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In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction (Review)

Siristatidis CS, Maheshwari A, Vaidakis D, Bhattacharya S

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[Intervention Review]

In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction

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ABSTRACT

Background

Polycystic ovarian syndrome (PCOS) occurs in 4% to 7% of all women of reproductive age and 50% of women presenting with subfertility. Subfertility affects 15% to 20% of couples trying to conceive. A significant proportion of these women ultimately need assisted reproductive technology (ART). In vitro fertilisation (IVF) is one of the assisted reproduction techniques employed to raise the chances of achieving a pregnancy. For the standard IVF technique, stimulating follicle development and growth before oocyte retrieval is essential, for which a large number of different methods combining gonadotrophins with a gonadotrophin-releasing hormone (GnRH) agonist or antagonist are used. In women with PCOS, the supra-physiological doses of gonadotrophins used for controlled ovarian hyperstimulation (COH) often result in an exaggerated ovarian response, characterised by the development of a large cohort of follicles of uneven quality, retrieval of immature oocytes, and increased risk of ovarian hyperstimulation syndrome (OHSS). A potentially effective intervention for women with PCOS-related subfertility involves earlier retrieval of immature oocytes at the germinal-vesicle stage followed by in vitro maturation (IVM). So far, the only data available have derived from observational studies and non-randomised clinical trials.

Objectives

To assess the effectiveness and safety of IVM followed by IVF or ICSI versus conventional IVF or ICSI among women with PCOS undergoing assisted reproduction.

Search methods

This is the second update of this review. We performed the search on 17 April 2018.

The search was designed with the help of the Cochrane Gynaecology and Fertility Group Information Specialist, for all published and unpublished randomised controlled trials (RCTs).

We searched the the Cochrane Gynaecology and Fertility Group Specialised Register of controlled trials, CENTRAL via the Cochrane Central Register of Studies Online, MEDLINE, Embase, CINAHL, and the trial registers for ongoing and registered trials and the Open Grey database for grey literature from Europe. We made further searches in the National Institute for Health and Care Excellence (NICE) fertility assessment and treatment guidelines. We handsearched reference lists of relevant systematic reviews and RCTs, together with PubMed and Google for any recent trials that have not yet been indexed in the major databases.

Selection criteria

All RCTs on the intention to perform IVM before IVF or ICSI compared with conventional IVF or ICSI for subfertile women with PCOS, irrespective of language and country of origin.

Data collection and analysis

Two review authors independently selected studies, assessed risk of bias, extracted data from studies, and attempted to contact the authors of studies for which data were missing. Our primary outcomes were live birth per woman randomised and miscarriage. We performed statistical analysis using Review Manager 5. We assessed evidence quality using GRADE methods.

Main results

We found two RCTs suitable for inclusion in the review and six ongoing trials that have not yet reported results. Both included studies were published as abstracts in international conferences.

Both studies were at unclear or high risk of bias for most of the seven domains assessed. Common problems were unclear reporting of study methods and lack of blinding. The main limitations in the overall quality of the evidence were high risk of bias and serious imprecision.

There were no data on the primary outcomes of this review, namely live birth per woman randomised and miscarriage.

Both studies reported clinical pregnancy rate: there was evidence of an effect between IVM and IVF, favouring the former (odds ratio 3.10, 95% confidence interval 1.06 to 9.00; 71 participants; 2 studies; $I^2 = 0\%$; very low-quality evidence). The incidence of OHSS was zero in both studies in both groups.

There were no data for the other outcomes specified in this review.

Authors' conclusions

Though promising data on the in vitro maturation (IVM) technique have been published, unfortunately there is still no evidence from properly conducted randomised controlled trials upon which to base any practice recommendations regarding IVM before in vitro fertilisation (IVF) or intracytoplasmic sperm injection for women with polycystic ovarian syndrome. Regarding our secondary outcomes, very low-quality evidence showed that clinical pregnancy was higher with IVM when compared to IVF, whereas the incidence of ovarian hyperstimulation syndrome was zero in both studies in both groups. We are awaiting the results of six ongoing trials and eagerly anticipate further evidence from good-quality trials in the field.

PLAIN LANGUAGE SUMMARY

In vitro maturation in subfertile women with polycystic ovarian syndrome who are undergoing assisted reproduction

Review question

Is in vitro maturation efficient compared to standard assisted reproduction techniques (ART) in subfertile women with polycystic ovarian syndrome (PCOS)?

Background

Women with PCOS undergoing conventional ART are at an increased risk of ovarian hyperstimulation syndrome, a medical condition that can occur in women who take fertility medications to stimulate oocytes growth. The condition is associated with enlargement of both ovaries, fluid in the body of the woman, around her lungs and/or her heart, serious illness, and in rare cases, death. When women with PCOS take medications to stimulate their ovaries, the oocytes produced are often immature, which is the main reason that these oocytes are poorly fertilised and lead to low pregnancy rates. In addition, as previously noted, stimulation of the ovaries of women with PCOS with drugs often leads to ovarian hyperstimulation. These women may thus benefit from earlier retrieval of oocytes followed by their maturation in the laboratory, a technique known as in vitro maturation (IVM), as this would reduce the aforementioned risks. However, while successful fertilisation, embryo development, and term pregnancies resulting from IVM oocytes have been reported, some concern has been expressed regarding the safety of the method in terms of the health of the children born and the rate of genetic anomalies they carry. We reviewed the evidence up to April 2018, for the third time.

Study characteristics

We performed a comprehensive literature search of the standard medical databases (from database inception to 17 April 2018) in consultation with the Cochrane Gynaecology and Fertility Group Information Specialist, for all randomised controlled trials (studies in which participants are assigned to a treatment group using a random method) investigating the efficiency of IVM compared to conventional ART in subfertile women with PCOS. We searched for and included studies irrespective of language and country of origin. Two review authors independently selected and evaluated studies, extracted data, and attempted to contact the authors of studies for which data

were missing. We found two studies (71 women), published as abstracts in international conferences, and six ongoing trials that met our inclusion requirements.

Key results

Though promising data on the IVM technique have been published, unfortunately there is still no evidence concerning our primary outcomes of live-birth and miscarriage rates from properly conducted randomised controlled trials upon which to base any practice recommendations regarding IVM before ART for women with PCOS. Of the secondary outcomes specified in this review, very low-quality evidence showed that clinical pregnancy was higher when IVM was compared to conventional ART, whereas the incidence of ovarian hyperstimulation syndrome was zero in both studies in both groups. We are awaiting the results of six ongoing trials and eagerly anticipate further evidence from good-quality trials in the field.

Quality of the evidence

The quality of the evidence was very low for all outcomes.

Summary of findings for the main comparison. In vitro maturation compared to in vitro fertilisation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction

In vitro maturation compared to in vitro fertilisation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction

Patient or population: subfertile women with polycystic ovarian syndrome undergoing assisted reproduction
Setting: IVF Units
Intervention: IVM
Comparison: IVF

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with IVF	Risk with IVM			
Live birth	Not reported				
Miscarriage	Not reported				
Clinical pregnancy	Study population		OR 3.10 (1.06 to 9.00)	71 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a, b, c, d]
	194 per 1000	428 per 1000 (204 to 685)			
Ovarian hyperstimulation syndrome incidence	Study population		Not estimable	71 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a, b, c, d]
	0 per 1000	0 per 1000 (0 to 0)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IVF:** in vitro fertilisation; **IVM:** in vitro maturation; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Insufficient data about randomisation.

[b]Data obtained from abstract.
[c]No data available for heterogeneity.
[d]Included women had anovulatory polycystic ovaries not polycystic ovarian syndrome.

BACKGROUND

Description of the condition

Polycystic ovarian syndrome (PCOS) occurs in 4% to 7% of all women of reproductive age and 50% of women who will seek subfertility services at some point in their life (Archer 2004; Azziz 2005). Clear diagnostic criteria for this condition were drawn up at a consensus meeting of the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) (ESHRE/ASRM 2003), while more recently it has been proposed that definitions be based on anti-Müllerian hormone levels of greater than 5 ng/mL (Dewailly 2011). In anovulatory women with PCOS, the first-line approach to subfertility remains lifestyle changes (weight loss and exercise) along with clomiphene citrate. Other recognised options include surgical ovarian wedge resection, laparoscopic ovarian drilling, metformin, bromocryptine, or aromatase inhibitors (NICE 2004).

A proportion of women with PCOS do not respond to these conventional treatments and will ultimately need assisted reproductive techniques (ART). In women with PCOS, supra-physiological doses of gonadotrophins that are used for controlled ovarian hyperstimulation (COH) provoke the development of a large cohort of follicles of uneven quality. This can sometimes result in the retrieval of immature oocytes, which leads to poor fertilisation and lower cleavage, pregnancy, and live-birth rates. The addition of melatonin into the in vitro maturation (IVM) media has been proposed to improve the cytoplasmic maturation of the immature oocytes and the subsequent clinical outcomes (Kim 2013). Controlled ovarian hyperstimulation in women with PCOS poses a particular challenge as many of these women exhibit an exaggerated response to exogenous gonadotrophins (MacDougall 1993), although there is evidence that COH in women with PCOS results in similar outcomes when compared to women without PCOS (Heijnen 2006). As a consequence, many women face an increased rate of cycle cancellations and potential life-threatening complications due to ovarian hyperstimulation syndrome (OHSS). In addition, the retrieval of immature oocytes leads to reduced fertilisation and lower cleavage, pregnancy, and live-birth rates compared to the conventional in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycles (Son 2010; Qiao 2011; Zheng 2012).

Description of the intervention

In vitro maturation involves the in vitro culture of immature oocytes, from the germinal vesicle or the germinal vesicle breakdown stage, in special laboratory conditions until the metaphase II stage, along with the accompanying cytoplasmic maturation, when the oocyte is considered to be completely mature and ready to undergo fertilisation (Cha 1998; Yang 2017), before the largest follicle has surpassed 13 mm in mean diameter (Dahan 2016). This intervention is potentially useful for women with PCOS-related subfertility since these oocytes can retain their maturational and developmental competence (Trounson 1994). It is believed that women with PCOS who are at risk of developing OHSS following a conventional COH regimen might benefit from earlier retrieval of oocytes followed by IVM, thus reducing the risk of OHSS. Furthermore, doses and cost of the drugs would be lower, although there will be a cost to laboratory. On the other hand, the process of IVM could affect the quality of oocytes, as any intervention in their growth phase could affect oocyte maturation, fertilisation, and subsequent embryo development (Trounson 2001), leading to poor pregnancy outcomes (Barnes 1996; Suikkari 2008; Son 2010; Qiao 2011; de Ziegler 2012; Zheng 2012). In addition, there are no data on long-term outcomes.

How the intervention might work

An option for subfertile women with PCOS is the retrieval of oocytes that retain their functional competence with minimal or mild gonadotrophin stimulation, which stimulates the endometrium at a very low or zero level, mimicking natural environmental procedures. Of note, the ultrastructure of human oocytes matured in vitro is largely similar to those matured in vivo (Coticchio 2016). Successful fertilisation, embryo development, and term pregnancy resulting from IVM oocytes have been reported in stimulated cycles (Nagy 1996; Child 2001), natural cycles (Mikkelsen 2001; Yoon 2001; Benkhalifa 2009; Fadini 2009; Fadini 2013), and women with PCOS (Trounson 1994; Beckers 1999; Chian 1999; Cha 2000; Chian 2000; Child 2001; Child 2002; Lin 2003; Liu 2003; Gulekli 2004; Le Du 2005; Soderstrom-Anttila 2005; Son 2005; Zhao 2006; Son 2007; Zhao 2009; Roesner 2012; Siristatidis 2015), the first report having been published in the mid-1960s (Edwards 1965). While some concern has been expressed regarding the safety of the method with respect to the health of the children and the rate of congenital anomalies (Cha 2005), other studies have reported normal obstetric and neonatal outcomes (Mikkelsen 2005; Soderstrom-Anttila 2005; Shu-Chi 2006; Buckett 2007; Buckett 2008; Roesner 2017).

Why it is important to do this review

When choosing between different IVF protocols for subfertile women with PCOS, a balance needs to be achieved between benefits and harms. Successful fertilisation, embryo development, and term pregnancy resulting from IVM oocytes have been reported in stimulated cycles. However, despite the publication of a number of studies in this area showing that IVM is a low-risk and patient-friendly procedure (Sauerbrun-Cutler 2015; Siristatidis 2015), it is unclear whether IVM offers any benefit to women with PCOS who are undergoing COH, as an alternative to conventional IVF. In addition, there are upcoming studies in the literature that are attempting to find the optimal protocol to be used in subfertile women with PCOS. We have therefore undertaken a second update of this systematic review to ascertain whether IVM is superior to conventional IVF treatment in women with PCOS (Siristatidis 2009; Siristatidis 2013).

OBJECTIVES

To assess the effectiveness and safety of IVM followed by IVF or ICSI versus conventional IVF or ICSI among women with PCOS undergoing assisted reproduction.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) that compared IVM with conventional ART (IVF or ICSI) in women with PCOS for inclusion in this review. If we identified a factorial design (e.g. trials with four groups: IVM alone, IVF alone, IVM + drug, IVF + drug), we would pool data where IVM followed by IVF or ICSI was compared with conventional IVF or ICSI.

We did not include quasi-randomised trials. Cross-over trials were not eligible for inclusion unless pre-cross-over data were available, in which case only these data would be used in this review.

Types of participants

Inclusion criteria

All studies that included subfertile women described as having PCOS were eligible. Polycystic ovarian syndrome was defined by the ESHRE/ASRM criteria (ESHRE/ASRM 2003). Considering the wide variation of diagnostic criteria used for PCOS studies, we included studies utilising different criteria if the broad definition matched that of the ESHRE/ASRM criteria.

We also included trials involving couples with various categories of subfertility alongside PCOS, irrespective of age, parity, and previously administered treatments for subfertility. If only pooled data were available, we considered a study to be eligible if at least 80% of the participants had PCOS.

Exclusion criteria

We excluded trials of ovum recipients and others in which assisted hatching was used, as an issue of embryo quality impairment might be introduced. Had there been insufficient information about the clinical diagnosis, we would have contacted the authors of primary trials.

Types of interventions

Conventional IVF or ICSI after COH versus IVM followed by IVF or ICSI. We included embryo transfers of both fresh and frozen, but not mixed embryos.

We excluded trials evaluating alternative interventions in which the option of IVM or conventional ART was not randomised (e.g. ovarian drilling, use of the oral contraceptive pill, metformin, aromatase inhibitors, steroids, progestins, growth hormone, L-arginine).

Studies using different protocols for IVM, for example human chorionic gonadotrophin (hCG) or gonadotrophin priming for the maturation of oocytes before IVM, were eligible as long as they compared women with PCOS undergoing COH programmes.

All ovarian stimulation protocols were eligible (use of gonadotrophin-releasing hormone agonists (GnRHa), GnRH antagonists, gonadotrophins alone (recombinant or urinary preparations), or clomiphene with gonadotrophins). In all the above cases, pooling data was our intended purpose.

Types of outcome measures

Primary outcomes

1. Live birth per woman. Defined as the delivery of one or more living fetuses after 22 completed weeks of gestation. No cumulative results from more than one cycle were to be considered.
2. Miscarriage (defined as the loss of the pregnancy before 22 completed weeks of gestational age) rate per clinical pregnancy.

Secondary outcomes

1. Effectiveness
   a. Clinical pregnancy per woman, where clinical pregnancy was defined as evidence of a foetal heart on ultrasound at seven plus two gestational weeks
   b. Cycle cancellation
   c. Oocyte fertilisation
2. Adverse effects
   a. Ovarian hyperstimulation
   b. Preterm birth
   c. Congenital anomalies of the newborn

Search methods for identification of studies

We searched for all published and unpublished RCTs evaluating IVM versus IVF/ICSI in subfertile women with PCOS. We applied no language restrictions. The search was designed with the help of the Cochrane Gynaecology and Fertility Group Information Specialist.

Electronic searches

We searched:

1. the Cochrane Gynaecology and Fertility Group Specialised Register of controlled trials from inception to 17 April 2018 (Appendix 1) (ProCite platform);
2. CENTRAL via the Cochrane Central Register of Studies Online (CRSO) (searched on 17 April 2018) (Appendix 2) (web platform);
3. MEDLINE (from 1946 to 17 April 2018) (Appendix 3) (Ovid platform);
4. Embase (from 1980 to 17 April 2018) (Appendix 4) (Ovid platform);
5. CINAHL (Cumulative Index to Nursing and Allied Health Literature) (from 1961 to 17 April 2018) (Appendix 5) (EBSCO platform).

We also searched the following websites:

1. trial registers for ongoing and registered trials: US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov); and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) (searched 17 April 2018) (Appendix 6);
2. the Open Grey database for grey literature from Europe (www.opengrey.eu/) (searched 17 April 2018) (Appendix 7).

The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials described in Chapter 6 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). The Embase and CINAHL searches are combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/search-filters.html).

Searching other resources

We made further searches in the National Institute of Clinical Excellence (NICE) fertility assessment and treatment guidelines (NICE 2004). We handsearched reference lists of relevant systematic reviews and RCTs, together with PubMed and Google for any recent trials that have not yet been indexed in the major databases.

Data collection and analysis

Selection of studies

Two review authors (CS and AM) independently assessed the titles and abstracts retrieved by the search for compliance with the above criteria. We planned to seek additional information from the authors of trials that appeared to meet the eligibility criteria but for which aspects of methodology were unclear or data were in an unsuitable form for meta-analysis. There was no disagreements related to study eligibility. We documented the selection process with a PRISMA flow chart.

Data extraction and management

We extracted the following data from the included studies.

1. Trial characteristics
   a. Randomisation (truly randomised, pseudo-randomised, or not stated)
   b. Allocation concealment, scored according to the categories specified by Cochrane: adequate, unclear, inadequate, or not used
   c. Trial design: multicentre or single centre, single-phase or cross-over design
   d. Duration, timing, and location of the trial (single centre or multicentre), duration of follow-up:
      i. outcome data used for primary analysis complete (follow-up to live birth); randomised women accounted for; intention-to-treat analysis;
      ii. completeness of data uncertain;
      iii. outcome data incomplete with 5% of cycles commenced missing some outcome data.
   e. Source of funding
   f. Co-intervention:
      i. where any intervention other than that being investigated in the study protocol was equivalent in the treatment and control groups;
      ii. issue of co-intervention not considered;
      iii. co-intervention definitely existed.
   g. Definitions of PCOS were examined, e.g. if they matched the ESHRE/ASRM criteria, were too restrictive, or too vague
2. Baseline characteristics of the studied groups
   a. Cause and duration of pre-existing subfertility
   b. Age of the women and parity
   c. Investigative work-up
   d. Other causes of subfertility
   e. Previously administered treatment(s)
3. Interventions
   a. Type of intervention and control
   b. Dose and type of regimen
4. Outcomes
   a. Outcomes reported
   b. How outcomes were defined
   c. Timing of outcome measurements

Assessment of risk of bias in included studies

We used the Cochrane 'Risk of bias' assessment tool to assess the included studies for selection, performance, detection, attrition, reporting, and other bias. There were no disagreements. We described our judgements in detail the 'Risk of bias' table in the 'Characteristics of included studies' table.

Measures of treatment effect

For dichotomous data (e.g. live-birth rates), our aim was to use the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs) with 95% confidence intervals (CIs) for all outcomes. Where data to calculate ORs were not available, we would have utilised the most detailed numerical data available that might facilitate similar analyses of included studies.

Unit of analysis issues

We performed analysis per woman or couple randomised for live birth, clinical pregnancy, and complication rates. We counted multiple live births (twins, triplets) as a single live-birth event. Data that prevented valid analysis (e.g. 'per cycle' data) would be briefly summarised in an Additional table but would not be meta-analysed. We would include only first-phase data from cross-over trials. If studies reported only 'per cycle' data, we contacted the study authors to request 'per woman' data.

Dealing with missing data

We sent corresponding authors two emails in an attempt to obtain missing data from the original trials of the included and ongoing studies.

Our initial intention was to analyse data on an intention-to-treat basis. In the case of unobtainable data, we planned to undertake imputation of individual values for live-birth rate only. We assumed that live births had not occurred in participants without a reported outcome. For other outcomes, we analysed only the available data.

Assessment of heterogeneity

We identified heterogeneity by visual inspection of forest plots and by using a standard Chi^2 test with significance set at $P < 0.1$. We used the I^2 statistic to estimate the total variation across RCTs that was due to heterogeneity, considering an I^2 greater than 50% as indicative of substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

In order to avoid, or at least minimise, reporting biases (e.g. publication bias, multiple publication bias, language bias, etc.), we performed a comprehensive search for eligible studies and were alert for duplication of data. If there were 10 or more studies in an analysis, we would use a funnel plot to explore the possibility of small-study effects.

Data synthesis

We used Review Manager 5 for input of data and statistical analysis (RevMan 2012), in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We planned that if the studies were sufficiently similar, we would combine the data using a fixed-effect model.

An increase in the odds of a particular outcome, which might be beneficial (e.g. live birth) or detrimental (e.g. adverse effects), would be displayed graphically in the meta-analyses to the right of

the centre-line, and a decrease in the odds of an outcome to the left of the centre-line. We would use a fixed-effect analysis if the underlying effect size was the same for all trials in the analysis; if not, we would use a random-effects analysis.

Subgroup analysis and investigation of heterogeneity

We planned that where data were available, we would conduct subgroup analyses to determine the separate evidence within the following subgroups:

1. average age for women of less than and over 35 years;
2. various types of subfertility;
3. different protocols for COH;
4. parity of women;
5. previous COH for IVF attempts.

Had we detected substantial heterogeneity, we would have explored possible explanations for it in sensitivity analyses. We would have taken any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect.

Sensitivity analysis

We planned to conduct sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding eligibility and analysis. These analyses would consider whether the review conclusions would have differed if:

1. eligibility was restricted to studies without high risk of bias;
2. a random-effects model had been adopted;
3. alternative imputation strategies had been implemented;
4. the summary effect measure was risk ratio rather than odds ratio.

Overall quality of the body of evidence: 'Summary of findings' table

We prepared a 'Summary of findings' table using GRADEpro GDT (GRADEpro GDT 2018). This table presents the overall quality of the body of evidence for the main review outcomes (clinical pregnancy and OHSS incidence) using the five GRADE criteria: study limitations, consistency of effect, imprecision, indirectness, and publication bias (Higgins 2011). Two review authors independently assessed the quality of the evidence for each outcome. We justified, documented, and incorporated judgements about the quality of the evidence (high, moderate, low, or very low) when reporting the results for each outcome. Data were not available for the outcomes of live birth per woman randomised and miscarriage, the primary outcomes specified in this review.

RESULTS

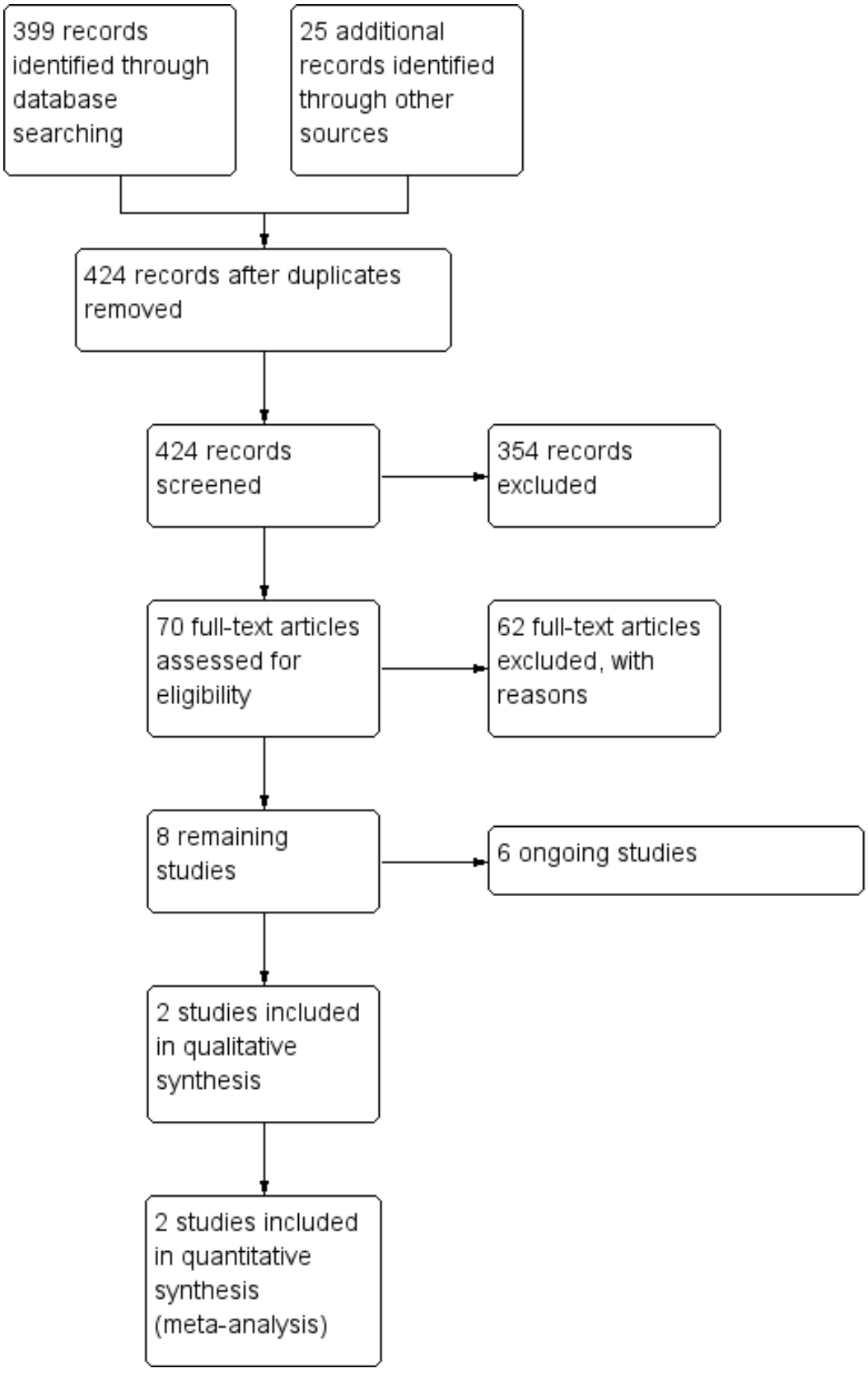
Description of studies

Results of the search

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies tables.

We initially identified 399 articles from the main databases and 25 articles from the databases of ongoing studies (424 in total) as providing data comparing conventional IVF with IVM in women with PCOS. Based on the abstract we excluded 354 records. We retrieved the full texts of the remaining 70 articles, and based on the full text excluded 62 articles. Two RCTs, published as abstracts, met the inclusion criteria for this review (Gidoni 2013; Shavit 2015), as well as six ongoing studies (ISRCTN61229302; NCT00867763; NCT01473459; NCT03134482; NCT03463772; NCT03405701). (See Figure 1)

Figure 1. Study flow diagram.



We sent two emails to authors of the two included studies (published as abstracts), and four further emails (and the appropriate reminders) to the authors of three ongoing studies, ISRCTN61229302; NCT00867763; NCT01473459, and the study of Xu 2012 for unpublished data, or regarding data before inclusion, as well as for methodological details. We received responses from one of the ongoing studies (NCT01473459), and from the study of Xu 2012, but the data provided did not allow us to include these studies in the current review.

Included studies

Study design and setting

Two RCTs (Gidoni 2013; Shavit 2015), published as abstracts, met the inclusion criteria of this review. Both were single-centre studies conducted in IVF units in Israel.

Participants

The included studies involved 71 subfertile women undergoing ART, one study of women with anovulatory polycystic ovaries (n = 50) and one study of women with PCOS (n = 21).

Interventions

Both studies compared IVM (primed with three days of gonadotrophins) with a GnRH antagonist protocol.

Outcomes

Neither of the studies reported live birth or miscarriage. Of the secondary outcomes specified in this review, both studies reported on clinical pregnancy and OHSS incidence.

Excluded studies

Of the 424 records identified after removal of duplicates, 354 studies were excluded initially on the basis of the abstract (Figure 1).

Of the remaining 70 papers, 62 were retrieved but were subsequently excluded as non-RCTs or as not answering the precise review question (see Characteristics of excluded studies).

Risk of bias in included studies

As described in detail in the 'Risk of bias' table in Characteristics of included studies, we rated the risk of bias as unclear or high for most domains in both included studies (Figure 2, Figure 3). Both studies had a published conference abstract in international databases. After emailing the study authors we were unable to retrieve any further data. We assessed one study as at unclear risk of reporting bias (Gidoni 2013). However, we assessed both studies as at unclear risk of other sources of bias. The considerable impact of all types of bias on the reliability of the results contributed to our decision to reduce the quality of the evidence to very low for both outcomes.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

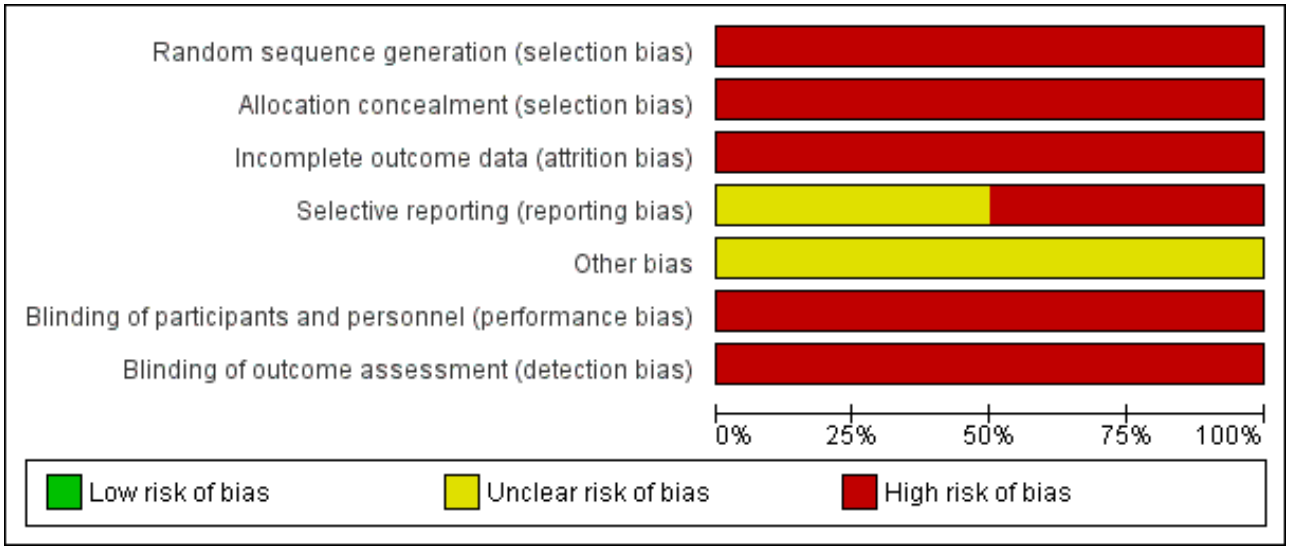
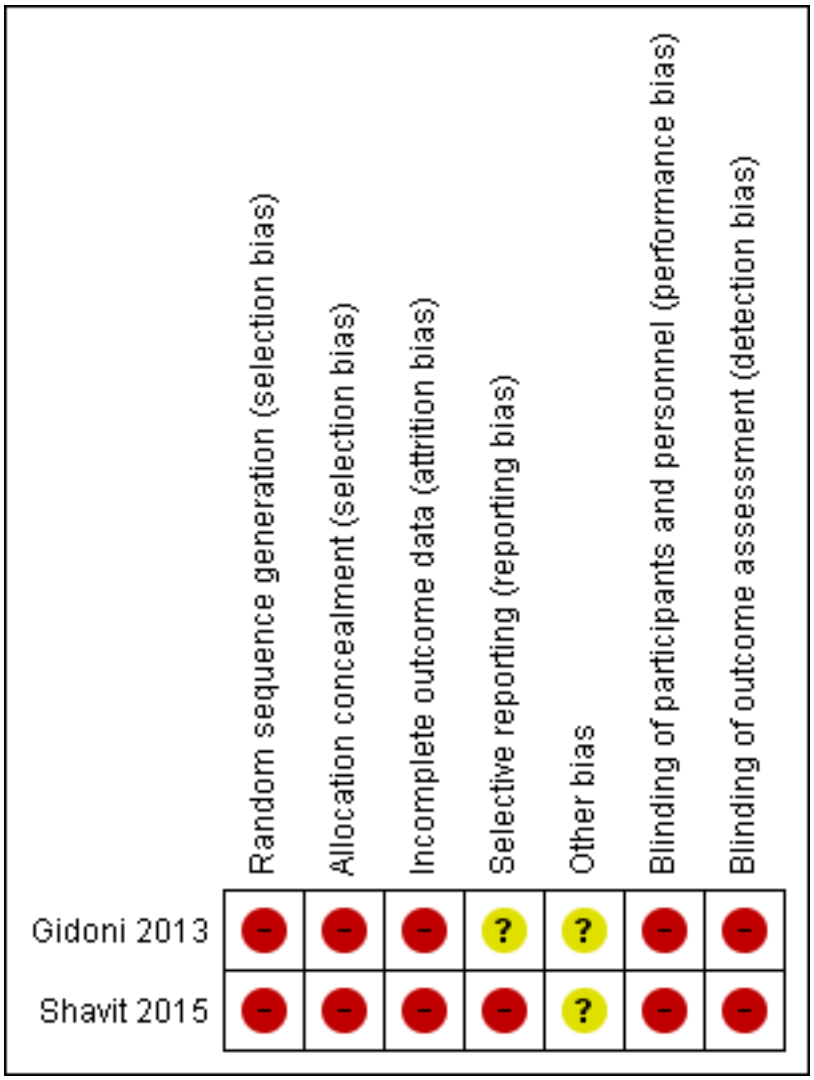


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** In vitro maturation compared to in vitro fertilisation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction

We found two studies assessing the role of IVM in subfertile women with PCOS undergoing ART in this second update of the review (Gidoni 2013; Shavit 2015; Summary of findings for the main comparison).

In vitro maturation versus in vitro fertilisation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction

Primary outcomes

Live-birth rate per woman randomised

Data were not available.

Miscarriage

Data were not available.

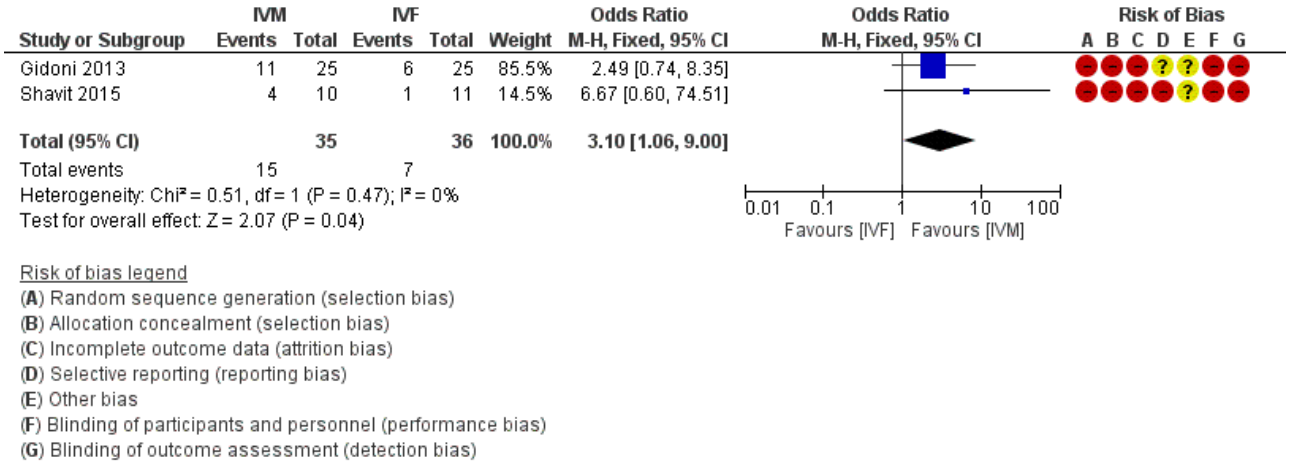
Secondary outcomes

Effectiveness

Clinical pregnancy per woman

Both included studies reported this outcome. There was evidence of an effect between IVM and IVF, favoring IVM (odds ratio 3.10, 95% confidence interval 1.06 to 9.00; 71 participants; 2 studies; I^2 = 0%; very low-quality evidence; Analysis 1.1; Figure 4). This means that if the clinical pregnancy rate was 19.4% with conventional IVF, in women with PCOS undergoing IVM it would be between 20.4% and 68.5%.

Figure 4. Forest plot of comparison: 1 IVM versus IVF, outcome: 1.1 Clinical pregnancy.



Cycle cancellation

Data were not available.

Oocyte fertilisation

Data were not available.

Adverse effects

Ovarian hyperstimulation

Both included studies reported this outcome. Zero cases of OHSS were reported in both groups (odds ratio not estimable; 71 participants; 2 studies; I^2 not applicable; very low-quality evidence; Analysis 1.2).

Preterm birth

Data were not available.

Congenital anomalies of the newborn

Data were not available.

DISCUSSION

Summary of main results

In this 2018 update of the review, interpretation of results remains limited by the absence of adequately conducted RCTs. We found only two trials presented as abstracts in international conferences and published as supplements in journals. As we found no data on the primary outcomes set for this review, namely live birth and miscarriage, the data provided could not answer the question of this review. Of the secondary outcomes examined, very low-quality evidence showed that clinical pregnancy was higher when IVM was compared to IVF, whereas the incidence of OHSS was zero in both groups in both studies that reported this outcome. However, we found six ongoing studies that are still recruiting participants. Consequently, any effect of IVM relative to traditional IVF/ICSI in terms of live-birth rates for women with PCOS remains unknown.

Overall completeness and applicability of evidence

In theory, recovery of immature oocytes followed by IVM could be developed as a safe alternative method for the treatment of these women as their oocytes retain their maturational and developmental competence (Trounson 1994); this procedure was carried out successfully in a variety of different species during the previous century (Pincus 1935; Edwards 1965). During our initial search, we found some evidence that IVM could provide a promising alternative to conventional IVF/ICSI in women with PCOS, especially to prevent OHSS, but this evidence was not based on robust data reported in RCTs. Instead, observational studies showed a high maturation rate of the oocytes (up to 80.3%) (Child 2001); fertilisation rates from 10%, Beckers 1999, up to 76.5%, Child 2001; clinical pregnancy rates from 21.5%, Cha 2005, to 50% per cycle, Holzer 2006; implantation rates around 18% (Child 2002; Holzer 2006); live-birth rates from 15.9% per retrieval, Child 2002, to 33% per cycle, Holzer 2006; and pregnancy complications at 13.2% (Cha 2005). Chromosomal abnormalities and outcomes were similar for IVM and conventional ART populations (Buckett 2005; Li 2005; Foix-L'Hélias 2014). Case-control retrospective studies reported similar results with oocyte maturation rates up to 84% (Chian 2000); fertilisation rates from 43%, Soderstrom-Anttila 2005, to 70%, Le Du 2005; and pregnancy rates from 22%, Sandraa 2006, to 55.6%, Fukuda 2006; while rates of miscarriage, ectopic pregnancy, and late foetal loss were similar for IVM and IVF or ICSI groups of women with PCOS (Buckett 2008). The studies compared different protocols of IVM in women with PCOS, finding that human chorionic gonadotrophin priming, which was not dose-dependent (Gulekli 2004), raised the maturation rate from 69% to 84% (Chian 2000); fertilisation rate from 45%, Chung 2000, up to 80%, Ge 2008; pregnancy rate from 31% up to 38.5%; and live-birth rate up to 33% (Ge 2008). Follicle-stimulating hormone priming increased the pregnancy rate from 0% to 29% (Mikkelsen 2001).

In the absence of robust results from high-quality/appropriate trials, we are still unable to comment on the advantages or disadvantages of the technique. We must await the conclusions of the six ongoing studies identified in this review, and furthermore wish to highlight the need for properly designed RCTs in the field. There is still a requirement to offer women with PCOS a promising alternative to conventional ART, and IVM seems to be one (Cha 2005; Le Du 2005; Siristatidis 2015); the problem is that data showing this are from observational and non-comparative studies. Moreover, adequate follow-up of trial participants in terms of neonatal and postneonatal outcomes is necessary.

Quality of the evidence

There were no RCTs and no relevant data on live birth and miscarriage when IVM was compared to conventional IVF/ICSI in subfertile women with PCOS. Of the secondary outcomes examined, very low-quality evidence showed that clinical pregnancy was higher when IVM was compared to IVF/ICSI, whereas the incidence of OHSS was zero in both groups in both studies that reported this outcome (as shown in Summary of findings for the main comparison). The limitations of this evidence include the absence of sufficient data on the randomisation process; the fact that data were obtained only from abstracts and no data were available for the assessment of heterogeneity; and finally the fact that women in one of the included studies were described as having anovulatory polycystic ovaries and not PCOS (Gidoni 2013).

Potential biases in the review process

We believe that we have made every effort to minimise biases in the review process. We conducted a systematic search of the literature for RCT evidence that was not restricted by language or date of publication. We attempted to make contact with authors of primary studies to obtain additional methodological or outcome data, or both. We followed Cochrane methods in the review process.

Agreements and disagreements with other studies or reviews

The conclusions of this review are in agreement with those of the previous versions of the review (Siristatidis 2009; Siristatidis 2013). In contrast, there are publications that support the standard use of IVM, including in subfertile women with PCOS, but the data are from non-RCTs (Chian 2004; Reinblatt 2008; Grynberg 2013; Ellenbogen 2014), while others do not advise the standard administration of the technique, as new COH protocols are better in terms of pregnancy outcomes (de Ziegler 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Though promising data on the in vitro maturation (IVM) technique have been published, unfortunately there remains no evidence from properly conducted randomised controlled trials (RCTs) upon which to base any practice recommendations regarding IVM before in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) for women with polycystic ovarian syndrome (PCOS). Of the secondary outcomes specified in this review, very low-quality evidence showed that clinical pregnancy was higher when IVM was compared to IVF, whereas the incidence of ovarian hyperstimulation syndrome was zero in both groups in both studies that reported this outcome. We are awaiting the results of six ongoing trials and eagerly anticipate further evidence from good-quality trials in the field. Until more evidence is available, either from the six ongoing trials or from further well-designed RCTs in the field, IVM cannot be the preferred first-line treatment for subfertile women with PCOS, and it might be appropriate to continue to offer conventional IVF/ICSI.

Notably, there is growing evidence that for this category of patients the optimal method to be offered is a 'freeze-all policy', after a conventional ovarian stimulation and IVF/ICSI, followed by transfers in frozen replacement cycles.

Implications for research

We aimed to provide a clear overview of the differences between IVM and conventional IVF/ICSI in order to facilitate a decision over which treatment is better for women with PCOS. Unfortunately, we included only two studies published in the form of abstracts, while another six studies are currently ongoing, hence we could arrive at no robust conclusions. Proper RCTs with sufficient power and appropriate endpoints (live-birth and miscarriage rates must be the primary outcomes) that compare IVM with conventional assisted reproductive technology and that are performed according to CONSORT guidelines are urgently needed in women with PCOS and subfertility.

It may be that the only category of patients for whom IVM might be beneficial is fertility preservation cases, where there is no time to stimulate the ovaries. For these patients, IVM can be offered only by select IVF centres with adequate expertise, and RCT might not be the optimal type of study; instead, a prospective collection of data through cohort studies may be more appropriate.

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NCT03134482. Comparison of Clinical Outcomes Between IVM and Minimal Stimulation IVF in Patients With PCOS [Comparison of Clinical Outcomes Between in Vitro Maturation and Minimal Stimulation in Vitro Fertilization in Patients With Polycystic Ovarian Syndrome; Prospective, Randomized Controlled, Parallel, Open-label, Clinical Trial]. ClinicalTrials.gov/show/NCT03134482 (first received May 1, 2017). [https://www.clinicaltrials.gov/ct2https://clinicaltrials.gov/ct2/show/record/NCT03134482]

NCT03405701 *{published data only}*

NCT03405701. IVM Versus IVF in High Antral Follicle Count Patients [The Effectiveness and Safety of in Vitro Maturation of Oocytes Versus in Vitro Fertilization in Women With High Antral Follicle Count (AFC): a Randomised Controlled Trial]. clinicaltrials.gov/show/NCT03405701 (first received January 23, 2018). [https://www.clinicaltriClinicalTrials.gov Identifier: NCT03405701]

NCT03463772 *{published data only}*

NCT03463772. IVM versus standard in vitro fertilization in infertile patients diagnosed with PCOS [In Vitro Maturation Versus Standard in Vitro Fertilization in Infertile Patients Diagnosed With Polycystic Ovaries Syndrome: a Study Protocol for a Single-center Prospective, Randomized Controlled Clinical Trial]. ClinicalTrials.gov/show/NCT03463772 (first reveived March 13, 2018). [ClinicalTrials.gov Identifier: NCT03463772]

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gidoni 2013

Methods	Authors only state that it was a "prospective randomized study".
Participants	50 women with anovulatory polycystic ovaries
Interventions	IVM with 3 days of gonadotrophins vs GnRH antagonist flexible protocol
Outcomes	Total number of mature oocytes, fertilisation, cleavage rates, "top quality" embryos, number of embryos transferred, clinical pregnancy, number of frozen embryos, and OHSS incidence

Gidoni 2013 *(Continued)*

Notes	Women described as having anovulatory polycystic ovaries but not PCOS. Data obtained from abstract presented in a conference. Assaf Harofeh Medical Center, IVF Unit, Zerifin, Israel

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No data available for the specific type of bias, even when sought
Allocation concealment (selection bias)	High risk	No data available for the specific type of bias, even when sought
Incomplete outcome data (attrition bias) All outcomes	High risk	No data available for the specific type of bias, even when sought
Selective reporting (reporting bias)	Unclear risk	Details not stated, outcomes relevant to this review were reported.
Other bias	Unclear risk	No data available for the specific type of bias, even when sought
Blinding of participants and personnel (performance bias) All outcomes	High risk	No data available for the specific type of bias, even when sought
Blinding of outcome assessment (detection bias) All outcomes	High risk	No data available for the specific type of bias, even when sought

Shavit 2015

Methods	Authors only state that it was a "prospective randomized controlled trial".
Participants	21 women with PCOS
Interventions	IVM with 3 days of gonadotrophins and hCG vs GnRH antagonist "routine" protocol
Outcomes	Total number of mature oocytes, fertilisation rates, "top quality" embryos, average dose of gonadotrophins, pregnancy rate, and OHSS incidence
Notes	Data obtained from abstract presented in a conference. Hillel Yaffe Medical Center, IVF Unit, Hadera, Israel

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No data available for the specific type of bias, even when sought

Shavit 2015 *(Continued)*

Allocation concealment (selection bias)	High risk	No data available for the specific type of bias, even when sought
Incomplete outcome data (attrition bias) All outcomes	High risk	No data available for the specific type of bias, even when sought
Selective reporting (reporting bias)	High risk	No data available for the specific type of bias, even when sought
Other bias	Unclear risk	No data available for the specific type of bias, even when sought
Blinding of participants and personnel (performance bias) All outcomes	High risk	No data available for the specific type of bias, even when sought
Blinding of outcome assessment (detection bias) All outcomes	High risk	No data available for the specific type of bias, even when sought

GnRH: gonadotrophin-releasing hormone
hCG: human chorionic gonadotrophin
IVF: in vitro fertilisation
IVM: in vitro maturation
OHSS: ovarian hyperstimulation syndrome
PCOS: polycystic ovarian syndrome

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barnes 1995	Case report
Barnes 1996	Prospective observational study
Beckers 1999	Prospective observational study
Benkhalifa 2009	Observational study
Bos-Mikich 2011	Observational study
Buckett 2005	Retrospective observational study
Buckett 2007	Retrospective analysis
Buckett 2008	Retrospective study
Cha 1998	Retrospective case-control study
Cha 2000	Prospective observational study
Cha 2005	Prospective observational study
Chian 1999	Retrospective observational study (as letter to the editor)

Study	Reason for exclusion
Chian 2000	Prospective randomised study comparing priming versus non-priming with hCG in women with PCOS undergoing IVM
Chian 2004	Case series
Child 2001	Retrospective case-control study
Child 2002	Prospective observational study
Choi 2012	Not an RCT
Chung 2000	Prospective randomised study comparing priming versus non-priming with hCG in women with PCOS undergoing IVM
De Vos 2016	Not an RCT
Filali 2008	Retrospective observational study
Fukuda 2006	Retrospective observational study
Ge 2008	Prospective randomised study comparing different culture media in 62 women with PCOS undergoing IVM
Gremeau 2012	Retrospective case–control study
Gulekli 2004	Prospective controlled study of priming with 10,000 IU versus 20,000 IU of hCG in 57 women with PCOS undergoing IVM
Harris 2010	Prospective observational study
Holzer 2006	Prospective observational study
Hreinsson 2003	Randomised prospective study comparing LH and hCG for oocyte maturation in an IVM programme
Junk 2012	Prospective cohort study
Kedem 2013	Not an RCT
Kim 2013	RCT evaluating the effect of melatonin supplementation on the clinical outcomes of IVM IVF transfer in 111 women with PCOS
Le Du 2005	Retrospective observational study
Li 2005	Prospective observational study
Lim 2009	Retrospective analysis
Lin 2003	Prospective observational study
Liu 2010	Prospective observational study
Lornage 2006	Retrospective analysis
Mikkelsen 2001	Randomised prospective study of 36 women with PCOS comparing priming versus non-priming with FSH before IVM

Study	Reason for exclusion
Mikkelsen 2003	Randomised prospective study on the interval between FSH administration and IVM in women with PCOS
NCT01237106	Protocol of a non-RCT
NCT01843569	Protocol of a non-RCT
Roesner 2012	Retrospective analysis
Sandraa 2006	Retrospective observational study
Shalom-Paz 2012	Retrospective evaluation
Shavit 2014	Not an RCT
Shu-Chi 2006	Retrospective observational study
Soderstrom-Anttila 2005	Retrospective observational study
Son 2005	Retrospective observational study
Son 2007	Not an RCT
Sánchez 2017	Does not answer the question of this review. Not an RCT
Trounson 1994	Retrospective observational study
Vieira 2008	Prospective controlled trial in 5 participants with PCOS and 8 participants with male or tubal causes of subfertility undergoing IVM comparing the meiotic spindle and chromosomal distribution of IVM oocytes and IVM rates
Vieira 2010	Prospective controlled trial in 13 participants with PCOS and 27 participants with male or tubal causes of subfertility undergoing IVM comparing the meiotic spindle and chromosomal distribution of IVM oocytes and IVM rates
Walls 2012	RCT comparing ICSI with IVF in 8 women with PCOS
Walls 2015a	Not an RCT
Walls 2015b	Not an RCT
Walls 2016	Not an RCT
Xu 2012	Not an RCT
Yu 2012	Retrospective study
Zhang 2007	Observational study
Zhao 2006	Retrospective observational study
Zhao 2009	Retrospective study
Zheng 2012	RCT of 82 women with PCOS undergoing IVM cycles comparing priming versus non-priming with hCG

FSH: follicle-stimulating hormone
hCG: human chorionic gonadotrophin
ICSI: intracytoplasmic sperm injection
IU: international units
IVF: in vitro fertilisation
IVM: in vitro maturation
LH: luteinising hormone
PCOS: polycystic ovarian syndrome
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ISRCTN61229302

Trial name or title	A multicentre randomised controlled trial comparing in vitro maturation of oocytes with in vitro fertilisation in women with an increased risk of ovarian hyperstimulation syndrome
Methods	Multicentre, randomised, active-controlled, parallel-group trial with non-randomised pilot study
Participants	Target sample size 450 (400 couples, preceded by a pilot study of 50 non-randomised IVM cycles) Inclusion criteria: 1. Women with PCOS according to the Rotterdam criteria (the Rotterdam European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine-sponsored PCOS consensus workshop group, 2004) who not did achieve an ongoing pregnancy after ovulation induction (with clomiphene citrate or LEO and rFSH) 2. Women with an IVF or ICSI indication and increased risk for developing OHSS (history of OHSS or cycle cancellation for imminent OHSS) Exclusion criteria: 1. Woman or partner younger than 18 years and women older than 38 years 2. Unable to speak or read the Dutch language 3. Medical contraindication for pregnancy or childbirth 4. Positive serology for hepatitis B or C or HIV 5. Diminished ovarian reserve: early follicular serum FSH > 10 IU/L and/or poor response during earlier COH/IVF or COH/ICSI with ≥ 150 IU rFSH/day 6. Persisting ovarian cysts > 30 mm diameter
Interventions	Couples will be randomised to either: IVM/ICSI strategy 1. The maximum number of IVM cycles per couple is 2. 2. The IVM cycle will be sonographically and endocrinologically monitored (serum oestradiol concentration). 3. In women with severe oligomenorrhoea or amenorrhoea priming of the ovaries may be performed (after induction of withdrawal bleeding with 7 days 10 mg progestogens orally, if necessary). 4. Ovarian priming consists of subcutaneous administration of 150 IU rFSH on cycle days 3 through 5. 5. In primed cycles, 10,000 IU of hCG will be administered subcutaneously when the dominant follicle is identified. Oocyte retrieval is scheduled for 38 hours after administration of hCG. 6. Directly after oocyte retrieval, luteal support is started with oestradiol 2 mg orally 3 times a day and progesterone 200 mg vaginally 3 times a day from oocyte retrieval plus 1 day. 7. A maximum number of 2 embryos will be transferred per cycle. Remaining embryos can be selected for cryopreservation according to the standard IVF/ICSI procedures and criteria. OR IVF/ICSI strategy

ISRCTN61229302 *(Continued)*

	1. The maximum number of IVF/ICSI cycles per couple is 1. 2. After pre-treatment with an oral contraceptive pill or induction of withdrawal bleeding with 7 days 10 mg progestogens orally, COH will be started from the 4th day after the end of pre-treatment with daily subcutaneous injections with 100 to 225 IU rFSH. From stimulation day 6 onwards, a GnRH antagonist (0.25 mg) will be daily injected subcutaneously for pituitary downregulation. 3. The cycle will be sonographically monitored starting at day 3 after stopping oral contraception (baseline ultrasound). When acquired numbers and diameters of follicles are reached, 10,000 IU hCG is administered subcutaneously, with oocyte retrieval scheduled for 34 to 36 hours after hCG. After oocyte retrieval, standard IVF or ICSI procedure will follow. 4. Directly after oocyte retrieval, luteal support is started by administration of progesterone 200 mg vaginally 2 times a day. 5. The maximum number of embryos that can be transferred is 2. Remaining embryos can be selected for cryopreservation according to standard IVF/ICSI procedures and criteria.
Outcomes	Primary outcome: Cumulative live-birth rate after IVM/ICSI or COH/IVF/ICSI strategy including pregnancies from cryoembryos transferred within 12 months after the end of IVM/ICSI or COH/IVF/ICSI treatment. Secondary outcomes: 1. Pregnancy/childbirth: detailed information on maternal complications will be obtained from the obstetrician treating the woman concerned. 6 weeks after the expected day of delivery all women will be contacted by telephone to ask for information on the delivery and on the health of the child, and for consent to contact the health centre where she gave birth. If a child has been hospitalised, the paediatrician treating the child will be contacted for further information. 2. Paediatric follow-up: follow-up will consist of evaluation on the following domains using internationally accredited and validated tests: motor development, cognitive development, and behaviour. Follow-up visits will be scheduled at age 6 months, 1, 2, and 5 years. 3. Economic evaluation: a distinction will be made between costs of medical interventions (direct costs) and costs resulting from productivity losses (indirect or time costs). Standardised unit costs will be calculated for all centres based on actual expenses made during the study. Subsequently, unit costs will be applied to resource use as observed in the participating centres. Resource utilisation will be documented using individual patient data in the case record forms. In addition, each woman will receive a questionnaire for details on associated direct costs of professional care, and on indirect costs like transportation and productivity loss. These questionnaires will be sent at 4, 12, 24, and 48 weeks after treatment start. Resource unit prices will reflect the unit of staff, materials, equipment, housing, depreciation, and overhead. Endpoint for cost-effectiveness will be euros/live birth for either strategy. 4. Patient quality of life study: before starting a treatment cycle, the day before oocyte retrieval and the day after oocyte retrieval and 3 weeks after a treatment cycle participants will be asked to fill out a validated questionnaire on quality of life (Fertility quality of life tool (FertiQoL), www.fertiqol.org).
Starting date	1 January 2010
Contact information	Register: Netherlands Trial Register Primary sponsor: Jeroen Bosch Hospital Name: JP Bruin, de Address: Postbus 90153 5200 Center for Reproductive Medicine P.O. Box 90153 ME Den Bosch the Netherlands Telephone: +31 (0)73 6998660 Email: j.d.bruin@jbz.nl
Notes	Trial website: www.studies-obsgyn.nl/ivm Status of trial: recruiting

NCT00867763

Trial name or title	In vitro maturation with in vitro fertilisation (IVF) compared to mild in vitro fertilisation (IVM vs IVF)
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: cross-over assignment Masking: open-label Primary purpose: health services research
Participants	Ages: 21 to 41 years Inclusion criteria: under 42 years of age, female, normal uterine cavity, BMI 18 to 34 kg/m^2 Exclusion criteria: donor eggs, donor sperm, myoma over 5 cm, current hydrosalpinx, abnormal uterine cavity
Interventions	Arm 1: IVM and IVF. No stimulation with gonadotrophins, eggs harvested early Arm 2: mild IVF (low doses of gonadotrophin stimulation followed by conventional IVF)
Outcomes	Primary outcome measure: cost-effectiveness Secondary outcome measure: ongoing pregnancy rates per cycle
Starting date	March 2009
Contact information	Joe B Massey, MD, Batzofin Fertility Services
Notes	This study has suspended participant recruitment (investigator changed location, requires new training effort). ClinicalTrials.gov identifier: NCT00867763

NCT01473459

Trial name or title	Comparison between two fertility protocols in obese polycystic ovary syndrome patients
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	Estimated enrolment: 40 participants Age: 18 to 40 years Inclusion criteria: BMI > 30, PCOS, failure of COH treatment
Interventions	Arm 1: IVM treatment No gonadotrophin stimulation. Ovum pick-up will be from antral follicles of immature oocyte, which will be matured in the lab and fertilised by ICSI. Embryo transfer will take place on days 2 or 3. Arm 2: IVF antagonist protocol Stimulation with gonadotrophins and use of GnRH antagonists. Ovulation induction will be performed with GnRH agonist. After ovulation there will be ovum pick-up and fertilisation in the lab. Embryo transfer will take place on days 2 or 3.

NCT01473459 *(Continued)*

Outcomes	Reported as "fertility results"
Starting date	April 2012
Contact information	Tal Shavit, MD; 972-50-6246712; email: tal.shavit@gmail.com
Notes	This study is not yet open for participant recruitment. Hillel Yaffe Medical Center, Hadera, Israel, 38100 ClinicalTrials.gov identifier: NCT01473459

NCT03134482

Trial name or title	Comparison of clinical outcomes between in vitro maturation and minimal stimulation in vitro fertilization in patients with polycystic ovarian syndrome; prospective, randomized controlled, parallel, open-label, clinical trial
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	Ages eligible for study: 20 years to 39 years Estimated enrolment: 240 participants Inclusion criteria: 1. Women diagnosed with PCOS under 40 years of age (PCOS diagnosis is based on Revised 2003 Rotterdam criteria of PCOS) Exclusion criteria: 1. Severe male factor subfertility requiring testicular sperm extraction or oligoasthenoteratozoospermia 2. Couples requiring pre-implantation genetic screening or diagnosis 3. Women had undergone ovarian stimulation 30 days before assisted reproductive technology 4. Women with severe endometriosis or dysfunctional uterine bleeding 5. Women with severe uterine factor subfertility (e.g. submucosal myoma, intramural myoma protruding endometrium, severe intrauterine adhesion, etc.) 6. Women with ovarian malignancy 7. Women with severe tubal factor subfertility (e.g. persistent hydrosalpinx even after surgery) 8. Women had undergone treatment of malignancy 5 years before screening of this trial 9. Women with history of thromboembolism 10. Women aged 40 years or older 11. Women with stimulation dose over 150 IU of exogenous FSH
Interventions	Experimental: IVM 1. hCG-primed IVM procedure. Gonadotrophin is not used in this patient group. If the endometrial thickness in 6 mm or more and the mean diameter of largest follicle is 11 mm or less on menstrual cycle day 9 to 12 on ultrasonography, oocyte retrieval is planned 2 days later. 2. Recombinant hCG injection (priming) is given 36 hours before oocyte retrieval, followed by ICSI for oocyte fertilisation.

NCT03134482 *(Continued)*

	3. The biochemical pregnancy is confirmed by serum beta hCG 15 days after oocyte retrieval. 4. The clinical pregnancy is confirmed when gestational sac is detected by transvaginal ultrasonography 3 weeks after oocyte retrieval. 5. Procedure: IVM 6. No gonadotrophin is used, but hCG priming is utilised 36 hours before oocyte maturation. Active comparator: minimal-stimulation IVF 1. Minimal-stimulation IVF procedure. These women are stimulated with 150 IU or less of recombinant FSH from menstrual cycle day 3 in GnRH antagonist protocol. 2. If the mean diameters of 2 or more follicles are 17 mm or more, oocyte retrieval is planned 2 days later. 3. Recombinant hCG is triggered 36 hours before oocyte retrieval, followed by ICSI for oocyte fertilisation if needed. 4. The biochemical pregnancy is confirmed by serum beta hCG 14 days after oocyte retrieval. 5. The clinical pregnancy is confirmed when gestational sac is detected by transvaginal ultrasonography 3 weeks after oocyte retrieval. 6. Procedure: minimal-stimulation IVF 7. IVF with minimal use of gonadotrophin, i.e. 150 IU or less of recombinant FSH, followed by hCG triggering in GnRH antagonist protocol.
Outcomes	Primary outcome: clinical pregnancy rate Secondary outcome: OHSS incidence rate
Starting date	Actual start date of study: 1 May 2017 Estimated primary completion date: 23 September 2018 Estimated study completion date: 23 September 2019
Contact information	Contact: You Shin Kim, MD, PhD; 82-2-2002-0303; email: medikys@cha.ac.kr Principal Investigator: You Shin Kim, MD, PhD, Fertility Center of CHA Gangnam Medical Center, CHA University
Notes	CHA Fertility Center, Seoul station Recruiting Seoul, Korea, Republic of, 04367 Contact: You Shin Kim, MD, PhD; 2-2-2002-0303; email: medikys@cha.ac.kr CHA Gangnam Medical Center Recruiting Seoul, Korea, Republic of, 06135 Contact: You Shin Kim, MD, PhD; 82-2-2002-0303; email: medikys@cha.ac.kr ClinicalTrials.gov identifier: NCT03134482 Status: recruiting

NCT03405701

Trial name or title	The effectiveness and safety of in vitro maturation of oocytes versus in vitro fertilization in women with high antral follicle count (AFC): a randomised controlled trial
Methods	Study type: interventional (clinical trial) Allocation: randomised Intervention model: parallel assignment Masking: none (open-label)

NCT03405701 *(Continued)*

	Primary purpose: treatment
Participants	Estimated enrolment: 546 participants Ages eligible for study: 18 to 40 years Inclusion criteria: 1. Women with high AFC (≥ 24 antral follicles in both ovaries), including PCOS, polycystc ovaries or high AFC 2. Having indications for ART 3. Having ≤ 2 IVM/IVF attempts 4. Permanent resident in Vietnam 5. Agree to have all embryos frozen on day 3 6. Agree to have ≤ 2 embryos transferred in a subsequent frozen transfer 7. Not participating in another IVF study at the same time Exclusion criteria: 1. Oocyte donation cycles 2. PGD cycles
Interventions	1. Active comparator: IVM Receiving FSH (menotrophin (Menopur), Ferring) for 2 days on day 2/3 of the menstrual cycle (spontaneous/OCP administration) and an ultrasound scan will be performed subsequently. Oocytes retrieval will be performed 42 hours after the last injection. Prematuration will last for 24 to 30 hours. Intracytoplasmic sperm injection will be used for insemination. Freeze-only on day 3 and frozen embryo transfer will be performed on the subsequent cycle using HRT protocol with a maximum of 2 embryos transferred. 2. Active comparator: IVF Undergoing controlled ovarian hyperstimulation for IVF with rFSH (menotrophin (Menopur), Ferring) in GnRH antagonist protocol, treatment monitoring using ultrasound scans and blood tests. Gonadotrophin-releasing hormone agonist triggering will be used for final oocytes maturation. Intracytoplasmic sperm injection will be used for insemination. Freeze-only on day 3 and frozen embryo transfer will be performed on the subsequent cycle using HRT protocol with a maximum of 2 embryos transferred.
Outcomes	Primary outcome measure: ongoing pregnancy resulting in live birth resulting from the first embryo transfer of the started treatment cycle Secondary outcome measures: clinical pregnancy and foetal complications and characteristics
Starting date	Actual start date of study: 25 January 2018 Estimated primary completion date: 31 December 2019 Estimated study completion date: 30 June 2020
Contact information	Contact: Vu NA Ho, MD; +84935843336; email: bsvu.hna@myduchospital.vn Contact: Lan N Vuong, MD, PhD; +84903008889; email: drlan@yahoo.com.vn
Notes	Mỹ Đức Hospital Recruitment status: recruiting ClinicalTrials.gov identifier: NCT03405701

NCT03463772

Trial name or title	In vitro maturation versus standard in vitro fertilization in infertile patients diagnosed with polycystic ovaries syndrome: a study protocol for a single-center prospective, randomized controlled clinical trial
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	Ages eligible for study: 20 to 38 years Estimated enrolment: 350 participants Inclusion criteria: 1. Infertile couples scheduled for their first IVF cycle 2. Women diagnosed with PCOS 3. Voluntary participation and informed consent obtained Exclusion criteria: 1. Couple with contraindication for IVF or ICSI 2. Couples receiving donor sperm or donor eggs 3. Couples with indications or have plan to receive PGD and PGS 4. Sperm analysis diagnosed as azoospermia 5. Either male partner or female partner with an abnormal chromosome karyotype (chromosome polymorphisms were not included) 6. Women who have undergone unilateral ovariectomy
Interventions	Arm 1: IVM Controlled ovarian stimulation protocol will not performed in this group of participants. Transvaginal ultrasound scanning on natural cycle will be used to monitor the follicle size. Oocyte retrieval scheduled to take place once the endometrium reached at least 6 mm thickness and there was no follicle larger than 10 mm. After oocyte retrieval, the COCs will be cultured for 28 h to 32 h in special IVM media to obtain the matured oocytes. All the metaphase II oocytes will be inseminated by means of ICSI. All embryos will be cultured to blastocyst stage and vitrified. Arm 2: Standard IVF Ovarian stimulation will be performed by a standard protocol using GnRH-ant in association with rFSH and hCG. Oocyte retrieval is scheduled for 36 (±2) hours after hCG injection. The retrieved COC will be inseminated using ICSI or conventional IVF according to the semen analysis. All embryos will be cultured to blastocyst stage and vitrified.
Outcomes	Primary outcome measures: 1. Proportion of ongoing pregnancy leading to live birth Secondary outcome measures: 1. Implantation 2. Clinical pregnancy 3. Miscarriage 4. Preterm birth 5. Birth weight 6. Large for gestational age 7. Small for gestational age 8. Congenital anomaly 9. Perinatal mortality

NCT03463772 *(Continued)*	10.Foetal or neonatal death 11.Moderate/severe OHSS
Starting date	April 2018
Contact information	Contact 1: Xiaoying Zheng; 86-10-82265033; email: zheng_xiaoying@126.com Contact 2: Rui Yang; 86-10-82265080; email: yrjeff@126.com
Notes	This study is not yet open for participant recruitment. Peking University Third Hospital Beijing, Beijing, China, 100191 ClinicalTrials.gov identifier: NCT03463772

AFC: antral follicle count
ART: assisted reproductive technology
BMI: body mass index
COC: cumulus oocyte complexes

COH: controlled ovarian hyperstimulation
FSH: follicle-stimulating hormone

GnRH: gonadotrophin-releasing hormone
GnRH-ant: gonadotrophin-releasing hormone antagonist

hCG: human chorionic gonadotrophin
HRT: hormone replacement therapy

ICSI: intracytoplasmic sperm injection

IU: international units

IVF: in vitro fertilisation

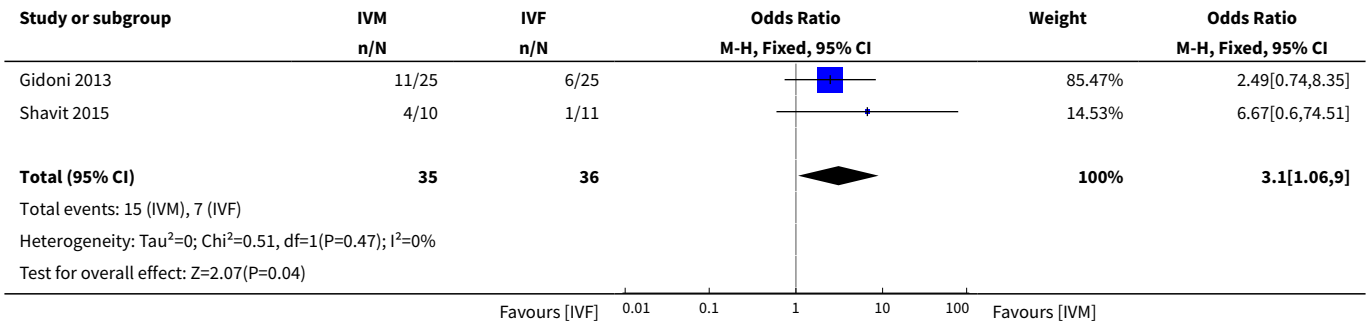
IVM: in vitro maturation
LEO: laparoscopic electrocoagulation of the ovaries
OCP: oral contraceptive pills
OHSS: ovarian hyperstimulation syndrome
PCOS: polycystic ovarian syndrome
PGD: pre-implantation genetic diagnosis
PGS: pre-implantation genetic screening
rFSH: recombinant follicle-stimulating hormone

DATA AND ANALYSES

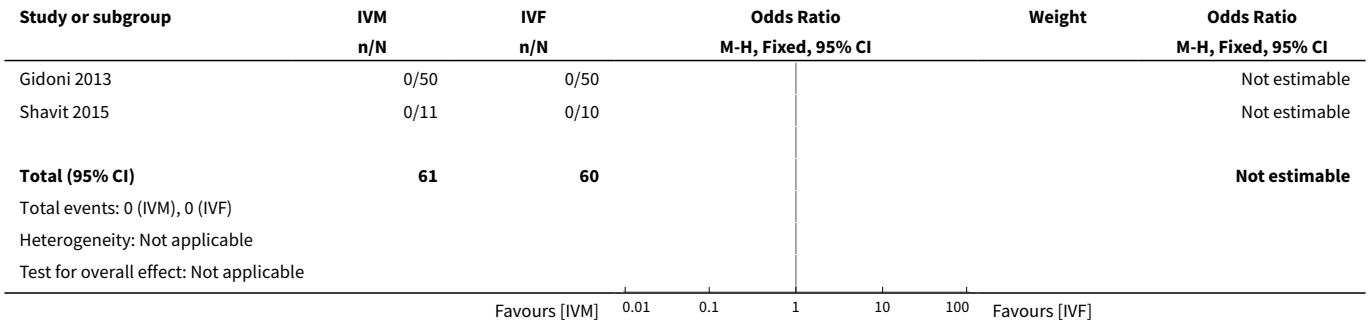
Comparison 1. In vitro maturation versus in vitro fertilisation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical pregnancy	2	71	Odds Ratio (M-H, Fixed, 95% CI)	3.10 [1.06, 9.00]
2 OHSS incidence	2	121	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 In vitro maturation versus in vitro fertilisation, Outcome 1 Clinical pregnancy.



Analysis 1.2. Comparison 1 In vitro maturation versus in vitro fertilisation, Outcome 2 OHSS incidence.



APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Specialised Register search strategy

Searched 17 April 2018

Procite Platform

Keywords CONTAINS "polycystic ovary syndrome" or "PCOS" or "anovulation" or "amenorrhea" or "amenorrhoea" or "ovarian dysfunction" or "ovarian failure" or "Oligo-amenorrhea" or "oligo-ovulation" or "oligoanovulatory "or "oligoamenorrhea" or "oligo-ovulatory" or Title CONTAINS "polycystic ovary syndrome" or "PCOS" or "anovulation" or "amenorrhea" or "amenorrhoea" or "ovarian dysfunction" or "ovarian failure" or "Oligo-amenorrhea" or "oligo-ovulation" or "oligoanovulatory" or "oligoamenorrhea" or "oligo-ovulatory"

AND

Keywords CONTAINS "IVM" or "in vitro maturation" or "in vivo maturation" or "oocyte immaturity" or "oocyte maturation" or "oocyte preparation techniques" or Title CONTAINS "IVM" or "in vitro maturation" or "in vivo maturation" or "oocyte immaturity" or "oocyte maturation" or "oocyte preparation techniques" (42 hits)

Appendix 2. CENTRAL via the Cochrane Central Register of Studies Online (CRSO) search strategy

Searched 17 April 2018

Web platform

#1 MESH DESCRIPTOR Polycystic Ovary Syndrome EXPLODE ALL TREES 975

#2 (polycystic adj5 ovar*):TI,AB,KY 2107

#3 (PCOS or PCOD):TI,AB,KY 1686

#4 leventhal:TI,AB,KY 20

#5 #1 OR #2 OR #3 OR #4 2313

#6 MESH DESCRIPTOR In Vitro Oocyte Maturation Techniques EXPLODE ALL TREES 10

#7 (in vitro adj5 matur*):TI,AB,KY 138

#8 IVM:TI,AB,KY 106

#9 (oocyte* adj5 matur*):TI,AB,KY 457

#10 (immatur* adj5 oocyte*):TI,AB,KY 87

#11 #6 OR #7 OR #8 OR #9 OR #10 594

#12 #5 AND #11 81

Appendix 3. MEDLINE search strategy

Searched 1946 to 17 April 2018

Ovid platform

1 Polycystic Ovary Syndrome/ (12649)

2 (polycystic adj5 ovar$).ti,ab,sh. (14233)

3 PCOS.ti,ab,sh. (9117)

4 PCOD.ti,ab,sh. (280)

5 (stein-leventhal or leventhal).tw. (715)

6 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw. (85)

7 or/1-6 (17100)

8 exp In Vitro Oocyte Maturation Techniques/ (902)

9 (in vitro adj5 matur$).tw. (10135)

10 IVM.tw. (2804)

11 (oocyte$ adj5 matur$).tw. (14095)

12 (immatur$ adj5 oocyte$).tw. (2268)

13 or/8-12 (20891)

14 7 and 13 (472)

15 randomized controlled trial.pt. (458772)

16 controlled clinical trial.pt. (92329)

17 Randomized Controlled Trials/ (115529)

18 Random allocation/ (93877)

19 Double-blind method/ (145297)

20 Single-blind method/ (25008)

21 or/15-20 (747335)

22 clinical trial.pt. (509690)

23 exp clinical trials/ (0)

24 (clin$ adj25 trial$).ti,ab,sh. (381378)

25 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh. (162568)

26 Placebos/ (33868)

27 placebo$.ti,ab,sh. (208237)

28 random$.ti,ab,sh. (1185005)

29 Research design/ (95889)

30 or/22-29 (1773035)

31 animal/ not (human/ and animal/) (4413998)

32 21 or 30 (1797409)

33 32 not 31 (1635933)

34 14 and 33 (87)

Appendix 4. Embase search strategy

Searched 1980 to 17 April 2018

Ovid platform

1 exp ovary polycystic disease/ (23246)

2 (polycystic adj5 ovar$).ti,ab,sh. (19704)

3 PCOS.ti,ab,sh. (13921)

4 PCOD.ti,ab,sh. (377)

5 (stein-leventhal or leventhal).tw. (566)

6 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw. (90)

7 or/1-6 (27066)

8 exp in vitro oocyte maturation/ (1258)

9 (in vitro adj5 matur$).tw. (12100)

10 IVM.tw. (3841)

11 (oocyte$ adj5 matur$).tw. (17294)

12 (immatur$ adj5 oocyte$).tw. (2841)

13 or/8-12 (25622)

14 7 and 13 (882)

15 Clinical Trial/ (964209)

16 Randomized Controlled Trial/ (495134)

17 exp randomization/ (77876)

18 Single Blind Procedure/ (31024)

19 Double Blind Procedure/ (145965)

20 Crossover Procedure/ (54970)

21 Placebo/ (309585)

22 Randomi?ed controlled trial$.tw. (179133)

23 Rct.tw. (28028)

24 random allocation.tw. (1767)

25 randomly.tw. (372435)

26 randomly allocated.tw. (29351)

27 allocated randomly.tw. (2307)

28 (allocated adj2 random).tw. (794)

29 Single blind$.tw. (20651)

30 Double blind$.tw. (181005)

31 ((treble or triple) adj blind$).tw. (765)

32 placebo$.tw. (266160)

33 prospective study/ (441083)

34 or/15-33 (2098780)

35 case study/ (53662)

36 case report.tw. (350881)

37 abstract report/ or letter/ (1032536)

38 or/35-37 (1428530)

39 34 not 38 (2050424)

40 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5940372)

41 39 not 40 (1911916)

42 14 and 41 (181)

Appendix 5. CINAHL search

Searched 1961 to 17 April 2018

EBSCO platform

#	Query	Results
S22	S5 AND S9 AND S21	8
S21	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	1,224,729
S20	TX allocat* random*	8,631
S19	(MH "Quantitative Studies")	19,277
S18	(MH "Placebos")	10,766
S17	TX placebo*	50,582
S16	TX random* allocat*	8,631
S15	(MH "Random Assignment")	46,926
S14	TX randomi* control* trial*	146,929
S13	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	950,538
S12	TX clinic* n1 trial*	223,249
S11	PT Clinical trial	86,215
S10	(MH "Clinical Trials+")	238,885
S9	S6 OR S7 OR S8	417
S8	TX (oocyte* N5 matur*)	229
S7	TX IVM	92
S6	TX (in vitro N5 matur*)	210
S5	S1 OR S2 OR S3 OR S4	3,238
S4	TX ovar* N1 (scelerocystic or degeneration)	6
S3	TX PCOS or TX PCOD	1,688
S2	TX polycystic N3 ovar*	2,737
S1	(MM "Polycystic Ovary Syndrome")	1,708

Appendix 6. ClinicalTrials.gov and WHO ICTRP search

From inception to 17 April 2018

Web platform

1 Polycystic Ovary Syndrome

2 PCOS

3 stein-leventhal or leventhal

4 In vitro adj matur$

5 IVM

6 In vitro maturation

Appendix 7. OpenGrey literature

From inception to 17 April 2018

Web platform

“IVM” and “PCOS”

WHAT'S NEW

Date	Event	Description
27 June 2018	New search has been performed	The review has been updated. Updating of the Background section adding new references Update of search of studies: eight studies were excluded, six ongoing studies, two included studies in the form of abstracts
27 June 2018	New citation required but conclusions have not changed	Conclusions not changed

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 1, 2009

Date	Event	Description
23 July 2013	New search has been performed	Update of studies and Methods; one study reported as a randomised controlled trial was excluded; three ongoing studies were found reporting no results; final conclusion not changed
23 July 2013	New citation required but conclusions have not changed	Update of Methods; still no studies available for inclusion
7 April 2011	New search has been performed	To be made stable
22 January 2008	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Contact author

CS Siristatidis: wrote the protocol and updated the review twice.

Co-review authors

Dr Abha Maheshwari: updated the protocol and made a major contribution to selection of studies.

Dr Dennis Vaidakis: made a major contribution in the last update in the selection of studies and writing of text.

Prof Siladitya Bhattacharya: initiated and corrected the protocol and the updates of the review.

All authors have agreed upon the final version of the review.

DECLARATIONS OF INTEREST

Charalampos S Siristatidis: no conflicts of interest to disclose.

Abha Maheshwari: no conflicts of interest to disclose.

Dennis Vaidakis: no conflicts of interest to disclose.

Siladitya Bhattacharya: no conflicts of interest to disclose.

SOURCES OF SUPPORT

Internal sources

- University of Aberdeen, UK.

  Assisted Reproduction Unit, University of Aberdeen UK.
- National and Kapodistrian University of Athens, Greece.

  Assisted Reproduction Unit, Third Department of Obstetrics and Gynecology

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update, we moved the outcome of "miscarriage" from the secondary to the primary outcomes and defined it as "per clinical pregnancy".

NOTES

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pregnancy Rate; Fertilization in Vitro [*methods]; In Vitro Oocyte Maturation Techniques [*methods]; Infertility, Female [*etiology]; Oocyte Retrieval [*methods]; Polycystic Ovary Syndrome [*complications]; Randomized Controlled Trials as Topic; Sperm Injections, Intracytoplasmic

MeSH check words

Female; Humans; Pregnancy