Comparative Effectiveness Review
Number 217

Management of Infertility

Evidence Summary

Background

Condition and Therapeutic Strategies

"Infertility" has traditionally been defined as failure to achieve pregnancy after 12 months of regular unprotected intercourse with the same partner (or after 6 months for women greater than 35 years of age). However, as many as half of such couples will conceive without intervention over the next 12-24 months. Because of this, the term "subfertility" is preferred by many.[1] From a population perspective, couples who meet the dichotomous criteria for "infertility" include couples who are "normal" but who are in the upper end of the population distribution for "time to pregnancy," and couples who have a physiological or anatomical cause for a prolonged time to pregnancy. However, to be concise, we will use the term "infertility" throughout this report.

Self-reported infertility in the United States, using the 12-month definition, affected approximately 6 percent of married women aged 15-44 in the 2006-2010 National Survey of Family Growth (the most recent available data).[2] In one population-based study, approximately 10 percent of pregnant women reported receiving infertility treatment, with 29 percent of these women using fertility-enhancing medications; 21 percent using assisted reproductive technology (ART),

Purpose of Review

Evaluate the comparative effectiveness and safety of treatments for common causes of infertility.

Key Messages

- The ability to compare the effectiveness of treatments would be enhanced by greater consistency in reporting of outcomes, particularly live birth rates, as well as reporting of diagnosis-specific outcomes for treatments, such as assisted reproductive technology, that are used for multiple diagnoses.
- Letrozole most likely results in more live births with lower multiple births than clomiphene alone in women with polycystic ovary syndrome.
- For women with unexplained infertility, there is most likely shorter time to pregnancy for women with immediate in vitro fertilization (IVF) than for those who undergo other treatments prior to IVF. For the outcomes of live birth, multiple births, ectopic pregnancy, miscarriage, low birthweight, and ovarian hyperstimulation syndrome however, there may be no difference between the two groups.
- Across all diagnoses, elective single-embryo transfer results in slightly lower live birth rates but substantially lower reductions in multiple birth rates than multiple-embryo transfer.

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including in vitro fertilization (IVF); 15 percent using artificial insemination with fertility-enhancing drugs; and 23 percent using other treatments, including surgery.[3] Other estimates of the prevalence of infertility treatment are similar.[4-8] Particularly in the United States, where availability of infertility services is variable depending on a number of factors, particularly insurance coverage, utilization of infertility treatments may underestimate the overall burden of infertility.

The most common demographic factor associated with female infertility is "advanced reproductive age," although the probability of pregnancy begins to decline by the mid-20's, the slope of decline sharply increases by age 35.[9] Other common causes of female infertility include polycystic ovary syndrome (PCOS), endometriosis, occlusion of the fallopian tubes from prior infectious disease,6 and infertility secondary to cancer treatment.[10-12] Isolated male factor infertility affects approximately 17 percent of couples seeking treatment, with 34.6 percent of couples having both male and female diagnoses.[13]

Treatment options are usually dependent on the underlying etiology of infertility. For female causes, options include surgical management of tubal occlusion, surgical treatment of endometriosis, ovarian "drilling" for treatment of PCOS, use of ovulation-induction agents including oral (clomiphene citrate or letrozole) and injected drugs (gonadotropins), artificial insemination with either partner or donor sperm (depending on partner fertility status), and ART, which includes both traditional IVF (fertilization of the egg by the sperm occurs without direct manipulation) and IVF with intra-cytoplasmic sperm injection (ICSI) (fertilization occurs via direct injection of sperm into the egg).[14,15] Treatment options for male factor infertility include medical treatment of a diagnosed endocrinopathy or other conditions affecting sperm production, empiric treatments with hormonal or other agents, surgical management of varicocele, intrauterine insemination, IVF, ICSI, or use of donor sperm.[16] Options appropriate for some diagnoses (e.g., ovulation induction in PCOS or unexplained infertility) may not be appropriate for others (e.g., women with documented tubal occlusion). In other cases, the appropriate comparisons may involve sequencing or combinations of treatment options—for example, one strategy might consist of several cycles of ovulation induction, followed by ART only if pregnancy does not occur, compared to proceeding directly to ART. Note that throughout this report, we use the term "adjunct treatments" to refer to interventions performed within a major treatment category (for example, comparison of metformin to placebo as pretreatment in women with PCOS undergoing IVF).

Although there has been ongoing debate about the most appropriate outcome for evaluation of infertility treatments, there is a growing consensus that live birth is the most important patient-centered outcome.[17,18] Trade-offs between outcomes (particularly multiple gestations), time to pregnancy, and out-of-pocket costs might be different between the various treatment strategies even if cumulative live birth rates were identical.

Different treatments also carry different safety risks. There are known short-term risks such as ovarian hyperstimulation syndrome (OHSS) or acute risks associated with any surgery. Surgery may have additional longer-term risks which may affect subsequent fertility (such as scarring or decreased ovarian reserve with procedures such as laparoscopic ovarian drilling (LOD). The literature suggests that observed associations between infertility treatment and female reproductive cancers, particularly ovarian cancer, are likely the result of the underlying infertility rather than treatment itself. There is, however, some uncertainty surrounding some cancer outcomes in subgroups of patients.[19-21]

Some adverse pregnancy outcomes, such as preterm birth, are associated with infertility treatment; however, many of the conditions associated with infertility are also associated with

these adverse outcomes, complicating assessment of comparative effectiveness.[22-25] There may also be direct effects of some treatments that have unclear implications for long-term health in children born after these treatments.[26,27] Finally, infertility clearly has an emotional impact,[12,28,29] and the comparative effects of infertility treatments on quality of life are an important consideration for both women and men.

There may be significant variation in outcomes of different treatments in specific subpopulations. For example, age affects the likelihood of conception, and the risk of many pregnancy complications associated with infertility treatments, such as preterm birth or low birthweight, are also increased with higher maternal age. Obesity is common in women with PCOS, and, like older maternal age, is also associated with adverse pregnancy outcomes independent of its association with infertility. The utilization and outcomes of infertility treatment differ among different racial and ethnic groups, even after adjusting for insurance coverage.[30-33]

Finally, a unique subpopulation is women who donate oocytes for use by other couples in ART. There are almost no data on the long-term safety of multiple courses of ovulation induction for the purposes of oocyte donation.[34] In addition, there are complex ethical and legal considerations, including the balance between fair compensation and inducement,[35] and sharing information about donors with recipients.[36]

Scope and Key Questions

This systematic review evaluates the comparative safety and effectiveness of available treatment strategies for women of reproductive age (18–44) who are infertile due to PCOS, endometriosis, unknown reasons, or tubal or peritoneal factors; the comparative safety and effectiveness of available treatment strategies for couples with male factor infertility; and the short- and long-term health outcomes of donors in infertility.

The specific Key Questions (KQs) addressed in this review are listed below, and Figure A displays the analytic framework that guided our work.

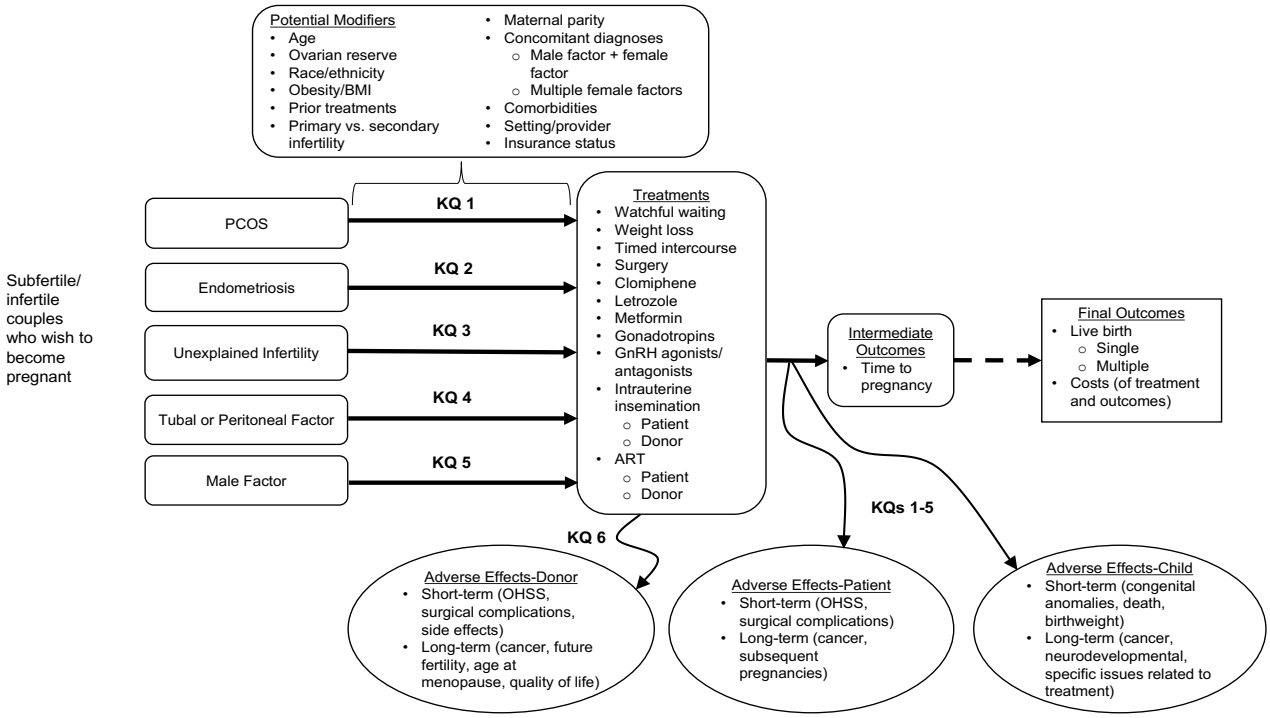
- KQ 1. What are the comparative safety and effectiveness of available treatment strategies for women with polycystic ovary syndrome who are infertile and who wish to become pregnant?
  - KQ 1a. Does the optimal treatment strategy vary by patient characteristics such as age, ovarian reserve, race, body mass index (BMI), presence of other potential causes of female infertility, or presence of male factor infertility?
- KQ 2. What are the comparative safety and effectiveness of available treatment strategies for women with endometriosis who are infertile and who wish to become pregnant?
  - KQ 2a. Does the optimal treatment strategy vary by patient characteristics such as age, ovarian reserve, race, BMI, stage of endometriosis, presence of other potential causes of female infertility, or presence of male factor infertility?
- KQ 3. What are the comparative safety and effectiveness of available treatment strategies for women who are infertile for unknown reasons and who wish to become pregnant?
  - KQ 3a. Does the optimal treatment strategy vary by patient characteristics such as age, ovarian reserve, race, BMI, presence of other potential causes of female infertility, or presence of male factor infertility?
- KQ 4. What are the comparative safety and effectiveness of available treatment strategies for women with tubal or peritoneal factors (e.g., pelvic adhesions) who are infertile and who wish to become pregnant?

- KQ 4a. Does the optimal treatment strategy vary by patient characteristics such as age, ovarian reserve, race, BMI, presence of other potential causes of female infertility, or presence of male factor infertility?

- KQ 5. What are the comparative safety and effectiveness of available treatment strategies for couples with male factor infertility and no evidence of an underlying diagnosis associated with infertility in the female partner?
  - KQ 5a. Does the optimal treatment strategy vary by characteristics in either partner such as age, ovarian reserve, race, or BMI?

- KQ 6. What are the short- and long-term health outcomes of donors in infertility?
  - KQ 6a. For female oocyte donors:
    1. Do specific aspects of the pre-donation evaluation identify potential donors at greater risk for short- or long-term adverse outcomes (e.g., OHSS, quality-of-life issues)?
    2. Do short- and long-term outcomes differ among different stimulation/retrieval protocols?
  - KQ 6b. For male semen donors:
    - Are there long-term health, quality-of-life, or other adverse outcomes associated with donation?

Figure A. Analytic framework



Abbreviations: ART=assisted reproductive technology; BMI=body mass index; GnRH=gonadotropin-releasing hormone; KQ=Key Question; OHSS=ovarian hyperstimulation syndrome; PCOS=polycystic ovary syndrome

Methods

Detailed methods are available in the full report and the posted protocol (http://effectivehealthcare.ahrq.gov/index.cfm).

Literature Search Strategy

To identify relevant published literature, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews, limiting the searches to studies conducted in adults and published from January 1, 2007, to October 3, 2018. Selection of the 2007 start date was based on establishing a one-year overlap with the search dates from a previous Agency for Healthcare Research and Quality (AHRQ) evidence report that assessed ART[37] and input from Key Informants, who felt that the previous AHRQ review and more recent existing Cochrane reviews in this topic area would identify relevant high-quality studies. An experienced search librarian guided all searches. The exact search strings used are given in Appendix A of the full report.

We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles. The reference lists for identified pivotal articles were manually hand-searched and cross-referenced against our database, and additional relevant articles not already under consideration were retrieved for screening. All citations were imported into an electronic bibliographical database (EndNote® Version X7; Thomson Reuters, Philadelphia, PA).

As a mechanism to ascertain publication bias in recent studies, we searched ClinicalTrials.gov to identify completed but unpublished studies (we also explored the possibility of publication bias in any quantitative synthesis of the included literature through meta-analysis techniques).

Approaches to identifying relevant gray literature included notification through the Federal Register to stakeholders, such as drug and device manufacturers, of the opportunity to submit scientific information packets. We also searched the ClinicalTrials.gov study registry and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal to identify potentially relevant study records, and subsequently searched for relevant articles from completed studies.

We specified our inclusion and exclusion criteria based on the PICOTS (populations, interventions, comparators, outcomes, timing, and settings) identified for each question. For citations retrieved from PubMed, Embase, and the Cochrane Database of Systematic Reviews, two reviewers independently screened each title and abstract for potential relevance to the research questions using prespecified inclusion/exclusion criteria. Articles included by either reviewer underwent full-text screening. Articles meeting eligibility criteria at the full-text stage were included for data abstraction. Based on their clinical and methodological expertise, a pair of researchers were assigned to abstract data from each of the eligible articles. One researcher abstracted the data, and the second over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus could not be reached.

Risk of Bias Assessment of Individual Studies

We assessed methodological quality, or risk of bias, for each individual study using a components approach, assessing each study for specific aspects of design or conduct (such as allocation concealment for randomized controlled trials (RCTs), or use of methods to address potential confounding), as detailed in AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[38] Briefly, we rated each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies. For each study, one investigator assigned a summary quality rating, which was then

reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached.

We also rated quality for identified systematic reviews to provide additional context for the findings of the included studies. Rating was performed using AMSTAR (A Measurement Tool to Assess the Methodological Quality of Systematic Reviews).[39] For each study, one investigator assigned a summary quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached. Reviews were then assigned overall quality scores of good (low risk of bias), fair (moderate risk of bias), or poor (high risk of bias). The consistency of the findings from these systematic reviews were incorporated in to our strength of evidence ratings as described below.

Data Synthesis

We began by summarizing key features of the included studies for each KQ. To the degree that data are available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes. If not reported, 95-percent confidence intervals for dichotomous outcomes (e.g., live birth rates) were calculated from the numbers provided in the study.

We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis, decision analysis, or simulation model). For a meta-analysis, feasibility depends on the volume of relevant literature (requiring at least three relevant studies), conceptual homogeneity of the studies (similar intervention comparisons and outcome definitions), completeness of the reporting of results, and the adequacy and completeness of any existing meta-analyses.

Strength of the Body of Evidence

We graded the strength of evidence (SOE) for each outcome assessed using the approach described in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[38,40,41] We also explored the consistency of our findings with recent systematic reviews and discussed agreement or disagreement, along with possible causes for disagreement and impact on strength of evidence ratings, in the results. A summary rating of high, moderate, or low strength of evidence was assigned for each outcome after discussion by two reviewers. When no evidence was available, or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn, a grade of "insufficient" was assigned. This four-level rating scale consisted of the following definitions:

- High Strength of Evidence—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable; i.e., another study would not change the conclusions.
- Moderate Strength of Evidence—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low Strength of Evidence—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient Strength of Evidence—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.

Results

We briefly summarize the results of our literature searches, description of included studies, key points, and strength of evidence for each KQ. Note we only list here comparisons and outcomes with strength of evidence rated as low, moderate, or high. Full findings are available in the full report.

Summary of Studies

The literature search yielded 17,391 citations. In total, 1,909 studies were screened in full text, in which 1,748 were excluded for reasons listed in Figure 2 and Appendix D in the full report. We identified 161 articles describing 151 unique studies. The relationship of studies to the review questions is as follows: 56 studies relevant to KQ 1, 7 studies relevant to KQ 2, 50 studies relevant to KQ 3, 8 studies relevant to KQ 4, 23 studies relevant to KQ 5, and 5 studies relevant to KQ 6 (some studies were relevant to more than one KQ). There were also 21 studies relevant to findings across all KQs.

Key Question 1. PCOS

We identified 61 articles[42-102] describing 56 studies that addressed the comparative safety and effectiveness of available treatment strategies for infertility in women with PCOS.

Key findings for outcomes in couples where the primary cause of infertility is PCOS include:

- Letrozole has a higher live birth rate than clomiphene citrate alone and lower multiple births, with no difference in ectopic pregnancy, or miscarriage (moderate for all outcomes), low birthweight, or time to pregnancy (low SOE for both these outcomes).
- Clomiphene citrate does not result in higher live birth rates compared with metformin (moderate SOE). Differences are also not found in the rates of multiple birth, ectopic pregnancy, or time to pregnancy (low SOE for all outcomes). There is a higher rate of miscarriage with combination clomiphene and metformin than clomiphene alone (low SOE)
- Letrozole or letrozole and berberine have a higher live birth rate than berberine alone (low SOE) with no difference in multiple births, miscarriage, or low birthweight rates (low SOE)
- There was no difference between clomiphene and tamoxifen for the outcomes of live birth or miscarriage (low SOE)
- There was no difference between laparoscopic ovarian drilling (LOD) and oral agents for live birth (moderate SOE) or miscarriage rates (low SOE). Multiple births were reduced given LOD (moderate SOE).
- Live birth (low SOE) and miscarriage rates (moderate SOE) did not differ between IVF treatment strategies.
- There was no difference in live birth rates for women who underwent lifestyle modification in combination with IVF compared with IVF alone (moderate SOE)
- There was no difference between type 1 diabetes mellitus diagnoses in children conceived with ART compare to children conceived with no fertility treatment (moderate SOE)
- As with other indications for IVF, use of single-embryo transfer is associated with slightly lower live birth rates but significantly reduced multiple gestation rates (low SOE)

In general, SOE was judged insufficient or low for most outcomes, with the a few exceptions including live births with the use of letrozole versus clomiphene or oral agents versus surgical management, and miscarriage between clomiphene and metformin or oral agents and surgical management which were rated moderate SOE. A common limitation across all comparisons was lack of precision for estimates of rare but important harms such as OHSS or surgical complications (Table A).

Table A. Summary of strength of evidence for major outcomes—KQ 1 (PCOS)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
Oral agents alone: Letrozole vs. Berberine vs. Berberine + Letrozole	Live birth (any/ patient)	1 RCT[81] (644)	**Improvement**: Letrozole or letrozole and berberine increase live birth rates compared to berberine alone.	Low (Imprecise, 1 study)
	Pregnancy complications: Multiple births	1 RCT[81] (644)	**No difference**: No significant difference between letrozole, berberine, or combination therapy	Low (Imprecise, 1 study
	Pregnancy complications: Miscarriage	1 RCT[81] (644)	**No difference**: No significant difference between letrozole, berberine, or combination therapy	Low (Imprecise, 1 study
	Neonatal outcomes: Birthweight	1 RCT[81] (644)	**No difference**: No significant difference between letrozole, berberine, or combination therapy	Low (Imprecise, one study
Oral agents alone: Letrozole vs. Clomiphene	Live birth (any/ patient)	2 RCTs[44,85] (909) 1 SR (9 studies, 1783 patients)[103]	**Improvement**: Letrozole has higher live birth rates than clomiphene.	Moderate (Imprecise)
	Pregnancy complications: Multiple births	3 RCTs[44,76,85] (886) 1 SR (11 studies, 2385 patients)[103]	**Improvement**: Letrozole has lower rates of multiple birth compared to clomiphene	Moderate (Inconsistent)
	Pregnancy complications: Ectopic pregnancy	3 RCTs[44,76,85] (886)	**No difference**: No difference between letrozole and clomiphene.	Moderate (Imprecise)
	Pregnancy complications: Miscarriage	3 RCTs[44,76,85] (886) 1 SR (12 studies, 2385 patients)[103]	**No difference**: No statistical difference between letrozole and clomiphene	Moderate (Imprecise)
	Neonatal outcomes: Birthweight	1 RCT[44] (750)	**No difference**: No significant difference in birthweight between letrozole and clomiphene	Low (1 study)
	Time to pregnancy	1 RCT[44] (750)	**No difference**: No significant difference in time to pregnancy between clomiphene vs. letrozole	Low (1 study)

Table A. Summary of strength of evidence for major outcomes—KQ 1 (PCOS) (continued)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
Oral agents alone: Clomiphene vs. Metformin vs. Metformin + Clomiphene	Live birth (any/ patient)	3 RCTs[53,72,79] (842) 2 SRs (3 studies, 912 patients[104]); (9 studies, 1079 patients[105])	**No difference**: No statistical difference between clomiphene and metformin or between clomiphene and combination therapy of metformin and clomiphene	Moderate (Suspected reporting bias)
	Pregnancy complications: Multiple births	3 RCTs[63,70,72] (921) 1 SR[105] (9 studies, 1079 patients)	**No difference**: No differences in multiple birth rates between clomiphene alone, metformin alone, and clomiphene plus metformin	Low (Imprecise, suspected reporting bias)
	Pregnancy complications: Ectopic pregnancy	3 RCTs[70,72,79] (1,005)	**No difference**: No difference between studied oral agents. Very few ectopic pregnancies overall.	Low (Imprecise findings with moderate study limitations)
	Pregnancy complications: Miscarriage	3 RCTs[63,70,72,79] (817) 1 SR[105] (9 studies, 1079 patients)	**Increase**: Higher rate of miscarriage in the combined therapy group (clomiphene and metformin) compared to clomiphene alone	Low (Suspected reporting bias, imprecise)
	Time to Pregnancy	1 RCT[53] (343)	**No difference**: No significant difference in time to pregnancy between clomiphene vs. metformin	Low (1 study)
Oral agents alone: Clomiphene vs. Tamoxifen	Live birth (any/ patient)	1 RCT[99] (88) 1 SR[106] (2 studies, 195 women)	**No difference**: No significant difference in live birth rates between tamoxifen and clomiphene	Low (Imprecise)
	Pregnancy complications: Miscarriage	1 RCT[99] (88) 1 SR[106] (2 studies, 195 women)	**No difference**: No significant difference in miscarriage rates between tamoxifen and clomiphene	Low (Iimprecise)

Table A. Summary of strength of evidence for major outcomes—KQ 1 (PCOS) (continued)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
Active Acupuncture + Clomiphene vs. Control Acupuncture + Clomiphene vs. Active Acupuncture + Placebo vs. Control Acupuncture + Placebo	Live birth	1 RCT[96] (1000)	**Improvement**: Live birth rates significantly higher for clomiphene vs. placebo; not significantly different for active vs. control Acupuncture	Low (1 study with potential risk of bias)
	Pregnancy complications: Ectopic pregnancy	1 RCT[96] (1000)	**No difference**: no significant difference in ectopic pregnancy rates between oral agents and acupuncture strategies.	Low (1 study with potential risk of bias)
	Pregnancy complications: Miscarriage	1 RCT[96] (1000)	**No difference**: no significant difference in miscarriage rates between oral agents and acupuncture strategies.	Low (1 study with potential risk of bias)
	Neonatal outcomes: Congenital Abnormalities	1 RCT[96] (1000)	**No difference**: no significant difference in congenital abnormality rates between oral agents and acupuncture strategies.	Low (1 study with potential risk of bias)
	Neonatal Death	1 RCT[96] (1000)	**No difference**: no significant difference in neonatal death rates between oral agents and acupuncture strategies.	Low (1 study with potential risk of bias)
Oral agents alone vs. LOD	Live birth (any/patient)	1 SR[107] (8 studies, 1,034 women)	**No difference**: No statistically significant differences between LOD and oral agents	Moderate (Suspected reporting bias)
	Pregnancy complications: Multiple births	1 SR[107] (15 studies, 1,129 women)	**Reduction**: There was a reduction in multiple births given LOD as compared to oral agents	Moderate (Suspected reporting bias)
	Pregnancy complications: Miscarriage	1 RCT[97] (80) 1 SR[107] (15 studies, 1,592 women)	**No difference**: No significant differences in miscarriage between LOD and oral agents	Low (Imprecise, suspected reporting bias)
Clomiphene citrate vs. low-dose FSH	Pregnancy complications: Ectopic pregnancy	3 RCTs[54,82,95] (1072)	**No difference**: Ectopic pregnancy rate did not differ between FSH and clomiphene strategies.	Low (Imprecise)

Table A. Summary of strength of evidence for major outcomes—KQ 1 (PCOS) (continued)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
Lifestyle modifications + IVF vs. IVF alone	Live birth	3 RCTs[75,78,87] (1688)	**No difference**: No difference in live birth rates for women who underwent lifestyle modification in combination with IVF compared with IVF alone	Moderate
ART IVF: GnRH agonist +/- IVF vs. GnRH antagonist +/- IVF	Live birth (cycle)	4 RCTs[48,52,68,71] (408)	**No difference**: No significant difference in included studies but varying interventions and comparators with low numbers of live birth	Low (Imprecise findings with moderate study limitations)
	Pregnancy complications: Miscarriage	3 RCTs[68,71,77] (279)	**No difference**: No differences in miscarriage rates for GnRH agonist vs. antagonist, or hCG medium, hCG-free medium with transfer, and hCG-free medium without transfer.	Moderate (Imprecise findings with moderate study limitations)
ART IVF: Fresh vs. Frozen Embryos in IVF for PCOS	Live birth (any/ cycle)	1 RCT[80] (1508)	**Improvement**: Live birth rates were significantly higher with frozen embryo transfer compared to fresh embryos	Low (1 study)
	Pregnancy complications: Multiple births	1 RCT[80] (1508)	**No difference**: No difference in multiple births with fresh versus frozen embryo transfer	Low (1 study)
	Pregnancy complications: Ectopic pregnancy	1 RCT[80] (1508)	**Reduction**: Ectopic pregnancies were reduced with frozen embryo transfer	Low (1 study)
	Pregnancy complications: Miscarriage	1 RCT[80] (1508)	**Reduction**: Miscarriages were reduced with frozen embryo transfer	Low (1 study)
	Neonatal Outcomes: Congenital abnormalities	1 RCT[80] (1508)	**No difference**: No difference congenital abnormalities with fresh versus frozen embryo transfer	Low (1 study)
	Neonatal Death	1 RCT[80] (1508)	**No difference**: No difference neonatal deaths with fresh versus frozen embryo transfer	Low (1 study)

Table A. Summary of strength of evidence for major outcomes—KQ 1 (PCOS) (continued)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
ART vs. no infertility treatment	Long-term outcomes: Child (type 1 diabetes mellitus)	1 Obs[90] (565,116 pregnancies)	No difference: No significant difference found between type 1 diabetes mellitus diagnoses in children born to patients with PCOS infertility conceived with ART compared to children conceived with no fertility treatment	Moderate (Imprecise)

[a]Criteria for downgrading strength of evidence is described as Rationale; when these criteria are insufficient for understanding the final strength of evidence, additional explanation is provided.

Abbreviations: ART=assisted reproductive technology; GnRH=gonadotropin-releasing hormone; hCG=human chorionic gonadotropin; IVF=in vitro fertilization; KQ=Key Question; LOD=laparoscopic ovarian drilling/diathermy; Obs=observational study; PCOS=polycystic ovary syndrome; RCT=randomized controlled trial; SR=systematic review

Key Question 2. Endometriosis

We identified seven individual studies that addressed infertility treatment for women with endometriosis.[91,92,108-112]

Key findings for couples where the primary cause of infertility is endometriosis in the female partner included:

- As with other indications for IVF, use of single-embryo transfer is associated with slightly lower live birth rates but significantly reduced multiple gestation rates (low SOE)
- The live birth rate per cycle was higher in couples who underwent ART than those who used intrauterine insemination (IUI) (low SOE)
- SOE was rated insufficient for all other comparisons/outcomes.

In general, the SOE across all outcomes was judged to be insufficient or low, primarily due to imprecision and small numbers of studies, especially for both short-term harms (such as OHSS) (Table B).

Table B. Summary of strength of evidence for major outcomes—KQ 2 (endometriosis)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
ART: IVF/ICSI vs. no treatment	Live birth	1 Obs[111] (69,028 cycles)	**Improvement**: For women with endometriosis, the live birth rate per cycle was higher in couples who underwent 2 embryo transfer (51.5%) as compared with single embryo transfer (46.6%) (p<0.0001)	Low (Imprecise)
IUI vs. ART	Live birth	1 Obs[92] (19,884)	**Improvement**: For women with endometriosis, the live birth rate per cycle was higher in couples who underwent ART than those who used IUI	Low (1 study)

[a]Criteria for downgrading strength of evidence is described as Rationale; when these criteria are insufficient for understanding the final strength of evidence, additional explanation is provided.

Abbreviations: ART=assisted reproductive technology; ICSI=intra-cytoplasmic sperm injection; IUI=intrauterine insemination; IVF=in vitro fertilization; KQ=Key Question; Obs=observational study

Key Question 3. Unexplained Infertility

We identified 50 individual studies that met inclusion criteria for KQ 3 and had unexplained infertility (infertility with no other documented female or male diagnosis).[75,91,92,111,113-158]

Key findings for couples with unexplained infertility included:

- There is no difference between the oral agents of letrozole and anastrozole for the outcome of ectopic pregnancy (low SOE) but evidence is insufficient for other outcomes of interest.
- There is no difference between letrozole and clomiphene for outcomes of multiple births or miscarriage (moderate SOE).
- There is no difference between differing adjunct treatments used in combination with oral agents and IUI for the outcomes of live birth, miscarriage, and OHSS (low SOE for all outcomes).
- There are no differences between immediate IVF versus other treatments prior to IVF for the outcomes of live birth, multiple births, ectopic pregnancy, miscarriage, low birthweight, and OHSS (low SOE for all outcomes). There is however shorter time to pregnancy with immediate IVF (moderate SOE).
- As with other indications for IVF, use of single-embryo transfer is associated with slightly lower live birth rates but significantly reduced multiple gestation rates (low SOE)

SOE for most outcomes was judged to be insufficient or low, primarily because of imprecision or small numbers of studies of fair quality. Two exceptions were multiple births and miscarriages for oral agents without IUI where an existing systematic review existed, and time to pregnancy between different strategies for sequencing treatment, where precision was reasonable. In both cases SOE for these outcomes was judged to be moderate (Table C).

Table C. Summary of strength of evidence for major outcomes—KQ 3 (unexplained infertility)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
Oral Agents Without IUI	Pregnancy complications: Ectopic pregnancy	2 RCTs[132,157] (1,168)	**No difference**: No difference between letrozole and anastrozole:	Low (Moderate study limitations)
	Pregnancy complications: Multiple births	1 SR[159] (5 studies, 395 patients)	**No difference**: No difference between letrozole and clomiphene citrate	Moderate
	Pregnancy complications: Miscarriage	3 RCTs[113,132,157] (1,248) 1 SR[159] (5 studies, 395 patients)	No difference: No difference between letrozole and clomiphene citrate	Moderate
Clomiphene Citrate vs. Expectant Management	Pregnancy complications: Ectopic Pregnancy	2 RCTs[136,149] (781)	**No difference**: No significant difference in ectopic pregnancy rates between clomiphene and expectant management	Low (Imprecise, heterogeneous interventions)
	Pregnancy complications: Miscarriage	2 RCTs[136,149] (781)	**No difference**: No significant difference in ectopic pregnancy rates between clomiphene and expectant management	Low (Imprecise, heterogeneous interventions)
Oral Agents vs. Unstimulated IUI vs. Expectant Management	Live birth	1 SR[160] (3 studies, 370)	**Improvement**: A significant increase in live births was found for women treated with IUI and ovarian hyperstimulation compared to women treated with IUI only	Low (Inconsistent)
Adjunct Treatments with Oral Agents and IUI	Live birth	5 RCTs[124,130,140,153,156] (1859)	**No difference**: No difference between adjunct treatments with oral agents and IUI	Low (Moderate study limitations)
	Pregnancy complications: Miscarriage	5 RCTs[130,138,142,143,156] (1859)	**No difference**: No difference between adjunct treatments with oral agents and IUI	Low (Moderate study limitations)
	Short term adverse effects of treatment: OHSS	3 RCTs[124,138,156] (1189)	**No difference**: No difference between adjunct treatments with oral agents and IUI	Low (Moderate study limitations)

Table C. Summary of strength of evidence for major outcomes—KQ 3 (unexplained infertility)(continued)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
Oral Agents With IUI vs. Gonadotropins With IUI	Pregnancy complications: Miscarriage	3 RCTs[144,152,155] (1,654)	**No difference**: No difference between oral agents with IUI versus gonadotropins with IUI	Low (Imprecise)
	Pregnancy complications: Multiple births	1 RCT[144] (742)	**Increased risk**: Greater multiple gestations with gonadotropins compared to either clomiphene or letrozole	Low (one study)
Immediate IVF vs. Other Treatments Prior to IVF	Live birth	3 RCTs[118,120,131,151] (812)	**No difference**: Live birth does not differ between differing strategies of other treatments prior to IVF	Low (Imprecise)
	Pregnancy complications: Multiple births	2 RCTs[118,131] (657)	**No difference**: No significant difference between other treatments prior to IVF and immediate IVF.	Low (Imprecise)
	Pregnancy complications: Ectopic pregnancy	3 RCTs[118,120,131,151] (812)	**No difference**: No significant difference between other treatments prior to IVF and immediate IVF.	Low (Imprecise)
	Pregnancy complications: Miscarriage	3 RCTs[118,120,131,151] (812)	**No difference**: No significant difference between other treatments prior to IVF and immediate IVF.	Low (Imprecise)
	Neonatal outcomes: Birthweight	2 RCTs[118,131] (657)	**No difference**: No significant difference between other treatments prior to IVF and immediate IVF.	Low (Imprecise)
	Time to pregnancy	2 RCTs[118,131] (657)	**Reduction**: Shorter time to pregnancy with immediate IVF compared with other treatments prior to IVF	Moderate
	Short term adverse effects of treatment: OHSS	2 RCTs[118,131] (657)	**No difference**: No significant difference between other treatments prior to IVF and immediate IVF.	Low (Imprecise)
ART: IVF vs. ICSI	Neonatal outcomes: Birth weight	1 Obs[91] (90,401 cycles)	**No difference**: No significant differences in rates of r low birth weight between ICSI versus conventional-IVF cycles	Low (1 study with moderate study limitations)

Table C. Summary of strength of evidence for major outcomes—KQ 3 (unexplained infertility)(continued)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
ART: Unspecified	Long-term outcomes: Child (cancer)	1 Obs[121] (33,840)	**No difference**: The overall cancer incidence was not elevated in children born after assisted conception for unexplained infertility.	Low (Moderate study limitations)

[a]Criteria for downgrading strength of evidence is described as Rationale; when these criteria are insufficient for understanding the final strength of evidence, additional explanation is provided.

Abbreviations: ART=assisted reproductive technology; ICSI=intra-cytoplasmic sperm injection; IUI=intrauterine insemination; IVF=in vitro fertilization; KQ=Key Question; Obs=observational study; RCT=randomized controlled trial

Key Question 4. Tubal and Peritoneal Factor Infertility

We identified eight individual studies[90,91,111,161-165] that addressed outcomes after treatment for tubal or peritoneal factor infertility.

Key findings for patients with tubal or peritoneal factor infertility included:

- As with other indications for IVF, use of single-embryo transfer is associated with slightly lower live birth rates but significantly reduced multiple gestation rates (low SOE)
- The live birth rate was lower in women undergoing ICSI as compared to conventional IVF (low SOE)
- There was no difference between type 1 diabetes mellitus diagnoses in children born to patients with tubal factor infertility conceived with ART compared to children conceived with no fertility treatment (moderate SOE)
- SOE was rated insufficient for all other comparisons/outcomes.

The SOE was judged to be insufficient for most outcomes primarily due to imprecision based on few studies meeting our inclusion criteria (Table D).

Table D. Summary of strength of evidence for major outcomes—KQ 4 (tubal and peritoneal factor infertility)

Comparison	Outcome	Study Design and Sample Size	Conclusion	Strength of Evidence (Rationale)[a]
ART: 2-embryo transfer vs. 1-embryo transfer	Live birth (patient)	1 Obs[111] (69,028 cycles)	**Improvement**. The live birth rate per cycle was higher in couples who underwent 2 embryo transfer as compared with single embryo transfer	Low (Imprecise)
ART: IVF+ICSI vs. IVF	Neonatal outcomes: Birth weight	1 Obs[91] (90,401 cycles)	**No difference**: No significant differences in rates of r low birth weight between ICSI versus conventional-IVF cycles	Low (1 study with moderate study limitations)
ART vs. no fertility treatment	Long-term outcomes: Child (type 1 diabetes mellitus)	1 Obs[90] (565,116 pregnancies)	**No difference**: No significant difference found between type 1 diabetes mellitus diagnoses in children born to patients with tubal factor infertility conceived with ART compared to children conceived with no fertility treatment	Moderate (Imprecise)

[a]Criteria for downgrading strength of evidence is described as Rationale; when these criteria are insufficient for understanding the final strength of evidence, additional explanation is provided.

Abbreviations: ART=assisted reproductive technology; ICSI=intra-cytoplasmic sperm injection; IVF=in vitro fertilization; KQ=Key Question; Obs=observational study

Key Question 5. Male Factor Infertility

We identified 23 individual studies[75,90-92,111,115,121,130,147,153,166-179] that addressed the comparative effectiveness or safety of interventions applied to patients with male factor infertility.

Key findings for patients with male factor infertility included:

- Live birth rate (moderate SOE) and miscarriage (low SOE) did not differ between intracytoplasmic sperm injection (ICSI) and intracytoplasmic morphological sperm injection (IMSI). Of note, IMSI is not used in the United States.
- There was no difference in live birth rates or any adverse pregnancy events between couples using frozen embryo versus fresh embryo transfer (low SOE)
- The overall cancer incidence was not elevated in children born after assisted conception for male factor infertility (low SOE).
- There was no difference between type 1 diabetes mellitus diagnoses in children born to patients with male factor infertility conceived with ART compared to children conceived with no fertility treatment (moderate SOE)
- Live birth rate (low SOE) improved with vitamin E or zinc supplementation relative to placebo or no supplementation.

- As with other indications for IVF, use of single-embryo transfer is associated with slightly lower live birth rates but significantly reduced multiple gestation rates (low SOE)

The SOE was judged to be insufficient or low for all outcomes except for the comparison of IVF versus ICSI for live birth and long term outcomes related to diabetes (Table E).

Table E. Summary of strength of evidence for major outcomes—KQ 5 (male factor infertility)

Comparison	Outcome	Study Design and Sample Size	Conclusion	Strength of Evidence (Rationale)[a]
ART IVF: ICSI or assisted hatching (1 embryo transferred) vs. ICSI or assisted hatching (multiple embryos transferred) TESE vs. ejaculated OAT	Live birth	2 Obs[111,171] (272,717 cycles)	**Improvement**. Greater live births with multiple embryos transferred compared to 1 embryo transferred	Low (Imprecise)
ART IVF: Frozen vs. fresh embryo transfer	Live birth	1 RCT[177] (2,157 patients)	**No difference**: no difference in live birth rates between couples using frozen embryo versus fresh embryo transfer	Low (1 study, heterogeneous infertility indication)
	Pregnancy complications: Ectopic pregnancy	1 RCT[177] (2,157 patients)	**No difference**: no difference in ectopic pregnancy rates between couples using frozen embryo versus fresh embryo transfer	Low (1 study, heterogeneous infertility indication)
	Pregnancy complications: Multiple births	1 RCT[177] (2,157 patients)	**No difference**: no difference in multiple birth rates between couples using frozen embryo versus fresh embryo transfer	Low (1 study, heterogeneous infertility indication)
	Pregnancy complications: Miscarriage	1 RCT[177] (2,157 patients)	**No difference**: no difference in miscarriage rates between couples using frozen embryo versus fresh embryo transfer	Low (1 study, heterogeneous infertility indication)
	Neonatal outcomes: Birthweight	1 RCT[177] (2,157 patients)	**No difference**: no difference in low birthweight rates between couples using frozen embryo versus fresh embryo transfer	Low (1 study, heterogeneous infertility indication)
	Neonatal outcomes: Congenital anomalies	1 RCT[177] (2,157 patients)	**No difference**: no difference in congenital anomalies rates between couples using frozen embryo versus fresh embryo transfer	Low (1 study, heterogeneous infertility indication)

Table E. Summary of strength of evidence for major outcomes—KQ 5 (male factor infertility) (continued)

Comparison	Outcome	Study Design and Sample Size	Conclusion	Strength of Evidence (Rationale)[a]
IVF vs. ICSI	Live birth	3 RCTs[166,170,173] (497 patients) 2 Obs[168,172] (771,661 cycles)	No difference. Meta-analysis of 3 RCTs does not demonstrate a difference between ICSI and IMSI.	Moderate (Moderate study limitations)
	Pregnancy complications: Miscarriage	1 RCT[166] (121 patients) 1 Obs[168] (499,135 cycles) 1 SR[180] (6 studies, 552 women)	No difference. Both included studies and an existing systematic review supported no difference in miscarriage. SOE was reduced because of quality of included studies and imprecision of findings.	Low (High study limitations, imprecise)
	Neonatal outcomes: Birthweight	1 RCT[166] (121 patients) 3 Obs[91,168,172] (862,062 cycles)	No difference: No significant differences in rates of low birth weight between ICSI versus conventional-IVF cycles	Low (Moderate study limitations)
ART: Unspecified	Long-term outcomes: Child (cancer)	1 Obs[121] (924,427 patients)	No difference: The overall cancer incidence was not elevated in children born after assisted conception for male factor infertility.	Low (Moderate study limitations)
	Long-term outcomes: Child (type 1 diabetes mellitus)	1 Obs[90] (565,116 pregnancies)	No difference: No significant difference found between type 1 diabetes mellitus diagnoses in children born to patients with male factor infertility conceived with ART compared to children conceived with no fertility treatment	Moderate (Imprecise)
Other strategies: Antioxidant use for Male Infertility	Live birth	1 SR[181] (4 studies of 277 couples)	Improvement: Increase in live birth rate associated with vitamin E or zinc supplementation relative to placebo or no supplementation	Low (Imprecise, small studies)

[a]Criteria for downgrading strength of evidence is described as Rationale; when these criteria are insufficient for understanding the final strength of evidence, additional explanation is provided.

Abbreviations: ART=assisted reproductive technology; ICSI=intra-cytoplasmic sperm injection; IVF=in vitro fertilization; KQ=Key Question; OAT=oligo-astheno-teratozoospermia; Obs=observational study; RCT=randomized controlled trial; TESE=extracted testicular sperm

Key Question 6. Donors in Infertility

We identified one fair-quality RCT[182] and four retrospective observational studies, three fair-quality[183-185] and one poor-quality,[186] that addressed short- or long-term health outcomes of donors in infertility.

Key findings for outcomes of sperm and oocyte donors included:

- For oocyte donors, observational studies suggest a lower incidence of OHSS with GnRH agonist trigger than with human chorionic gonadotropin (hCG) trigger (low SOE). However, there was a lack of evidence on any long-term outcomes.
- There was a lack of evidence on any short or long-term outcomes for sperm donors

Table F summarizes the SOE for KQ 6 and specifically for the incidence of OHSS with GnRH agonist trigger versus hCG trigger. All other short- and long-term outcomes had insufficient SOE or were not evaluated in the limited set of included studies.

Table F. Summary of strength of evidence for major outcomes—KQ 6 (donors in infertility)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
GnRH agonist (leuprolide acetate) vs. hCG trigger	Short term adverse effects of treatment: OHSS	2 Obs[183,184] (3824)	**Improvement**: Lower incidence of OHSS with GnRH agonist trigger than with hCG trigger.	Low (Moderate study limitations, imprecise)

[a]Criteria for downgrading strength of evidence is described as Rationale; when these criteria are insufficient for understanding the final strength of evidence, additional explanation is provided.

Abbreviations: GnRH=gonadotropin-releasing hormone; hCG= human chorionic gonadotropin; KQ=Key Question; Obs=observational study; OHSS=ovarian hyperstimulation syndrome

Findings Applicable Across All Infertility Diagnoses

We identified 26 articles[21,167,187-210] described in 21 studies that addressed outcomes after treatment for infertility and adjusted for cause of infertility and therefore were considered relevant across all infertility diagnoses.

Findings applicable across all KQs for patients who undergo IVF/ICSI include:

- Clomiphene or gonadotropins ever use was not associated with increased risk of maternal cancer (low SOE).
- Women who undergo IVF demonstrated an increased risk of ovarian neoplasms and colorectal malignancies (low SOE) compared to women who do not undergo IVF. There is no evidence of a difference in invasive ovarian cancers (low SOE).
- For children born after ART, ICSI may be associated with an increased risk of autism compared to IVF (low SOE).
- In the United States, live birth rates after IVF/ICSI are lower for African-Americans than for other racial/ethnic groups after adjusting for other prognostic factors (low SOE).

- Elective single-embryo transfer is associated with lower live birth rates but a significant reduction in multiple birth rates compared to multiple-embryo transfer (low SOE for both outcomes).
- There was no difference in the odds of low birth weight between ICSI versus conventional IVF cycles (low SOE). However, among couples undergoing ART with a singleton pregnancy, frozen embryo transfers result in a higher average birthweight, with a subsequent reduction in the incidence of low birthweight and an increase in the incidence of macrosomia (low SOE).

Table G summarizes the SOE for findings that are applicable across all infertility diagnoses.

Table G. Summary of strength of evidence for major outcomes—all infertility diagnoses

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
Clomiphene citrate and gonadotropin	Long-term outcomes: Maternal cancer	1 Obs[187] (9892 patients)	No difference. Ever use of clomiphene citrate was not statistically significantly associated with maternal ovarian, breast, endometrial, lung, thyroid, colon, or melanoma cancer. Gonadotropin use was not associated with increased risk for breast or endometrial cancer	Low (Size of cohort not sufficient to detect modest increases in risk)
ART: IVF	Live birth (by race)	1 Obs[211] (13,473 cycles)	Greater disparity. Lower live birth rate for blacks as compared to white ($p<0.001$)	Low (Imprecise, 1 study)
	Live birth (by number of embryos transferred)	1 Obs[111] (69,028 cycles)	Improvement. Increased live birth rate per cycle with 2 embryo transfer as compared to single embryo transfer	Low (Imprecise, findings with moderate study limitations)
	Pregnancy complications: Multiple births (by number of embryos transferred)	1 Obs[111] (69,028 cycles)	Greater risk. Multiple live birth rates are significantly higher with a 2-embryo transfer than a single embryo transfer, but do not increase further with 3- or 4-embryo transfers	Low (Imprecise, findings with moderate study limitations)
	Neonatal outcomes: Birthweight	1 Obs[193] (8,948)	No difference: No significant difference in rates of low birthweight using ART by assisted hatching, source of oocytes/ semen, number of embryos or ICSI	Low (Imprecise)
	Neonatal outcomes: Congenital Anomalies	1 Obs[197] (64,861)	Greater risk. Risk of birth defects was greater in infants conceived using ART	Low (1 study)

Table G. Summary of strength of evidence for major outcomes—all infertility diagnoses (continued)

Comparison	Outcome	Study Design (Sample Size)	Conclusion	Strength of Evidence (Rationale)[a]
ART: IVF	Long-term outcomes: Child (Autism)	1 Obs[188] (42,383)	Greater risk. Risk of autism was greater in children conceived with ART with ICSI as compared to ART without ICSI	Low (Imprecise)
	Long-term outcomes: Maternal (cancer)	2 Obs[167,209] (280,950)	Greater risk. IVF was associated with a statistically significant increased risk of all ovarian neoplasms and borderline ovarian tumors, and colorectal cancer No difference: IVF however was not associated with an increased risk of invasive ovarian cancer, or melanoma	Low (Imprecise, older study)
IVF+ICSI vs. IVF	Neonatal outcomes: Birth weight	1 Obs[91] (90,401 cycles)	No difference: No significant difference in the odds of low birth weight between ICSI versus conventional-IVF cycles	Low (1 study with moderate study limitations)

[a]Criteria for downgrading strength of evidence is described as Rationale; when these criteria are insufficient for understanding the final strength of evidence, additional explanation is provided.

Abbreviations: ART=assisted reproductive technology; ICSI=intra-cytoplasmic sperm injection; IUI=intrauterine insemination; IVF=in vitro fertilization; KQ=Key Question; Obs=observational study

Discussion

In this Comparative Effectiveness Review, we reviewed 151 studies described in 161 publications that directly compared infertility management strategies in couples with infertility due to PCOS (KQ 1) or endometriosis (KQ 2); unexplained infertility (KQ 3); tubal and peritoneal factor infertility (KQ 4); and male factor infertility (KQ 5). We also explored the comparative safety and effectiveness of management strategies for donors in infertility (KQ 6). Although the ultimate goal with any infertility management strategy is to improve live birth rates of healthy infants to a healthy couple, many studies initially identified in our review only reported on pregnancy rates or focused on other short-term outcomes and did not differentiate by the underlying causes of infertility. Our findings are based on those 151 studies which evaluated the comparative effectiveness of infertility management strategies in couples with a known cause of infertility (including unexplained infertility) and which evaluated the outcome of live birth or another long-term outcome.

Findings in Relation to What Is Already Known

The 2008 AHRQ Evidence Report on "Effectiveness of ART"[37] found that approximately 80 percent of the 478 included studies were performed outside the United States, and that the majority of RCTs did not report delivery rates and obstetric outcomes. In that review, most studies did not have sufficient power to detect clinically meaningful differences in live birth rates, and had still lower power to detect differences in less frequent outcomes such as multiple births and

complications. In addition, the previous report focused on outcomes of specific treatments (ovulation induction, superovulation, and IVF/ICSI) rather than a wider range of potential treatments, and infertility diagnosis was considered as subgroup analyses, rather than the primary basis for comparing treatments.

Methods for evidence synthesis, in particular for rating strength of evidence, have also been revised since that report. Although an increasing number of studies are using live birth rate as the primary outcome, the majority of the literature, particularly randomized trials, is still based on pregnancy or ongoing pregnancy. Lack of precision for comparative estimates of rates for less common but important outcomes, such as complications, continues to be a major limitation.

We compared our findings to evidence-based guidelines from the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK), and the American Society for Reproductive Medicine (ASRM). In general, findings of our review were concordant with the guidelines, with differences primarily attributable to differences in inclusion/exclusion criteria.

For women with PCOS, both NICE and ASRM support use of clomiphene citrate alone as first-line therapy, with the NICE guidance recommending ultrasound monitoring for dose adjustment to minimize risk of multiple pregnancy, followed by combination therapy with metformin or gonadotropins for women who do not conceive after a 3-6 month course of clomiphene alone. Both our review and NICE suggest letrozole may be superior to clomiphene as first line therapy, and that pretreatment with metformin may improve outcomes in women with PCOS being treated with gonadotropins.

For women with endometriosis, ASRM concluded that evidence for surgical treatment of women with mild to moderate endometriosis was insufficient to recommend treatment, while the NICE guidance suggests some benefit, and our review was inconclusive. For those patients going directly to ART, surgical treatment of endometriosis, including endometrioma, prior to ART does not improve outcomes.

For women with unexplained infertility, NICE recommends against use of oral agents entirely, while ASRM suggests clomiphene plus IUI may improve cycle fecundity compared to expectant management; our review found insufficient evidence. Based on our review, immediate IVF results in higher live birth rates and shorter time to pregnancy in women aged 38-42 compared with a trial of clomiphene and IUI or gonadotropins and IUI, with most live births ultimately resulting from IVF.

For women with suspected tubal factor infertility, both NICE and ASRM recommend imaging for diagnosis (which is outside the scope of our review), although, when ART is readily available and affordable, proceeding directly to ART without a definitive diagnosis of tubal disease may be more efficient.

For male factor infertility, our review found no relevant findings compared to the recommendations, primarily because of limited data on live birth outcomes.

For both male and female donors, both NICE and ASRM recommend psychological evaluation and counseling, including, for females, the short term risks of ovarian stimulation and oocyte collection; our review found evidence on outcomes was limited only to the known short-term risks of these procedures, with no evidence on potential longer term risks.

For long-term outcomes in women and children after infertility treatment, our review found limited or inconsistent evidence. Risks of adverse longer term maternal cancer outcomes were generally not increased after adjustment for the risk associated with infertility itself. ICSI

however may be associated with an increased risk of neurodevelopmental disorders in children compared to those conceived through IVF. The NICE guidance was generally consistent with this assessment, and recommended that patients should be informed that any absolute risk was low, while there was still uncertainty about longer-term outcomes.

In general, our current review's findings are consistent with the NICE and ASRM guidelines—there is a general consensus that the overall body of evidence for many aspects of infertility treatment across all patient groups is limited. One consistent limitation is the relative paucity of studies utilizing live birth per couple as the primary outcome.

Applicability

Two broad issues relate to the overall applicability of the available evidence to clinical practice in the United States—one geographic and one temporal. Many of the RCTs meeting our criteria were performed outside of the United States. Leaving aside any issues related to differences in study oversight or reporting, the populations of these studies may differ from U.S. infertility patients in two potentially important ways.

The first issue is that there may be clinically relevant differences between populations in terms of non-clinical factors affecting outcomes. For example, live birth rates for African-American women undergoing ART in the US are lower than for white women[211], which may reflect issues related to socioeconomic status, insurance coverage, or other factors (such as well-established racial differences in the risk of many adverse pregnancy outcomes). Differences in access to infertility services between countries may lead to differences in the likelihood of treatment success. Although the estimate of any *relative* difference between two interventions derived from an unbiased RCT should in theory be independent of the probability of specific outcomes, the more clinically relevant *absolute* difference may be substantially different (e.g., the risk of preterm birth in African-American compared to white women is consistently elevated). To the extent that the probability of specific outcomes of interest may differ between populations because of differences in genetic risk, exposures to other factors affecting risk, or non-biological factors such as access to care, there may be substantial differences in estimates of absolute risk differences. For relatively uncommon but important outcomes, these differences might also affect precision of estimates—confidence intervals for any treatment effect will be wider in populations where the outcome is less common.

In addition to the potential impact of race/ethnicity, there may be important differences in the distribution of socioeconomic status between populations. Access to infertility diagnosis and treatment varies across countries, and certainly within the United States.[212] Differences in socioeconomic status could affect applicability in several ways. Differences in access to care may lead to differences in the spectrum of severity of "disease" for U.S. patients who given the financial burden of treatment options they may wait longer to undergo evaluations. Although summary statistics of baseline characteristics may allow some judgment of comparability, there may be potentially important differences in the distribution that are obscured by the typical reporting of means and standard deviations (particularly if the underlying characteristic is not normally distributed), or by differences within a given stage. Socioeconomic status may also potentially affect some important outcomes independently of any specific treatment—for example, neurodevelopmental outcomes such as specific learning skills may be strongly correlated with parental socioeconomic status.

The second issue is that changes in practice over time have a major impact on applicability, particularly for long-term outcomes. The long lag time between exposure to infertility treatment and the potential development of longer term outcomes such as cancer means that data available today

necessarily reflect women exposed to treatments at least 10 years in the past; even if the specific exposure is similar, there may be differences between past and current practice in potentially important attributes such as dosage, timing, patient selection criteria, use of adjunctive treatments, etc. For example, evidence that immediate use of IVF leads to shorter time to pregnancy than strategies where IVF is used only after a trial of agents such as clomiphene or gonadotropins has led to a change in guidelines.[213] which now suggest that the cumulative exposure to gonadotropins during the course of treatment is likely to decrease compared to earlier cohorts of women, reducing any long-term risks.

In addition, there may be cohort effects in terms of other exposures that may affect the absolute risk of some outcomes (e.g., changes in the use of postmenopausal hormone replacement therapy or ages of mammography screening affecting breast cancer risk), which in turn would impact any additional absolute risk due to exposure to infertility treatments. Because of this phenomenon, there is likely to always be some unresolvable uncertainty about long-term outcomes for both parents undergoing current infertility treatments and their children.

Research Recommendations

In an era of constrained resources, future clinical research, especially comparative effectiveness research—which helps resolve current uncertainties regarding clinical or policy decisions—should receive priority. For most of the KQs, there are multiple areas of remaining uncertainty based on the existing evidence. In part because of the diversity of causes and treatment options, it is difficult to make specific recommendations for specific topics.

Before setting a specific agenda for future research in infertility, we believe a more general approach to identifying priorities would be helpful. Achieving consensus on the relative priority of specific outcomes, incorporating the perspective of multiple stakeholders (similar to the approach used for developing a research agenda for comparative effectiveness research for uterine fibroids.[214,215] Ideally, these outcome priorities would be used for subsequent evidence syntheses and guideline development.

As part of this consensus process, additional areas of discussion include:

- Formal consideration of the limits of acceptability for specific quantitative harms (e.g., preterm birth) and clinically meaningful differences in benefits (e.g., live birth).
- Formal discussion of the potential role of cost-effectiveness in decision making, including issues of willingness-to-pay and appropriate choice of outcome. This is particularly important because there are significant methodological challenges to the use of "standard" measures such as quality-adjusted life expectancy in the setting of infertility treatment.
- Issues related to study design, particularly from the patient stakeholder perspective. For example, in settings where patients and/or clinicians may have strong preferences for specific treatments, recruitment into RCTs may be difficult.[216] In the uterine fibroid consensus process, patient stakeholders strongly preferred observational designs to randomized treatment assignment.[214] Discussion of potential trade-offs between risk of bias, efficiency, ability to measure all relevant potential confounders and effect modifiers, appropriateness of alternative approaches such as Zelen randomization (where subjects are randomized prior to consent, then allowed to either receive the assigned treatment or choose the alternative[217]), and the likelihood that a specific study design would resolve a specific area of uncertainty should all be included.

- Issues related to data reporting. Particularly for ART and other treatments which are used for multiple indications, reporting of results separately by indication in both randomized trials and large observational studies would be extremely useful. Although these subgroup results may have insufficient power to detect clinically relevant differences within the context of individual studies (particularly RCTs), their routine publication would eventually allow synthesis of results using methods such as meta-analysis (including individual-level meta-analysis.)

The Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) and the National ART Surveillance System (NASS), which includes data submitted through SART CORS (the majority of clinics providing ART as well as a smaller number of non-SART participating clinics who report directly to the Centers for Disease Control and Prevention (CDC), are outstanding examples of what a large-scale, population-based registry can achieve in terms of providing data on treatment outcomes. However, the major limitation of the database in the past has been that data are only published on a per-cycle, rather than per-couple, basis. Recently the database methods have changed and now they are publicly reporting the cumulative success rate per patient. Results, however, are still reported at the clinic level, so patients who receive care at more than one clinic do not have the full range of outcomes captured, and there is no mechanism for prospectively collecting long-term outcomes of patients or children. Facilitating reporting of results so that outcomes are reported on a per-couple basis will substantially improve the ability to generate estimates of the likely outcome of specific ART-related decisions.

Based on input from key informants and our technical expert panel (TEP), we structured the review based on infertility diagnosis, and required studies to report outcomes specifically by diagnosis, or to adjust for diagnosis in multivariable analyses. As noted above, this led to exclusion of a number of papers, particularly those related to ART methods. There is clear evidence that the probability of some outcomes of interest, both short-term (e.g., OHSS) and long-term (certain cancers) differs based on underlying diagnosis. Although this may not be the case for all outcomes, we believe it would be helpful for future studies of interventions performed in patients with different underlying diagnoses to report results separately by diagnosis. Within an individual study powered on the basis of the total patients, estimates of diagnosis-specific outcomes may be too imprecise to confidently rule out clinically relevant differences—consistency of reporting would allow formal synthesis of estimates across studies.

We found very limited evidence on outcomes among sperm or oocyte donors. Oocyte donors, who undergo controlled ovarian hyperstimulation and oocyte retrieval in the same manner as patients undergoing IVF using their own eggs, have, in theory, at least the same risk of short-term adverse events as patients. The frequency with which oocyte donors are used is increasing, and evidence from the SART CORS database suggests that the risk of certain pregnancy complications is lower when donor oocytes are used.[34,218] If demand for donor oocytes continues to increase, much more evidence on the specific short- and long-term outcomes of donation (especially if a donor undergoes multiple cycles) is needed.

Conclusions

There is evidence supporting some strategies for treatment of infertility, both for specific diagnoses and for couples with any diagnosis, in part because of recent adaptation of more rigorous methods for evaluating treatments for infertility, particularly regarding treatments for PCOS and approaches to timing of interventions in patients undergoing ART. In addition, ongoing refinements to the SART CORS database continue to make it a valuable

resource, particularly for data on short-term outcomes. However, given the diversity of infertility causes and treatments, there is considerable residual uncertainty about the optimal treatment options for specific patients. Consensus on which outcomes to report (such as encouraging reporting of live birth rates on a per couple basis as well as per cycle, and, for studies of treatment such as ART, reporting of both overall and diagnosis-specific outcomes) and which areas of uncertainty are most important to resolve (in order to prioritize research) is needed to improve the ability of patients and clinicians to make decisions about the most appropriate treatment.

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