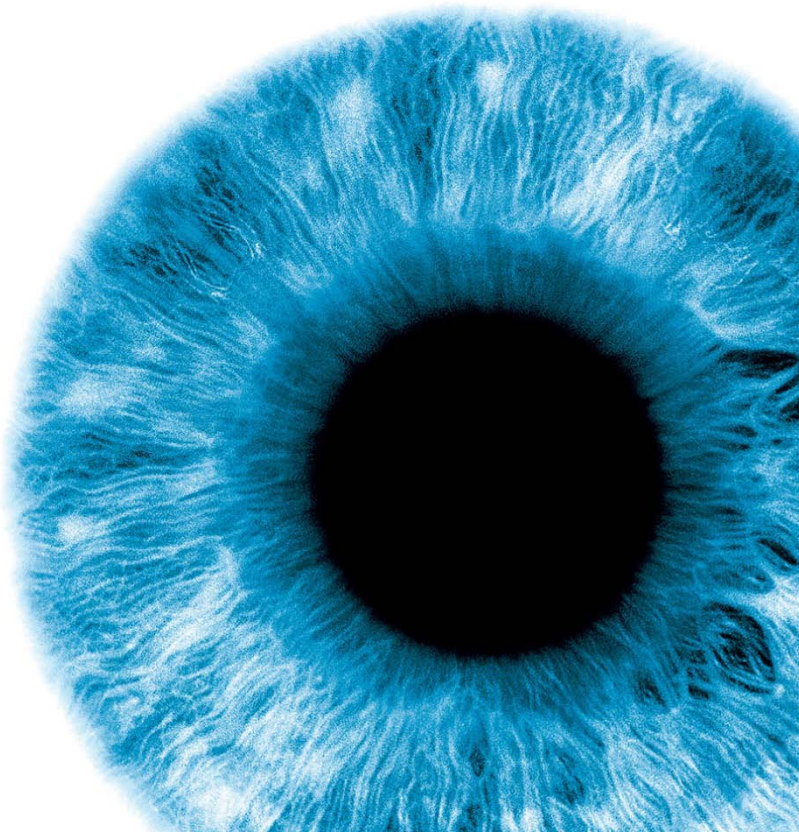
NICE National Institute for Health and Care Excellence

Fertility

Evidence Update March 2015

A summary of selected new evidence relevant to NICE clinical guideline 156 'Assessment and treatment for people with fertility problems' (2013)

Evidence Update 74



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Introduction

Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

[1] **Fertility. NICE clinical guideline 156 (2013)**

A search was conducted for new evidence from 01 December 2011 to 17 September 2014. A total of 11,087 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 35 references underwent a rapid critical appraisal process and then were reviewed by an Evidence Update Advisory Group, which advised on the final list of 15 items selected for the Evidence Update. See Appendix A for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 156 (NICE CG156). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal.

See the NICE guidelines manual for further information about updating NICE guidelines.

NICE Pathways

NICE Pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathway covers advice and recommendations related to this Evidence Update:

- Fertility. NICE Pathway

Quality standards

- Fertility problems. NICE quality standard 73

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance

Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on NICE CG156. Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from NICE CG156.

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

	Potential impact on guidance	
Key point	**Yes**	**No**
Investigation of fertility problems and management strategies • Hysterosalpingo-contrast-ultrasonography (ultrasound HSG) may be as effective as hysterosalpingography (HSG) for diagnosing fallopian tube occlusion, and both appear to have high sensitivity and specificity compared with laparoscopy.		✓
Ovulation disorders • In women with polycystic ovary syndrome, letrozole[2] appears to be associated with a higher live birth rate, lower rates of multiple pregnancy and lower incidence of ovarian hyperstimulation syndrome (OHSS) than clomifene citrate. • In women with polycystic ovary syndrome who are known to be resistant to clomifene citrate, metformin[3] plus gonadotrophins may be associated with higher live birth rates than gonadotrophins alone, without affecting rates of multiple pregnancies or OHSS.		✓ ✓
Procedures used during in vitro fertilisation (IVF) treatment • In women with polycystic ovary syndrome who are undergoing IVF, adding metformin[4] to gonadotrophins may not increase live birth rate compared with gonadotrophins alone, although incidence of OHSS may be reduced. • Cabergoline[5] may be associated with a reduction in OHSS without affecting rates of pregnancies or multiple pregnancies. • 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.		✓ ✓ ✓

[2] At the time of publication of this Evidence Update, letrozole did not have UK marketing authorisation for this indication and was not considered for NICE CG156.
[3] At the time of publication of this Evidence Update, metformin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
[4] At the time of publication of this Evidence Update, metformin did not have UK marketing authorisation for this indication and was not considered for NICE CG156.
[5] At the time of publication of this Evidence Update, cabergoline did not have UK marketing authorisation for this indication and was not considered for NICE CG156.

Key point	Potential impact on guidance	
	Yes	No
• Addition of gonadotrophin-releasing hormone (GnRH) agonists to the luteal support protocol may be associated with increases in live birth rate after IVF.	✓*	
Long-term safety of assisted reproductive technologies for women with infertility and their children • Children born after use of assisted reproduction procedures appear to have a greater likelihood of admission to hospital in the first 5 years of life than children born after natural conception.		✓
Areas not currently covered by NICE CG156 • Women with pregnancies conceived with IVF appear to be at greater risk of venous thromboembolism than women with pregnancies conceived naturally, particularly in the first trimester.		✓
• The choice or composition of culture media may affect live birth rates and the growth of children up to 2 years after birth.	✓*	
• Culturing embryos in low oxygen concentration (about 5%) may result in higher live birth rates than culturing at atmospheric oxygen concentrations.		✓
• Intentional endometrial injury in the month before embryo implantation may be associated with higher rates of live birth than control.		✓

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE. For further details of this evidence in the context of current guidance, please see the full commentary.

1 Commentary on new evidence

These commentaries focus on the 'key references' identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Section headings are taken from NICE CG156.

1.1 Principles of care

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.2 Initial advice to people concerned about delays in conception

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.3 Investigation of fertility problems and management strategies

Investigation of suspected tubal and uterine abnormalities

NICE CG156 recommends that women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography (HSG) to screen for tubal occlusion. This is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy. Where appropriate expertise is available, screening for tubal occlusion using hysterosalpingo-contrast-ultrasonography (ultrasound HSG) should be considered because it is an effective alternative to hysterosalpingography for women who are not known to have comorbidities.

Maheux-Lacroix et al. (2014) conducted a systematic review and meta-analysis of 30 studies to compare ultrasound HSG with laparoscopy for diagnosis of tubal occlusion in women with fertility problems. The review identified studies that assessed the accuracy of ultrasound HSG for diagnosing tubal occlusion among women with infertility or recurrent spontaneous miscarriages. Studies using ultrasound HSG to confirm tubal occlusion after tubal sterilisation were excluded. If studies compared the accuracy of laparoscopy with ultrasound HSG and standard HSG, results for ultrasound HSG and standard HSG were compared directly. Studies using consecutive or random series of patients and case-control studies were included. A positive result was defined as the presence of an occluded tube.

The 30 identified studies used varying methods for ultrasound HSG: 24 studies used a vaginal probe and flexible balloon catheter; 4 used an abdominal probe and rigid catheter; and 2 studies used either method. The contrast agent was saline solution in 13 studies, galactose solution in 15 studies and sulphur hexafluoride in 1 study. Doppler technology was used in 13 studies, and 3-dimensional devices were used in 5 studies.

Meta-analysis of 28 studies (n=1551; 2740 tubes assessed) showed that ultrasound HSG had sensitivity of 92% for diagnosing tubal occlusion (95% confidence interval [CI] 82 to 96%) and specificity of 95% (95% CI 90 to 97%). The other 2 studies were excluded from meta-analysis because they did not report results for each fallopian tube separately.

In 9 studies (n=582; 1055 tubes assessed), both ultrasound HSG and standard HSG were compared with laparoscopy as the reference standard. For ultrasound HSG, the sensitivity was 95% (95% CI 78 to 99%) and specificity was 93% (95% CI 89 to 96%). For standard HSG, the sensitivity was 94% (95% CI 74 to 99%) and specificity was 92% (95% CI 87 to

95%). The difference between imaging methods was not significant (p=0.4). Sensitivity analyses showed no significant differences in sensitivity or specificity for 2-dimensional versus 3-dimensional imaging or for saline compared with other contrast agents.

Limitations of the individual studies included that 14 studies were assessed as high risk of bias in at least 1 of 4 categories assessed. Consecutive series of patients were reported in only 6 studies, so the other studies could have selection bias. A clear definition of a positive test and adequate reporting of blinding was present in 19 studies. Overall, 10 studies were considered at high risk of bias because either more than a month passed between assessments or more than 10% of tubes were excluded from the final analysis. The authors noted that the results might not be fully applicable to people with fertility problems because 2 of the studies additionally recruited women who had recurrent miscarriage. Reasons for dropping out of studies included poor visualisation or the woman did not return for the second assessment or the women had cervical stenosis or pain. All studies had complete comparison against the same reference standard (laparoscopy).

This 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. No impact on NICE CG156 is 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.

Key reference

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

1.4 Medical and surgical management of male factor fertility problems

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.5 Ovulation disorders

World Health Organization (WHO) Group II ovulation disorders

Aromatase inhibitors in polycystic ovary syndrome

NICE CG156 recommends offering women with WHO Group II anovulatory infertility (predominantly polycystic ovary syndrome) one of the following ovarian stimulation treatments: clomifene citrate, metformin[6], or a combination of these drugs. The choice of treatment option should take into account potential adverse effects, ease and mode of use, the woman's BMI, and the monitoring needed.

NICE CG156 does not include recommendations on the use of aromatase inhibitors for ovarian stimulation in polycystic ovary syndrome.

Franik et al. (2014) conducted a Cochrane review of 26 randomised controlled trials (RCTs; n=5560) of aromatase inhibitors in women with anovulatory polycystic ovary syndrome and infertility. Trials with a crossover design were excluded unless the data for the first phase were available separately, because successful treatment resulting in pregnancy would prevent crossover to the other group. Ovulation induction was followed by sexual intercourse in 15 studies and by intrauterine insemination in 3 studies. The primary efficacy outcome of interest was live birth rate per woman randomised, but only 12 of the identified studies

[6] At the time of publication of this Evidence Update, metformin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

reported this outcome. The primary outcome of interest for adverse events was ovarian hyperstimulation syndrome (OHSS).

Letrozole[7] significantly increased live birth rate compared with clomifene citrate (odds ratio [OR]=1.64, 95% CI 1.32 to 2.04, p<0.00001; 9 studies, n=1783), with no difference in rates of OHSS (relative risk [RR]=0.00, 95% CI −0.01 to 0.00, p=0.55; 9 studies, n=2179). Letrozole was associated with lower rates of multiple pregnancy than clomifene citrate (OR=0.38, 95% CI 0.17 to 0.84, p=0.017; 11 studies, n=2385). In 2 studies of letrozole versus laparoscopic ovarian drilling (n=407), no significant difference in live births were seen between groups.

The quality of the evidence was rated as low for live birth and pregnancy outcomes because of poor reporting of blinding, and possible publication bias. Additionally, studies that reported live birth often reported higher clinical pregnancy rates in the letrozole group than studies that did not report live birth. The authors noted that if all studies reported live birth then the results might be less favourable to letrozole, so their findings should be interpreted with caution.

This 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, because of the low quality of the evidence base, no impact on NICE CG156 is expected.

Key reference

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

Metformin plus gonadotrophins in polycystic ovary syndrome

NICE CG156 recommends offering women with WHO Group II anovulatory infertility (predominantly polycystic ovary syndrome) one of the following ovarian stimulation treatments: clomifene citrate, metformin[8], or a combination of these drugs. The choice of treatment option should take into account potential adverse effects, ease and mode of use, the woman's BMI, and the monitoring needed.

Additionally, for women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate, one of the following second-line treatments should be considered: laparoscopic ovarian drilling, combined treatment with clomifene citrate and metformin if not already offered as first-line treatment, or gonadotrophins. Treatments should be considered on the basis of clinical circumstances and the woman's preference.

Palomba et al. (2014) conducted a systematic review and meta-analysis of 7 RCTs (n=334) of metformin compared with placebo or no treatment in women with polycystic ovary syndrome treated with gonadotrophins. Crossover studies were included, but data from the pre-crossover phase only were used for meta-analysis. Studies of gonadotrophin treatment before in vitro fertilisation (IVF) were excluded. Primary outcomes were live birth rate and pregnancy rate.

Lack of response to clomifene citrate was a specific inclusion criterion in 4 studies, and another 3 studies reported inclusion of women with clomifene resistance. Insulin resistance was an inclusion criterion in 2 studies, whereas in another 2 studies all participants had normal glucose tolerance. The dosage of gonadotrophins varied across studies, as did the length of time that metformin was used before administration of gonadotrophin. Metformin was continued until ovulation triggering in 3 studies and to pregnancy test in 4 studies.

[7] At the time of publication of this Evidence Update, letrozole did not have UK marketing authorisation for this indication and was not considered for NICE CG156.
[8] At the time of publication of this Evidence Update, metformin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

Metformin plus gonadotrophins was associated with a significantly higher live birth rate compared with gonadotrophins alone (OR=1.94, 95% CI 1.10 to 3.44., p=0.02; 2 studies, n=180, 661 cycles). Adding metformin to gonadotrophins also significantly increased the pregnancy rate (OR=2.25, 95% CI 1.50 to 3.38, p<0.001; 7 studies, n=334, 942 cycles). No significant effect of metformin was seen on multiple pregnancies, miscarriages or OHSS.

Overall, the quality of included studies was assessed as low because of possible confounding or bias resulting from unclear sequence generation, allocation concealment, and blinding, and incomplete outcome data. Non-standard criteria for diagnosing polycystic ovary syndrome were used in 2 studies. Additionally, because most women in the included studies had lack of response to clomifene citrate, this study may not be generalisable to all women with polycystic ovary syndrome. The authors concluded that further adequately powered RCTs are needed to investigate the effects of metformin in polycystic ovary syndrome.

This 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 gonadotrophins alone, without affecting rates of multiple pregnancies or OHSS. This evidence is unlikely to have impact on NICE CG156, because of the low quality of the included studies.

Key reference

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

1.6 Tubal and uterine surgery

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.7 Medical and surgical management of endometriosis

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.8 Unexplained infertility

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.9 Intrauterine insemination

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.10 Prediction of IVF success

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.11 Access criteria for IVF

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.12 Procedures used during IVF treatment

Review of reviews on assisted reproduction procedures

NICE CG156 makes several recommendations on procedures to be used during IVF treatment, including:

- Down regulation with gonadotrophin-releasing hormone (GnRH) agonists and antagonists to avoid premature luteinising hormone surges. When using GnRH agonists as part of IVF treatment, use a long down-regulation protocol.
- Controlled ovarian stimulation with either urinary or recombinant gonadotrophins. An individualised starting dose of follicle-stimulating hormone should be used when using gonadotrophins for ovarian stimulation.
- Conscious sedation for women undergoing transvaginal retrieval of oocyte. Women who have developed at least 3 follicles before oocyte retrieval should not be offered follicle flushing.

Single embryo transfer (fresh or frozen embryos) should be used for the first and second full embryo cycle in women aged 39 years or younger. In the third full IVF cycle transfer no more than 2 embryos. For women aged 40–42 years consider double embryo transfer. NICE CG156 states: do not use growth hormone as adjuvant treatment in IVF protocols.

Farquhar et al. (2014) conducted a review to summarise 58 published Cochrane reviews on assisted reproduction procedures. Of these, 19 reviews identified interventions that were effective, and 13 identified interventions that were promising. A total of 14 reviews found interventions that were ineffective or possibly ineffective, and 12 reviews were unable to reach conclusions because of lack of evidence. The primary outcome of this overview was live births, and secondary outcomes were clinical pregnancy, multiple pregnancy, miscarriage and OHSS.

Interventions that significantly improved live birth rates were:

- Endometrial injury performed in the month before ovulation induction (see Nastri et al. 2011 in the section 'Areas not currently covered by NICE CG156' in this Evidence Update for a full commentary on this review).
- Embryo culture in low oxygen concentrations (see Bontekoe et al. 2012 in the section 'Areas not currently covered by NICE CG156' in this Evidence Update for a full commentary on this review).
- Hyaluronic acid in embryo culture media (see Bontekoe et al. 2014 in the section 'Areas not currently covered by NICE CG156' in this Evidence Update for a full commentary on this review).
- Use of growth hormone in women who respond poorly to IVF.

Other notable findings included that use of GnRH antagonists instead of long GnRH agonist protocols for down regulation significantly reduced OHSS without affecting live birth rates. For ovarian stimulation, recombinant and urinary gonadotrophins were equally effective and safe. Long-acting follicle stimulating hormone was as safe and effective as daily follicle stimulating hormone.

Oocyte maturation using GnRH agonists was associated with lower rates of OHSS. This approach was also associated with lower live births and higher miscarriage compared with human chorionic gonadotrophin. Urinary human chorionic gonadotrophin may be a better choice than recombinant human chorionic gonadotrophin for final oocyte maturation because of availability and cost.

Approaches to pain relief during oocyte retrieval, including conscious sedation and analgesia, appear to be acceptable and satisfactory to women. However, follicle flushing during oocyte retrieval was not associated with improved pregnancy outcomes or oocyte yield, and was associated with longer operative times and more opiate analgesia.

A single-embryo implantation strategy resulted in lower live birth rates per cycle of IVF and lower numbers of multiple pregnancies compared with double embryo transfer. However, live birth rates after a single embryo transfer followed by a frozen and thawed embryo transfer are comparable to that with 1 cycle of double embryo transfer.

Intravenous hydroxyethyl starch was associated with a decreased incidence of severe OHSS, and cabergoline[9] was associated with reduced incidence of moderate OHSS in women at high risk (see Tang et al. 2012 in the section 'Procedures used during IVF' in this Evidence Update for a full commentary on this review). Withholding gonadotrophins ('coasting') did not have a beneficial effect on OHSS.

The main limitation of this review is that summarising a large number of reviews on a broad topic meant that nuances of the evidence in the original reviews were lost. Many of the original reviews were based on low or moderate quality evidence. However, the available evidence suggests that several interventions may improve the outcome of assisted reproduction procedures.

Key reference

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

Controlled ovarian stimulation in IVF

Metformin plus gonadotrophins in IVF for polycystic ovary syndrome

NICE CG156 recommends using either urinary or recombinant gonadotrophins for ovarian stimulation as part of IVF treatment.

Palomba et al. (2012) performed a systematic review and meta-analysis of 10 RCTs (n=900) of metformin[10] in women with polycystic ovary syndrome undergoing IVF or intracytoplasmic sperm injection (ICSI). The review included studies in which all women received gonadotrophin treatment and were randomised either to metformin or to placebo (7 studies) or no treatment (3 studies). Crossover studies were also included, but only data from the pre-crossover phase were used for meta-analysis.

Lack of response to clomifene citrate was an inclusion criterion in 2 studies, and 1 study specified insulin resistance as an inclusion criterion. The daily dose of metformin varied across studies from 1000 mg to 2500 mg; however 1500 mg was used most commonly (5 studies). Metformin was continued to different points in the IVF cycle including oocyte retrieval, embryo transfer and up to pregnancy test, with 1 study continuing metformin until the 12th week of pregnancy. Gonadotrophin protocols varied across studies.

Gonadotrophins plus metformin was not associated with a live birth rate significantly different from gonadotrophins plus placebo or no treatment (OR=1.69, 95% CI 0.85 to 3.34, p=0.132; 7 studies, n=702). The pregnancy rate was also not significantly different with the addition of metformin (OR=1.20, 95% CI 0.90 to 1.61, p=0.253; 9 studies, n=860). However, the rates of implantation were significantly increased in women who received gonadotrophins plus metformin (OR=1.42, 95% CI 1.24 to 2.75, p=0.04; 6 studies, n=541), and the rates of miscarriage were significantly decreased (OR=0.50, 95% CI 0.30 to 0.83, p=0.01; 8 studies, n=719). The rate of OHSS was significantly lower with metformin (OR=0.27, 95% CI 0.16 to 0.46; 9 studies, n=883).

Limitations of the individual studies included that 2 trials used non-standard methods for diagnosing polycystic ovary syndrome. Outcome measures were not fully reported in all trials and many confounding variables existed, such as differences in trial protocols, definition of clinical outcomes, patients' characteristics, and selection for infertility treatment. The risk of bias assessment rated 3 trials as 'unclear' for most categories. At least half of included studies had possible biases relating to sequence generation, allocation concealment,

[9] At the time of publication of this Evidence Update, cabergoline did not have UK marketing authorisation for this indication and is not recommended by NICE CG156.

[10] At the time of publication of this Evidence Update, metformin did not have UK marketing authorisation for this indication and is not recommended by NICE CG156.

incomplete outcome data or selective reporting. The findings that implantation rates increased and that miscarriages were significantly reduced with metformin are surprising because neither the pregnancy rate nor the live birth rate increased significantly.

This evidence suggests that in women with polycystic ovary syndrome who are undergoing IVF, adding metformin to gonadotrophins may not increase live birth rate compared with gonadotrophins alone, although incidence of OHSS may be reduced. This evidence is unlikely to affect NICE CG156 because of limitations of the evidence and the absence of an increase in live birth rate.

Key reference

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

Cabergoline for preventing OHSS

NICE CG156 recommends that clinics providing ovarian stimulation with gonadotrophins should have protocols in place for preventing, diagnosing and managing OHSS.

Tang et al. (2012) reported a Cochrane review of 2 RCTs (n=248) investigating the dopamine agonist cabergoline[11] for preventing moderate or severe OHSS in women undergoing assisted reproduction procedures. Studies were included if women were at high risk of OHSS and control groups were placebo, no treatment or other active treatment.

The prespecified primary outcomes of the systematic review were incidence of OHSS and live birth rate after fresh embryo transfer with oocytes from the same menstrual cycle. However neither of the 2 studies identified reported live birth rate. One study defined high risk of OHSS on the basis of the number and size of follicles and the number of oocytes retrieved; the other used serum oestradiol measurement to define risk of OHSS. The dosing also differed: in 1 study, cabergoline 0.5 mg daily was given for 8 days after injection of human chorionic gonadotrophin. The other study administered human albumin in the day of oocyte retrieval and gave cabergoline 0.5 mg for 3 weeks, starting the day after oocyte retrieval.

Cabergoline was associated with an overall reduction in moderate or severe OHSS (OR=0.40, 95% CI 0.20 to 0.77, p=0.007; 2 studies, n=230). However in subgroup analysis, moderate OHSS was significantly lower in women who received cabergoline (OR=0.38, 95% CI 0.19 to 0.78, p=0.009; 2 studies, n=230), but severe OHSS was not (OR=0.77, 95% CI 0.24 to 2.45, p=0.66; 2 studies, n=230). No significant effect on clinical pregnancy rate or multiple pregnancies was seen.

Both included studies had high risk of bias associated with incomplete outcome data and had unclear risk of allocation bias. However, the overall risk of bias was assessed to be moderate for both studies. The authors noted that the lack of effect of cabergoline on severe OHSS may be due to lack of statistical power, because severe OHSS occurred only in 6 women receiving cabergoline and 7 women on placebo. The authors noted that further studies evaluating clinical endpoints such as live birth are needed.

This review suggests that cabergoline may be associated with a reduction in OHSS without affecting rates of pregnancies or multiple pregnancies. This evidence is 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.

Key reference

Tang H, Hunter T, Hu Y et al. (2012) Cabergoline for preventing ovarian hyperstimulation syndrome. Cochrane Database of Systematic Reviews issue 2: CD008605

[11] At the time of publication of this Evidence Update, cabergoline did not have UK marketing authorisation for this indication and is not recommended by NICE CG156.

Embryo transfer strategies in IVF

NICE CG156 recommends that embryo quality should be evaluated at both cleavage and blastocyst stages, according to the Association of Clinical Embryologists (ACE) and UK National External Quality Assessment Service (UK NEQAS) for Reproductive Science Embryo and Blastocyst Grading schematic. Where a top-quality blastocyst is available, single embryo transfer should be used.

Maheshwari et al. (2013) did a systematic review and meta-analysis of 8 studies to compare embryo transfer at blastocyst stage with transfer at cleavage stage. The review sought studies on obstetric and perinatal outcomes in singleton pregnancies conceived with IVF or ICSI after transfer of embryos at blastocyst stage and cleavage stage. Observational studies were included in the analysis because an initial scoping search did not identify any RCTs of embryo transfer stage. Studies were excluded from analysis of they were case reports or case-series and if they did not have a comparator group. Additionally, studies had to report perinatal or obstetric outcomes and multiple pregnancies were excluded.

Baseline characteristics of the women in the 8 included studies differed between blastocyst-stage and cleavage-stage transfer groups. For example, in 5 studies women receiving blastocyst-stage transfer were younger than those undergoing cleavage-stage transfer. The cause of infertility also differed between groups. Cleavage-stage embryos were transferred on days 2–4 and blastocyst-stage embryos were transferred on days 4–6.

Blastocyst-stage transfer was associated with higher risk of very preterm delivery, defined as delivery before 32 weeks (RR=1.22, 95% CI 1.10 to 1.34, p=0.0001; 4 studies, 20,754 blastocyst-stage transfers versus 54,792 cleavage-stage transfers). Preterm delivery, defined as delivery before 37 weeks, was also significantly more likely after blastocyst-stage transfer (RR=1.27, 95% CI 1.22 to 1.13, p<0.00001; 6 studies, 21,330 blastocyst-stage transfers versus 55,642 cleavage-stage transfers). However, blastocyst-stage transfer was associated with a lower likelihood of delivery of a baby that was small for gestational age (RR=0.82, 95% CI 0.77 to 0.88, p<0.00001; 3 studies, 17,552 blastocyst-stage transfers and 45,376 cleavage-stage transfers). No significant differences were seen between groups for very-low birthweight, congenital anomalies, perinatal mortality, placenta previa, pre-eclampsia, or placenta abruption.

The authors noted that their study was limited by the absence of RCTs on this topic. Although individual studies adjusted for confounding factors, the meta-analysis could not adjust for confounding factors. Additionally, the women undergoing blastocyst-stage transfer and cleavage-stage transfer differed at baseline. The findings that preterm and very preterm deliveries increased but small for gestational age deliveries were lower raise questions about the presumed causal pathways. The authors concluded that a cautious approach to extended culture is needed until long-term safety data are available.

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, limitations in the evidence base mean that no impact on NICE CG156 is expected.

Key reference

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

Luteal phase support after IVF

NICE CG156 recommends offering women progesterone for luteal phase support after IVF treatment. However, it does not include recommendations on use of GnRH agonists during this stage of IVF.

In a systematic review and meta-analysis of 6 RCTs (n=2012), **Kyrou et al. (2011)** investigated the effects of adding GnRH agonist treatment in the luteal phase on live birth rates after IVF or ICSI. Of the identified studies, 4 used a long GnRH agonist protocol for ovarian stimulation, 1 used a GnRH antagonist, and 1 randomised women to either agonist or antagonist protocols (each arm was analysed separately in meta-analysis). The type, dose, administration, timing and duration of luteal support varied across studies both for the GnRH agonist study groups and the standard luteal support control groups. Most studies used ICSI for fertilisation, and all implanted embryos at the cleavage stage. The number of embryos transferred was not clear, but all studies allowed multiple embryo transfer.

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, 95% CI 0.11 to 0.22, p<0.00001; 5 study arms, n=1262). Results were similar when analysed separately depending on whether ovarian stimulation was performed with GnRH agonists or antagonists. Adding GnRH agonists to the luteal support phase when GnRH agonists were used for ovarian stimulation resulted in a risk difference of 0.14 (95% CI 0.05 to 0.23, p=0.003; 3 study arms, n=800). Adding GnRH agonists to the luteal support phase when GnRH antagonists were used for ovarian stimulation resulted in a risk difference of 0.19 (95% CI 0.11 to 0.27, p<0.00001; 2 study arms, n=462). However, use of GnRH agonists in luteal support was also associated with an increased rate of multiple pregnancy compared with control (risk difference=0.09, 95% CI 0.04 to 0.13, p=0.0002; 5 study arms, n=1651).

Only 2 of the included studies reported allocation concealment, which is a potential source of bias. The systematic review did not report the types of control used in the included studies (placebo, no treatment or other active treatment).

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 may have a potential impact on NICE CG156, which does not currently include recommendations about use of GnRH agonists for luteal support. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

Key reference

Kyrou 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

1.13 Intracytoplasmic sperm injection

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.14 Donor insemination

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.15 Oocyte donation

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.16 People with cancer who wish to preserve fertility

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.17 Long-term safety of assisted reproductive technologies for women with infertility and their children

Admissions to hospital for children born after IVF

NICE CG156 recommends informing people who are considering IVF treatment that the absolute risks of long-term adverse outcomes in children born as result of IVF are low.

Chambers et al. (2014) conducted a population-based study 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).

Data from the Western Australia Data-Linkage System, managed by the Western Australia Department of Health were obtained for births, deaths, hospital admissions and assisted reproduction procedures from October 1993 to September 2008. Analyses of data were adjusted to account for differences in maternal age, parity, year of birth and socioeconomic status of the mother. Children conceived by assisted reproduction procedures were more likely to be born to older nulliparous women in private hospitals and mothers were more likely to live in an area of socioeconomic advantage and were less likely to smoke.

For perinatal outcomes, children conceived by assisted reproduction procedures were more likely to be delivered by emergency caesarean section (adjusted OR=1.49, 95% CI 1.33 to 1.66) and to be born prematurely (before 37 weeks' gestation; adjusted OR=2.16, 95% CI 1.88 to 2.47). Additionally, children born after assisted reproduction procedures were more likely to have low birthweight (less than 2500 g; adjusted OR=2.15, 95% CI 1.85 to 2.50) and to be small for gestational age (birthweight less than the 10th percentile of all Australian infants; adjusted OR=1.18, 95% CI 1.02 to 1.36).

Children born after assisted reproduction procedures were significantly more likely to be admitted to hospital in the first 5 years of life (adjusted OR=1.2, 95% CI 1.1 to 1.3, p<0.001). This was an absolute difference of about 4 percentage points; from 46% of children born after natural conception being admitted in the first 5 years of life compared with 50% of children conceived using assisted reproduction procedures.

The length of stay in hospital at birth was about 3 days longer in children conceived after assisted reproduction procedures (p<0.001). For admissions after birth, the mean length of stay per hospital admission did not differ significantly between children born after assisted reproduction procedures and children conceived naturally. Hospital costs over the first 5 years of life were significantly higher for children conceived with assisted reproduction procedures (including birth admission; p<0.001), with an extra AUS$ 2490 spent per child, mostly due to the additional 3 days in hospital at birth.

A limitation of this study is that it could not account for the possibility that children born after assisted reproduction procedures may have been monitored more closely than children born after natural conception, leading to additional hospital admissions. The study also could not investigate factors related to the type of assisted reproduction procedures used or to the causes or severity of infertility.

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 is unlikely to affect NICE CG156 because the absolute increase in admissions to hospital was small.

Key reference

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

Areas not currently covered by NICE CG156

Risk of thromboembolism in pregnancies after conception using IVF

NICE CG156 does not include recommendations about risks of venous thromboembolism associated with IVF treatment.

Henriksson et al. 2013 conducted a cross-sectional study 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). Population data for 1990 to 2008 were taken from the Swedish national patient register and other registries, such as the IVF register and the birth register, and were linked using unique identification numbers.

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 (hazard ratio [HR]=1.77, 95% CI 1.41 to 2.23, p<0.001). The difference in risk of venous thromboembolism was greatest in the first trimester, with an incidence of 1.5 per 1000 women with IVF pregnancies and 0.3 per 1000 women with natural pregnancies (HR=4.05, 95% CI 2.54 to 6.46, p value not reported). There was no difference in risk before pregnancy or during the year after delivery.

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 (HR=1.42, 95% CI 0.86 to 2.36, p<0.0034). Again, the difference in risk of venous thromboembolism was greatest in the first trimester, with an incidence of 3.0 per 10,000 in women with IVF pregnancies compared with 0.4 per 10,000 in women with natural pregnancies (HR=6.97, 95% CI 2.21 to 21.96, p value not reported).

The authors noted that the heightened risk of pulmonary embolism in the first trimester after IVF may be due to the proximity in time to the IVF procedure. The use of exogenous oestrogen during the stimulation phase of treatment can result in increases in oestrogen levels of up to 100-fold. Exogenous oestrogen has been associated with risk of embolism in other areas such as contraception and menopause treatment.

Other limitations included the possibility of detection bias, because women who had undergone IVF may have been under closer surveillance. More complicated pregnancies resulting in fatal outcomes to the mothers were not included, which could underestimate the true risk of venous thromboembolism and pulmonary embolism.

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. This evidence is not expected to impact NICE CG156, which does not include recommendations about risks associated with IVF treatment.

Key reference

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

Effects of culture media on outcomes of IVF

NICE CG156 does not contain recommendations about selection or composition of culture media for use in IVF.

Bontekoe et al. (2014) conducted a Cochrane review 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. Trials compared a high dose of adherence compounds with either no adherence compounds or low doses of adherence compounds. Crossover studies were included but only data from the pre-crossover phase were used. Studies used IVF or ICSI with fresh or frozen-thawed embryos. The primary outcome was live births; secondary outcomes included multiple pregnancies and adverse effects such as miscarriage.

Enrolment of participants was consecutive in 9 studies, non-consecutive in 1 study and the rest have unclear enrolment. Strict inclusion and exclusion criteria were used in 8 studies, mainly focusing on the woman's age and number of previous failed treatment cycles. Most studies transferred multiple embryos, only 1 study transferred single embryos and 1 study did not report the number of embryos transferred. Live birth rate was reported in 6 studies.

Eight studies (n=1121) compared high-dose hyaluronic acid with no adhesion compound and 9 studies (n=2566) compared high versus low doses of hyaluronic acid. Fibrin sealant was compared with no fibrin sealant in 1 study (n=211). Analysis of 1 study was split into 2 arms for meta-analysis because the study assessed embryo transfer on day 3 or on day 5. The day-3 embryo transfer subgroup compared hyaluronic acid versus no adhesion compound and the day-5 transfer subgroup compared high with low doses of hyaluronic acid.

Overall, high-dose hyaluronic acid was associated with an increase in live births compared with low-dose or no hyaluronic acid (OR=1.41, 95% CI 1.17 to 1.69, p=0.0003; 6 studies, n=1950). In subgroup analysis the comparison of high-dose versus low-dose hyaluronic acid showed a significant effect on live births in favour of high-dose hyaluronic acid (OR=1.42, 95% CI 1.16 to 1.73, p=0.0006, 4 study arms, n=1626). However, the comparison of high dose versus no hyaluronic acid was not significant (OR=1.35, 95% CI 0.86 to 2.12, p=0.19; 3 study arms, n=224). Multiple pregnancies were significantly higher with high-dose hyaluronic acid compared with low-dose or no hyaluronic acid (OR=1.86, 95% CI 149 to 2.31, p<0.00001). No effects on miscarriages (4 studies) or ectopic pregnancies (1 study) were noted. The 1 trial of fibrin sealant did not report live birth rate, and no effect on clinical pregnancy rate was observed.

Most included studies had a high or unclear risk of bias relating to incomplete outcome data. However, risk of bias related to random sequence generation, blinding, and selective reporting was low. The studies of hyaluronic acid were rated as moderate quality overall but the study of fibrin sealant was rated as very low quality. The authors noted that the most important outcome measure to be addressed in future studies is live birth rate, but that other outcomes such as multiple pregnancies and miscarriage were not reported fully by existing studies.

In another study of culture media, **Kleijkers et al. (2014)** compared 2 types of culture medium to assess postnatal growth in the first 2 years of life. At a single centre in the Netherlands from July 2003 to December 2006, a total of 1432 IVF treatment cycles were alternately allocated to 1 of 2 types of culture media. The media allocation was introduced as a quality control measure within the treatment facility, thus the analysis of data was post hoc. Clinicians' who were scheduling appointments for oocyte retrieval did not know of the alternate medium policy, and neither did patients. All participants gave informed consent for use of their data.

Data were analysed only for singleton life births after fresh embryo transfer. All women admitted for IVF treatment had BMI less than 30 mg/kg² and were younger than 40 years. Questionnaires were sent to women 2 years after birth, requesting information on the child's height, weight and head circumference in the previous 2 years. These data are recorded routinely as part of children's health programmes in the Netherlands.

Overall, 715 embryos were cultured in Vitrolife medium, resulting in 168 live births (23.5% live birth rate) and 717 embryos were cultured in Cook medium, resulting in 126 live births (17.6%). The authors did not analyse these data in their report, and did not explain whether any external factors may have led to the almost 6% difference in live birth rates.

Of the 294 singleton live births, 29 were lost to follow-up because the parents declined to participate or could not be contacted. Of the remaining 265 children, 148 had been cultured in Vitrolife medium and 117 had been cultured in Cook medium. Characteristics of the mothers and factors relating to the assisted reproduction procedures seemed to be similar across groups; however statistical analysis of baseline characteristics was not reported.

Analyses were adjusted for parental height, weight, smoking habits age, and parity, and infants' gestational age at birth, and gender. At 2 years of age, children born after Vitrolife culture were 188 g heavier (p=0.005) and 4.9 mm taller (p=0.031) than those born after Cook culture.

Limitations of this study include that the absolute differences in weight and height are small and clinically relevant effects of these differences were not studied. No information was available about other factors that may have influenced postnatal growth, such as nutrition or childhood diseases. Furthermore it was not clear whether differences existed in birthweight or gestational age at birth. The authors noted that the effects of embryo culture media need to be more extensively studied to minimise short-term and long-term risks of adverse outcomes.

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. This evidence may have a potential impact on NICE CG156, which does not contain recommendations about choice of culture media. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

Key references

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

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

Oxygen concentration during embryo culture

NICE CG156 does not include recommendations about procedures used during embryo culture.

Bontekoe et al. (2012) conducted a Cochrane review of 7 RCTs (n=2422) comparing embryo culture at low oxygen concentrations (about 5%) with atmospheric oxygen concentrations (about 20%). Both IVF and ICSI were assessed and studies using frozen–thawed embryos were also eligible for inclusion. Crossover trials were included but only data from the pre-crossover phase were pooled. The primary outcome of interest was live birth rate per woman. Studies randomising oocytes or embryos (rather than women), those using alternate allocation and retrospective studies were excluded. The individual studies used strict inclusion criteria such as the number of mature oocytes, number of previous treatment failures, participants' age and number of fertilised oocytes.

Low oxygen concentrations during embryo culture were associated with a significantly higher live birth rate than atmospheric oxygen concentrations (OR=1.39, 95% CI 1.11 to 1.76, p=0.005; 3 studies, n=1291). The authors noted that using low oxygen concentrations would mean a typical clinic could increase its live birth rate from an estimated 30% to 32–43%. No significant differences were seen between groups in rates of multiple pregnancy, miscarriage, or congenital anomaly.

In subgroup analyses, oxygen concentration did not have a significant effect on live birth rate when embryos were transferred early – defined as day 3 of development (OR=1.51, 95% CI 0.84 to 2.69, p=0.17; 2 studies, n=340). However, low oxygen concentrations did have a significant effect on live births in late embryo transfer – defined as day 4 or later (OR=1.36, 95% CI 1.05 to 1.77, p=0.02; 3 studies, n=951).

Limitations of the individual studies include that intention-to-treat analysis was conducted in only 1 study. Risk of bias assessment of the included studies showed low or unclear risk of bias in most categories. All trials had a multiple embryo transfer policy but it was not possible to determine the number of singleton and multiple births. As a result, the data may not be accurate in describing live births per woman.

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, no impact on NICE CG156 is expected because the guideline does not specify laboratory conditions for culturing embryos.

Key reference

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

Endometrial injury to improve outcomes of assisted reproduction procedures

NICE CG156 does not contain recommendations on the use of endometrial injury as a method to improve outcomes after IVF.

Nastri et al. (2012) reported a Cochrane review of 5 RCTs (n=591) of endometrial injury performed up to 6 months before treatment with assisted reproduction procedures. Trials compared endometrial injury with either no treatment or a simulated procedure that could not cause endometrial injury. Crossover trials were included but only data from the pre-crossover phase were included in the meta-analysis. The primary outcomes of interest were live births per woman and miscarriages per clinical pregnancy.

Studies had differences in inclusion criteria: in 1 study women in their first cycle of IVF or ICSI were included; 3 studies included women with previous treatment failure only, and 1 study included women irrespective of previous treatment history. Endometrial injury was performed in the month before the embryo transfer in 4 studies and on the day of oocyte retrieval in the fifth study. Endometrial injury was performed once in 3 studies and twice in 1 study; the number of injuries was unclear in the remaining study. The method of endometrial injury used in included studies was not reported.

Endometrial injury in the month before starting ovulation induction was associated with a significant increase in live birth rate compared with control (OR=2.46, 95% CI 1.28 to 4.72, p=0.007; 2 studies, n=200). This corresponded to an absolute increase in live birth rate of 16 percentage points (from 17% in the control group to 33% in the endometrial injury group). Both studies that reported on live birth rate included only women with previous IVF failures. Miscarriage per clinical pregnancy was reported in only 1 trial with no significant differences observed (OR=1.13, 95% CI 0.17 to 7.45). Similar results were seen for multiple pregnancy rate (OR=0.87, 95% CI 0.23 to 3.30; 1 study). Additionally, the 1 study that performed endometrial injury on the day of oocyte retrieval reported a significantly lower clinical

pregnancy rate in the injury group compared with control (OR=0.30, 95% CI 0.14 to 0.63, p=0.002; n=156). Live birth rate data were not reported for this trial. No trials reported on the adverse events of pain or bleeding.

Overall, the risk of bias in individual studies was assessed as low or unclear. However, most studies had a high risk or bias due to lack of blinding of participants and study staff. The authors concluded that further trials of endometrial injury are needed to evaluate adverse events such as miscarriage, multiple pregnancy, pain and bleeding.

In another systematic review and meta-analysis, **El Toukhy et al. (2012)** assessed the effects of local endometrial injury reported in 8 studies (2 RCTs and 6 non-randomised controlled studies, n=901). The primary outcomes of interest were live birth or ongoing pregnancy rate and clinical pregnancy rate.

In 4 studies, women had undergone at least 1 previous cycle of IVF, but the number of previous attempts varied considerably between studies from 1 to 4 attempts. Three of these studies excluded women with conditions likely to cause implantation failure (uterine fibroids, endometriosis or hydrosalpinges). In 5 studies, endometrial injury was performed in the cycle before embryo transfer, and in the other 3 studies it was done in the same cycle (about 2–3 weeks before embryo transfer).

The frequency of endometrial injury varied from 4 times in 1 study, twice in 2 studies and once in the other 5 studies. The procedure was poorly described but generally involved moving an endometrial catheter upwards and downwards in the endometrial cavity a few times or 'until the abnormal endometrial echoes disappeared'. Comparator groups were described as no intervention but no additional details were provided about control groups, for example whether sham intervention was used.

All studies reported clinical pregnancy rate, which was significantly higher after endometrial injury in both randomised and non-randomised 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 (RR=2.63, 95% CI 1.39 to 4.96, p=0.003; 2 studies, n=193). Results for non-randomised studies were smaller in magnitude but still significant (RR=1.95, 95% CI 1.61 to 2.35, 5 studies, n=708).

In 4 non-randomised studies, live births or ongoing pregnancies were significantly higher after endometrial injury compared with control (RR=2.28, 95% CI 1.65 to 3.14, p<0.00001; n=443). No significant effect on miscarriages was seen in these studies. Only 1 RCT reported specifically on live birth, but no significant effect was seen.

The authors urged caution in interpreting their results because the included studies had methodological limitations including small sample sizes and that only 2 studies were randomised. Additionally the pregnancy rates in individual studies ranged from abnormally low to abnormally high. Further large RCTs are needed to evaluate the efficacy and safety of endometrial injury, and to establish how many times the procedure should be performed.

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, 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.

Key references

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

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

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Ovulation disorders

- Metformin and gonadotrophins for ovulation induction in patients with polycystic ovary syndrome

Procedures used during IVF treatment

- Neonatal and childhood outcomes for babies born after embryo transfer at either blastocyst or cleavage stage

Further evidence uncertainties for fertility problems can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Fertility. NICE clinical guideline 156 (2013)

NICE CG156 was a partial update of NICE clinical guideline 11 (NICE CG11), which was published in 2004. The scope of NICE CG156 was narrower from that of NICE CG11, and some of the recommendations from NICE CG11 were retained in NICE CG156 without new evidence. This Evidence Update used the full scope of NICE CG11, rather than the narrower scope used for the partial update NICE CG156.

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 01 December 2011 (the end of the search period of NICE CG156) to 17 September 2014:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)
- PsycINFO

A new search strategy was developed to cover all aspects of the guidance because no search strategy was published with the original 2004 version of the guidance.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for systematic reviews, RCTs and observational studies.

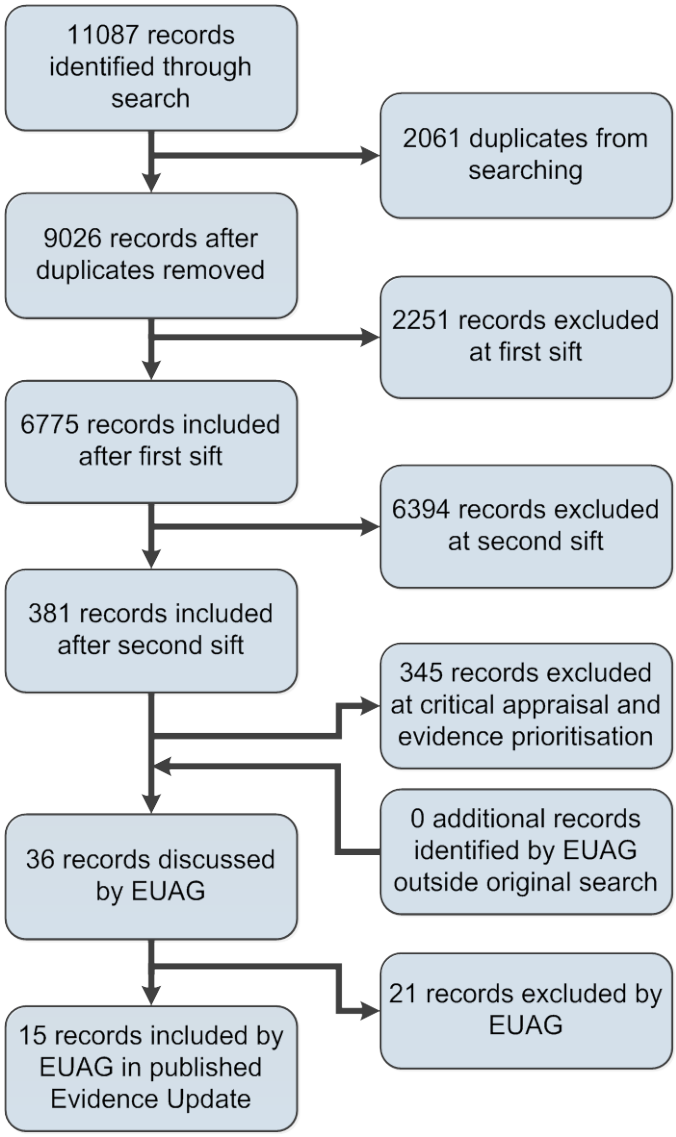
Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

See the NICE Evidence Services website for more information about how NICE Evidence Updates are developed.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp Fertility/
2	exp Infertility/
3	exp Infertility, Male/
4	Infertility, Female/
5	(fertil$ or sterility or infertil$ or subfertil$ or sub-fertil$ or subfecund$ or sub-fecund$).ti,ab.
6	((rate$ or chance$ or probabilit$ or likelihood or problem$ or delay$ or difficult$ or concern$) adj3 (fertil$ or conceiv$ or conception or infertil$)).ti,ab.
7	((rate$ or chance$ or probabilit$ or likelihood) adj3 pregnan$).ti,ab.
8	reproductive techniques/ or fallopian tube patency tests/ or exp insemination, artificial/ or ovulation detection/ or ovulation prediction/ or exp reproductive techniques, assisted/
9	((assist$ or artificial$) adj2 (reproduc$ or conceiv$ or conception)).ti,ab.
10	(IVF or ICSI or GIFT or insemination or intracytoplasmic sperm injection or intra-cytoplasmic sperm injection or ((gamete$ or zygote$ or embryo$ or blastocyst$) adj2 transfer$)).ti,ab.
11	(in vitro fertili$ or in-vitro fertili$ or invitro fertili$).ti,ab.
12	exp Fertility Agents/
13	exp Semen Analysis/
14	((semen or sperm$ or cervical mucus or tubal patency or fallopian tube patency) adj2 (analys$ or abnormal$ or quality or test$)).ti,ab.
15	((semen or sperm$ or oocyte$ or egg$ or embryo$ or zygote$ or gamete$) adj2 (donor$ or donation$ or sharing or freezing or frozen or cryopreserv* or vitrif*)).ti,ab.
16	((ovar$ or ovulat$) adj5 (induc$ or stimulat$ or hyperstimulat$)).ti,ab.
17	ovarian reserve.ti,ab.
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	(sperm$ adj (wash$ or disinfect$ or clean$ or steril$)).ti,ab.
20	viral load/
21	((viral or virus$) adj2 (load$ or titre$ or titer$ or burden$)).ti,ab.
22	20 or 21
23	exp Fertilization/
24	(fertili$ or conception or conceiv$).ti,ab.
25	23 or 24
26	22 and 25
27	18 or 19 or 26
28	animal/ not (animal/ and human/)
29	27 not 28
30	limit 29 to english language
31	limit 30 to yr="2011 -Current"

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

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