Appendix A. Exact Search Strings

PubMed® search strategy (September 17, 2015)

|----|---------------------------------------------------------------|
Embase® search strategy (September 17, 2015)
Platform: Embase.com

#1 'infertility'/exp OR 'anovulation'/exp OR 'infertility':ab,ti OR 'infertile':ab,ti OR 'subfertility':ab,ti OR 'subferti':ab,ti OR 'sub-fertility':ab,ti OR 'sub-fertile':ab,ti OR 'anovulation':ab,ti OR 'aspermia':ab,ti OR 'asthenozoospermia':ab,ti OR 'azoospermia':ab,ti OR 'oligospermia':ab,ti OR 'sertoli cell-only syndrome':ab,ti

#2 'infertility therapy'/exp OR 'diet therapy'/exp OR 'weight reduction'/exp OR 'exercise'/exp OR 'kinesiotherapy'/exp OR 'fertility promoting agent'/exp OR 'clomifene'/exp OR 'gonadorelin'/exp OR 'metformin'/exp OR 'hormone antagonist'/exp OR 'gonadotropin'/exp OR 'watchful waiting'/exp OR 'family planning'/exp OR 'ovulation detection'/exp OR 'gynecologic surgery'/exp OR 'arginine'/exp OR 'ascatic acid'/exp OR 'citrulline'/exp OR 'flavonoid'/exp OR 'corticosteroid'/exp OR 'low level laser therapy'/exp OR 'dexamethasone'/exp OR 'vasovasostomy'/exp OR 'urofollitropin'/exp OR 'electrocoagulation'/exp OR 'prenatal diagnosis'/exp OR 'artificial insemination'/exp OR 'ovulation prediction'/exp OR 'genetic screening'/exp OR 'letrozole'/exp OR 'goserelin'/exp OR 'ganirelix'/exp OR 'recombinant follitropin'/exp OR 'progesterone'/exp OR 'recombinant chorionic gonadotropin'/exp OR 'reproductive techniques'/ab,ti OR 'reproductive technology'/ab,ti OR 'reproductive technologies'/ab,ti OR 'assisted reproductive':ab,ti OR 'ivf':ab,ti OR 'in vitro':ab,ti OR invitation:ab,ti OR 'sperm injection':ab,ti OR 'ICSI':ab,ti OR 'IUI':ab,ti OR 'intrauterine insemination':ab,ti OR 'intrauterine implantation':ab,ti OR 'embryo transfer':ab,ti OR 'artificial insemination':ab,ti OR 'assisted pregnancy':ab,ti OR 'assisted reproduction':ab,ti OR 'ovulation induction':ab,ti OR 'ovarian stimulation':ab,ti OR 'ovarian hyperstimulation':ab,ti OR 'clomiphene':ab,ti OR 'serophene':ab,ti OR 'clomiphene citrate':ab,ti OR 'letrozole':ab,ti OR 'metformin':ab,ti OR 'gonadotropins':ab,ti OR 'granulocyte':ab,ti OR 'ovulator':ab,ti OR 'menopur':ab,ti OR 'repronex':ab,ti OR 'gosereilin':ab,ti OR 'Zoladex':ab,ti OR 'leuprolide':ab,ti OR 'Lupron':ab,ti OR 'nafarelin':ab,ti OR 'Synarel':ab,ti OR 'cetrorelix':ab,ti OR 'Cetrotide':ab,ti OR 'degarelix':ab,ti OR 'Firmagon':ab,ti OR 'ganirelix':ab,ti OR 'antagon':ab,ti OR 'exercise':ab,ti OR 'diet':ab,ti OR 'weight loss':ab,ti OR 'natural family planning':ab,ti OR 'timed intercourse':ab,ti OR 'Billings':ab,ti OR 'Creighton':ab,ti OR 'rhythm method':ab,ti OR 'standard days method':ab,ti OR 'calendar method':ab,ti OR 'basal body temperature method':ab,ti OR 'hysteroscopy':ab,ti OR 'hysteroscopic':ab,ti OR 'microhysteroscopy':ab,ti OR 'microhysteroscopic':ab,ti OR 'ovarian drilling':ab,ti OR 'donor oocytes':ab,ti OR 'ooocyte retrieval':ab,ti OR 'sperm donation':ab,ti OR 'sperm donor':ab,ti OR 'semen donation':ab,ti OR 'semen donor':ab,ti OR 'sperm extraction':ab,ti OR 'sperm retrieval':ab,ti OR 'sperm aspiration':ab,ti OR 'tesa':ab,ti OR 'micro tese':ab,ti OR 'mesa':ab,ti OR 'pesa':ab,ti OR 'ejaculatory duct resection':ab,ti OR 'recombinant human follicle stimulating hormone':ab,ti OR 'rhFSH':ab,ti OR 'rFSH':ab,ti OR 'hormone therapy':ab,ti OR 'laser vaporization':ab,ti OR 'laser vaporisation':ab,ti OR 'dexamethasone':ab,ti OR 'vasectomy reversal':ab,ti OR 'sterilization reversal':ab,ti OR 'superovulation':ab,ti OR 'follistim':ab,ti OR 'Gonal F':ab,ti OR 'Gonal-F':ab,ti OR 'Bravelle':ab,ti OR 'crinone':ab,ti OR 'endometrim':ab,ti OR 'prometrium':ab,ti OR 'fulguration':ab,ti OR 'endometriosis excision':ab,ti OR 'endometrioma excision':ab,ti OR 'ovarian cystectomy':ab,ti OR 'tubal ligation reversal':ab,ti OR 'tubal cannullation':ab,ti OR 'therapeutic donor insemination':ab,ti OR 'ovulation prediction':ab,ti OR


#4 #1 AND #2 AND #3

#5 Dates: 2007/01/01 – present

#6 Limit: English
"ovidrel":ab,ti OR "assisted hatching":ab,ti OR "preimplantation diagnosis":ab,ti OR "preimplantation genetic diagnosis":ab,ti OR "preimplantation screening":ab,ti OR "preimplantation genetic screening":ab,ti OR "preimplantation testing":ab,ti OR "preimplantation genetic testing":ab,ti

#3 'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocate*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR "clinical trials":ti,ab OR 'evaluation'/exp OR "evaluation study":ab,ti OR "evaluation studies":ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti OR 'cohort analysis':exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR follow up'/exp OR "follow up":ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ab,ti OR 'comparative studies':ab,ti OR 'evidence based medicine'/exp OR "systematic review":ab,ti OR 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp) AND [humans]/lim AND [embase]/lim

#4 #1 AND #2 AND #3

#5 #4 AND [2007-2015]/py

#6 #5 AND [english]/lim

Cochrane search strategy (September 17, 2015)
Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

#1 MeSH descriptor Infertility expolode all trees OR MeSH descriptor Anovulation explode all trees OR "infertility":ab,ti,kw OR "infertile":ab,ti,kw OR "subfertility":ab,ti,kw OR "subfertile":ab,ti,kw OR "sub-fertility":ab,ti,kw OR "sub-fertile":ab,ti,kw OR "aspermia":ab,ti,kw OR "asthenozoospermia":ab,ti,kw OR "azoospermia":ab,ti,kw OR "oligospermia":ab,ti,kw OR "sertoli cell-only syndrome":ab,ti,kw

#2 Dates: 2007/01/01 – present

#3 Limit: Cochrane Reviews

Grey Literature Searches

ClinicalTrials.gov (December 16, 2015)

<table>
<thead>
<tr>
<th>Condition</th>
<th>infertility OR infertile OR subfertility OR subfertile OR sub-fertility OR sub-fertile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limits</td>
<td>interventional studies</td>
</tr>
</tbody>
</table>

Total number of results exported: 858

Results were imported into Microsoft Excel and refined as follows:
1. Limited to studies with Completed status – 482 records removed, 376 remaining
2. Limited to studies registered from 2005 forward – 22 records removed, 354 remaining

Total number of results for screening: 354
ClinicalTrials.gov – Narrow search for the Appendix G. Supplemental Project to Assess the Transparency of Reporting for Trials Evaluating Treatment for Infertility (February 5, 2016)

<table>
<thead>
<tr>
<th>Search terms</th>
<th>infertility OR infertile OR subfertility OR subfertile OR sub-fertility OR sub-fertile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition terms</strong></td>
<td>polycystic ovary OR polycystic ovaries OR PCOS OR PCO</td>
</tr>
<tr>
<td></td>
<td>endometriosis OR endometrioma</td>
</tr>
<tr>
<td></td>
<td>unexplained OR ovarian reserve OR DOR OR ovarian response OR POR or responded OR maternal age OR AMA OR reproductive age</td>
</tr>
<tr>
<td></td>
<td>tubal factor OR peritoneal factor OR pelvic adhesions OR pelvic adhesive OR hydrosalpinx</td>
</tr>
<tr>
<td></td>
<td>OR tubal obstruction OR tubal blockage</td>
</tr>
<tr>
<td></td>
<td>male factor OR male infertility OR Oligozoospermia OR Oligospermia OR Azoospermia OR Asthenospermia OR Teratospermia</td>
</tr>
<tr>
<td></td>
<td>oocyte donor OR oocyte donation OR egg donation OR egg donor OR sperm donor OR sperm donation OR donor eggs OR donor oocytes OR donor sperm OR oocyte recipient</td>
</tr>
<tr>
<td>Limits</td>
<td>interventional studies</td>
</tr>
</tbody>
</table>

Total number of results: 494

WHO: International Clinical Trials Registry Platform Search Portal (January 27, 2016)

<table>
<thead>
<tr>
<th>KQs 1-6</th>
<th>infertility OR infertile OR subfertility OR subfertile OR sub-fertility OR sub-fertile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td></td>
</tr>
<tr>
<td>Recruiting status</td>
<td>All</td>
</tr>
</tbody>
</table>

Total number of results exported: 1708

Results were imported into EndNote® and refined as follows:

1. Removal of records originating from ClinicalTrials.gov (the ClinicalTrials.gov database was searched separately) -- 1013 records removed, 695 remaining
2. Keyword searches to identify records containing any of the following terms of interest: birth, delivery, ectopic, miscarriage, death, cancer, OHSS, ovarian hyperstimulation syndrome, time to pregnancy, costs– 442 records removed, 253 remaining

Total number of results for screening: 253
Appendix B. Data Abstraction Elements

Study Characteristics
- Study Identifiers
  - Study Name or Acronym
  - NCT number or other trial registry identifier
  - Last name of first author
- Additional Articles Used in This Abstraction
- Study Sites
  - Single center, Multicenter, Unclear/Not reported
  - Number of sites
- Geographic Location (Select all that apply)
  - US, Canada, UK/Europe, Latin America, Middle East (including Israel), Asia, Africa, Australia/NZ, Unclear/Not reported
- Study Design
  - RCT
  - Observational
- Funding Source (Select all that apply)
  - Government, Industry, Non-government/non-industry, Unclear/Not reported
- Setting (Select all that apply)
  - Subspecialty practice (infertility specialist, urologist, etc.); General gynecology practice; Family practice/general internist/nurse practitioner/other non-gynecologist primary care provider; Unclear/Not reported
- Study Definition of Infertility
  - No pregnancy after 12 months of regular intercourse for women <35 years old or 6 months for women 35 and older; Other (specify); Not applicable; Not reported
- Study Enrollment/Study Completion
  - N enrolled/included
  - N completed
- Key Question Applicability (Select all that apply)
  - KQ1, KQ2, KQ3, KQ4, KQ5, KQ6
- Baseline Characteristics – Record the following elements for Total Population, Women, Men, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)
  - Number of Patients (N and %)
  - Age in years
    - Mean
    - Median
    - Standard Deviation
    - Min
    - Max
    - 25% IQR
    - 75% IQR
    - Categorical
    - Other, specify
  - Race/Ethnicity (N and %)
- Hispanic or Latino
- Black/African American
- American Indian or Alaska Native
- Asian
- Native Hawaiian or Pacific Islander
- White
- Multiracial
- Other (specify)

- Were there significant differences noted between groups in any baseline characteristic? (Yes/No)
  - If yes, please explain the differences
- Comments

### Intervention Characteristics
- Is the comparison within a single intervention class or between classes?
- Intervention Descriptors
  - Describe the intervention received by each patient group.
- Indicate components of the intervention (For each Arm)
  - Oral Ovulation Induction with IUI
  - Oral Ovulation Induction without IUI
  - Surgical Management
  - Gonadotropins with IUI
  - Gonadotropins without IUI
  - IVF
  - ICSI
  - No intervention / expectant management
- Indicate all intervention characteristics that are varied in this study
  - IUI Details
    - IUI methods
    - Adjuvant treatments
  - Oral Ovulation Induction Details
    - Medication type
    - Timing of medication
    - Adjuvant treatments
    - Dose
  - Surgical Management Details
    - Female – Surgical approach (e.g., laparoscopic vs. open)
    - Female – Surgery vs. alternatives
    - Male – Surgical repair
  - Gonadotropin Details
    - Ovarian stimulation (non-IVF) – medication type
    - Ovarian stimulation (non-IVF) – timing
  - IVF Details
    - Pre-stimulation/adjuvant methods
    - Down regulation methods
    - Ovarian stimulation – medication type
- Ovarian stimulation – monitoring
- Ovarian stimulation – poor responders
- Ovarian stimulation – natural cycle IVF
- Ovulation triggering methods
- Oocyte retrieval methods
- Sperm retrieval methods
- Laboratory phase methods
- Embryo transfer – stage of development
- Embryo transfer – # of embryos
- Embryo transfer – transfer technique
- Luteal phase support
- Frozen embryos
- Prevention of ovarian hyperstimulation syndrome
  - ICSI Details
    - Sperm retrieval methods
    - Sperm injection methods
    - ICSI vs IVF
    - Other (specify)
- Comments

Outcomes
- Select the outcome reported on this form:
  - Live Birth
    - Singleton (reported per cycle)
    - Singleton (reported per patient)
    - Multiple (reported per cycle)
    - Multiple (reported per patient)
    - Any (reported per cycle)
    - Any (reported per patient)
  - Pregnancy Complications
    - Multiple births (and associated complications)
    - Ectopic pregnancies
    - Miscarriage
  - Neonatal Outcomes
    - Death
    - Birthweight
    - Congenital anomalies
  - Time to Pregnancy
    - Calendar time (months)
    - Number of cycles
  - Costs
    - Patient
    - Health system
    - Societal
  - Short-term Adverse Effects of Treatment
    - OHSS
- Surgical complications
  - Long-term Outcomes – Child
    - Neurodevelopment / other issues related to prematurity
    - Specific issues related to infertility treatment (epigenetic changes, sex chromosomal abnormalities, etc.)
    - Cancer (all types)
  - Long-term Outcomes – Maternal
    - Cancer
    - Subsequent fertility
  - Donor Women Outcomes
    - Short-term – OHSS
    - Short-term – Surgical Complications
    - Short-term – Adverse effects of treatments
    - Long-term – Downstream fertility
    - Long-term – Cancer
    - Long-term – Age at menopause
    - Quality of Life
  - Donor Men Outcomes
    - Quality of life
    - Short- and long-term health outcomes

- Any additional description / clarification of the outcome reported on this form
- Is this outcome form for a subgroup of interest? (Yes/No)
  - What subpopulation is this outcome reported for on this form?
    - Age
    - Race/ethnicity
    - Obesity/BMI
    - Ovarian reserve
    - History of prior treatment
    - Primary vs. secondary infertility
    - Maternal parity
    - Insurance status
    - Diagnostic criteria / evaluation
    - Presence or absence of male factor infertility
    - Other female causes of infertility
    - Hypertension
    - Diabetes
    - Women without male partners (single women or lesbian couples)
    - Anatomic cause of tubal occlusion (e.g. prior sterilization vs. adhesions)
    - Cause of male infertility
  - Any additional description / clarification of subgroup reported on this form
- Total N Analyzed for this outcome
- Timepoint reported on this form
  - Short-term
  - Long-term
- Specify actual timing of the outcome (in months)
- For each arm:
- N Analyzed (enter UNK if unknown)
- Unadjusted Result
  - Number of patients with outcome
  - % of patients with outcome
  - Events/denominator
  - Odds ratio
  - Hazard ratio
  - Relative risk
  - Mean
  - Median
  - Mean within group change
  - Mean between group change
  - Other (specify)
- Unadjusted Result Variability
  - 95% CI
  - IQR
  - Standard Error (SE)
  - Standard Deviation (SD)
  - Other % CI (specify)
  - Other (specify)
- Unadjusted Result, p-value between groups
- Unadjusted Result, indicate reference group (for comparison between groups)
- Adjusted Result
  - Number of patients with outcome
  - % of patients with outcome
  - Events/denominator
  - Odds ratio
  - Hazard ratio
  - Relative risk
  - Mean
  - Median
  - Mean within group change
  - Mean between group change
  - Other (specify)
- Adjusted Result Variability
  - 95% CI
  - IQR
  - Standard Error (SE)
  - Standard Deviation (SD)
  - Other % CI (specify)
  - Other (specify)
- Adjusted Result, p-value between groups
- Adjusted Result, indicate reference group (for comparison between groups)
- If adjusted data is recorded, indicate the adjustments applied
- Comments
Quality

- Study Type (select one): RCT, Cohort, Case-control, Cross-sectional
- If RCT, select Yes/No/Unclear for each of the following questions:
  - Selection Bias
    - Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?
    - Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization or use of sequentially numbered sealed envelopes)?
    - Were participants analyzed within the groups they were originally assigned to?
    - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
  - Performance Bias
    - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
    - Did the study maintain fidelity to the intervention protocol?
  - Attrition Bias
    - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
  - Detection Bias
    - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls?
    - Were the outcome assessors blinded to the intervention or exposure status of participants?
    - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
    - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
  - Reporting Bias
    - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?
- If Cohort, select Yes/No/Unclear for each of the following questions:
  - Selection Bias
    - Were participants analyzed within the groups they were originally assigned to?
    - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?
    - Did the strategy for recruiting participants into the study differ across study groups?
    - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
- Performance Bias
  - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
  - Did the study maintain fidelity to the intervention protocol?

- Attrition Bias
  - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?

- Detection Bias
  - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls?
  - Were the outcome assessors blinded to the intervention or exposure status of participants?
  - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
  - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
  - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?

- Reporting Bias
  - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?

* If Case-Control, select Yes/No/Unclear for each of the following questions:

- Selection Bias
  - Were cases and controls selected appropriately (e.g., appropriate diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status)
  - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?

- Performance Bias
  - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
  - Did the study maintain fidelity to the intervention protocol?

- Attrition Bias
  - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?

- Detection Bias
  - In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls?
  - Were the outcome assessors blinded to the intervention or exposure status of participants?
Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?

Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?

Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?

- **Reporting Bias**
  - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?

- **If Cross-sectional, select Yes/No/Unclear for each of the following questions:**
  - **Selection Bias**
    - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?
    - Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
  - **Performance Bias**
    - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
  - **Attrition Bias**
    - If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
  - **Detection Bias**
    - Were the outcome assessors blinded to the intervention or exposure status of participants?
    - Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
    - Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
    - Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
  - **Reporting Bias**
    - Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?

- **Other Bias**
  - If applicable, describe any other concerns that may impact risk of bias

- **Overall Study Rating (Good/Fair/Poor)**
  - **Good** (low risk of bias). These studies have the least bias, and the results are considered valid. These studies adhere to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
  - **Fair**. These studies are susceptible to some bias, but not enough to invalidate the results. They do not meet all the criteria required for a rating of good quality
because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

- **Poor** (high risk of bias). These studies have significant flaws that may have invalidated the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

  - If the study is rated as “Fair” or “Poor,” provide rationale.

- **Outcome-specific quality rating**
  - Do you think that any of the outcomes abstracted for this study should be assigned a quality rating DIFFERENT from the overall study rating? (No/Yes)
    - If you think any of the abstracted outcomes should have a quality rating different from the overall study, please provide the outcome(s), rating(s) and rationale(s).

**Applicability** – Use the PICOS format to identify specific issues, if any, that may limit the applicability of the study.

- **Population (P)**
  - Study population demographics not representative of intended population
  - Narrow or unrepresentative severity/stage/comorbidity

- **Intervention (I)**
  - Treatment protocol not representative of current practice
  - Change in standard of care

- **Comparator (C)**
  - Comparator not representative of current practice

- **Outcomes (O)**
  - Timing of outcome assessment

- **Setting (S)**
  - Standards or access to care vary from US setting
  - Specialty population or level of care

- **Comments**
Appendix C. List of Included Studies


Morad AWA and Abdelhamid AA. Prospective randomized study for hydrotubation with or without lidocaine before intrauterine insemination in unexplained infertility. Middle East Fertility Society Journal 2012;17(4):250-255.


Appendix D. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reasons cited. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Not a full publication or full text not available


Siristatidis CS, Bhattcharya S and Maheshwari A. In vitro maturation in sub fertile patients with polycystic ovarian syndrome undergoing assisted reproduction. Cochrane Database of Systematic Reviews 2007.

Not available in English


Not original data from an RCT, SR/MA, or observational study with comparator


Jungheim ES and Odibo AO. Fertility treatment in women with polycystic ovary syndrome: a decision analysis of different oral ovulation induction agents. Fertil Steril 2010;94(7):2659-64. PMID: 20451181.


Observational study sample size less than 100 subjects


**Not a study population of interest**


**No comparator of interest**


**No outcomes of interest**

Abu Hashim H, Bazeed M and Abd Elaal I. Minimal stimulation or clomiphene citrate as first-line therapy in women with polycystic ovary syndrome: a randomized controlled trial. Gynecol Endocrinol 2012;28(2):87-90. PMID: 21770837.


Rancourt RC, Harris HR and Michels KB. Methylation levels at imprinting control regions are not altered with ovulation induction or in vitro fertilization in a birth cohort. Hum Reprod 2012;27(7):2208-16. PMID: 22587996.


Outcomes not reported by underlying diagnosis or by using a multivariate model that includes diagnosis as one of the covariates


Bellavia M, de Geyter C, Streuli I, et al. Randomized controlled trial comparing highly purified (HP-hCG) and recombinant hCG (r-hCG) for triggering ovulation in ART. Gynecol Endocrinol 2013;29(2):93-7. PMID: 23116325.


D-24


Cheung CS, Chan CH and Ng EH. Stress and anxiety-depression levels following first-trimester miscarriage: a comparison between women who conceived naturally and women who conceived with assisted reproduction. Bوجه 2013;120(9):1090-7. PMID: 23631687.


Corchia C, Da Frè M, Di Lallo D, et al. Mortality and major morbidities in very preterm infants born from assisted conception or naturally conceived: Results of the area-based ACTION study. BMC Pregnancy and Childbirth 2014;14(1).


D-36


Kwon H, Choi DH and Kim EK. Absolute position versus relative position in embryo transfer: A randomized controlled trial. Reproductive Biology and Endocrinology 2015;13(1).


D-42


Maimburg RD and Vaeth M. Do children born after assisted conception have less risk of developing infantile autism? Hum Reprod 2007;22(7):1841-3. PMID: 17456530.


D-51


Vuong TN, Phung HT and Ho MT. Recombinant follicle-stimulating hormone and recombinant luteinizing hormone versus recombinant follicle-stimulating hormone alone during GnRH antagonist ovarian stimulation in patients aged >/=35 years: a randomized controlled trial. Hum Reprod 2015;30(5):1188-95. PMID: 25740882.


**Does not meet study design criteria by outcome type**


Elgafor El Sharkwy IA. Metformin versus laparoscopic unilateral ovarian drilling in clomiphene resistant women with polycystic ovary syndrome. Middle East Fertility Society Journal 2013;18(3):202-207.


Toshimitsu M, Nagamatsu T, Nagasaka T, et al. Increased risk of pregnancy-induced hypertension and operative delivery after conception induced by in vitro


## Appendix E. Characteristics of Included Studies

### Appendix Table E. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>ACRONYM</th>
<th>Study Design</th>
<th>Geographic Location</th>
<th>N Enrolled</th>
<th>N Completed</th>
<th>Underlying Diagnosis</th>
<th>Interventions</th>
<th>Outcomes (Subgroups analyzed)</th>
<th>Quality</th>
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<tr>
<td>Abdellah, 2011&lt;sup&gt;148&lt;/sup&gt;</td>
<td>KQ 1</td>
<td>RCT</td>
<td>Africa</td>
<td>147</td>
<td>140</td>
<td>PCOS</td>
<td>Letrozole 5 mg/d for 5 days, maximum treatment duration 6 consecutive cycles. Vs. Laparoscopic ovarian drilling (LOD)</td>
<td>Live Birth Miscarriage Multiple Births</td>
<td>Good</td>
</tr>
<tr>
<td>Aboulghar, 2010&lt;sup&gt;154&lt;/sup&gt;</td>
<td>KQ 1</td>
<td>RCT</td>
<td>Africa</td>
<td>84</td>
<td>NR</td>
<td>PCOS</td>
<td>Routine IVF/ICSI using highly purified uFSH (Fostimon) Vs. rFSH (Gonal F)</td>
<td>OHSS</td>
<td>Good</td>
</tr>
<tr>
<td>Abu Hashim, 2012&lt;sup&gt;169&lt;/sup&gt;</td>
<td>KQ 2</td>
<td>RCT</td>
<td>Africa</td>
<td>136</td>
<td>125</td>
<td>Endometriosis</td>
<td>IUI following hCG injection using Letrozole 5 mg/d Vs. CC 100 mg/d on cycle days 3-9</td>
<td>Live Birth Miscarriage</td>
<td>Good</td>
</tr>
<tr>
<td>Abu Hashim, 2011&lt;sup&gt;146&lt;/sup&gt;</td>
<td>KQ 1</td>
<td>RCT</td>
<td>Africa</td>
<td>176</td>
<td>165</td>
<td>PCOS</td>
<td>Laparoscopic ovarian diathermy (LOD) performed at least 8 weeks after the last CC dosage Vs. CC 50-150 mg/d for 5 days, maximum treatment duration 6 cycles</td>
<td>Live Birth Miscarriage OHSS</td>
<td>Fair</td>
</tr>
<tr>
<td>Abu Hashim, 2010&lt;sup&gt;161&lt;/sup&gt;</td>
<td>KQ 1</td>
<td>RCT</td>
<td>Africa</td>
<td>260</td>
<td>260</td>
<td>PCOS</td>
<td>Letrozole, 2.5 mg/d for 5 days, maximum treatment duration 6 cycles Vs. Laparoscopic ovarian diathermy (LOD)</td>
<td>Live Birth Miscarriage Multiple Births OHSS</td>
<td>Good</td>
</tr>
<tr>
<td>Amer, 2009&lt;sup&gt;157&lt;/sup&gt;</td>
<td>KQ 1</td>
<td>RCT</td>
<td>UK/Europe</td>
<td>188</td>
<td>188</td>
<td>PCOS</td>
<td>CC 50 - 150 mg/d, maximum treatment duration 3 cycles followed by IUI Vs. Timed intercourse</td>
<td>Live Birth Ectopic Pregnancy Miscarriage Multiple Births OHSS</td>
<td>Good</td>
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<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Geographic Location</th>
<th>N Enrolled</th>
<th>N Completed</th>
<th>Underlying Diagnosis</th>
<th>Interventions</th>
<th>Outcomes (Subgroups analyzed)</th>
<th>Quality</th>
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<tr>
<td>An, 2014&lt;sup&gt;138&lt;/sup&gt;</td>
<td>RCT</td>
<td>Asia</td>
<td>150</td>
<td>109</td>
<td>PCOS</td>
<td>Berberine was administered at a dosage of 3 x 500 mg daily for greater than or equal to 12 weeks before controlled ovarian stimulation. Vs. Metformin was administered at a dosage of 3 x 500 mg daily for greater than or equal to 12 weeks before controlled ovarian stimulation. Vs. Placebo was administered as one tablet three times daily for greater than or equal to 12 weeks before controlled ovarian stimulation.</td>
<td>Live Birth</td>
<td>Fair</td>
</tr>
<tr>
<td>Badawy, 2009&lt;sup&gt;189&lt;/sup&gt;</td>
<td>RCT</td>
<td>Middle East</td>
<td>996</td>
<td>996</td>
<td>Unknown</td>
<td>Letrozole 5 mg/d for 5 days Vs. Anastrozole 1 mg/d for 5 days Vs. CC 100 mg/d for 5 days Vs. Spontaneous pregnancy</td>
<td>Miscarriage Ectopic Pregnancy Birthweight Neonatal Death</td>
<td>Fair</td>
</tr>
<tr>
<td>Bagis, 2010&lt;sup&gt;188&lt;/sup&gt;</td>
<td>RCT</td>
<td>UK/Europe</td>
<td>228</td>
<td>226</td>
<td>Unknown, Male Factor</td>
<td>IUI performed 36 hours after hCG injection Vs. IUI performed 18 hours after hCG injection followed by second IUI performed 40 hours after hCG</td>
<td>Live Birth (Male Factor) Miscarriage</td>
<td>Fair</td>
</tr>
<tr>
<td>Balaban, 2011&lt;sup&gt;205&lt;/sup&gt;</td>
<td>RCT</td>
<td>Middle East</td>
<td>77 cycles</td>
<td>77 cycles</td>
<td>Male Factor</td>
<td>ICSI Vs. IMSI</td>
<td>Live Birth</td>
<td>Fair</td>
</tr>
<tr>
<td>Bedaiwy, 2009&lt;sup&gt;160&lt;/sup&gt;</td>
<td>Observational</td>
<td>Canada</td>
<td>251</td>
<td>251</td>
<td>PCOS</td>
<td>Intervention - PCOS patients with hyperinsulinemia, metformin (500 mg or 1000 mg BID) for the first 12 weeks of pregnancy. Vs. Controls - PCOS patients who were normo-insulinemic and did not receive metformin underwent ovulation induction</td>
<td>Live Birth Ectopic Pregnancy Miscarriage Birthweight Congenital anomalies</td>
<td>Fair</td>
</tr>
<tr>
<td>Belva, 2011&lt;sup&gt;206&lt;/sup&gt;</td>
<td>Observational</td>
<td>UK/Europe</td>
<td>120</td>
<td>120</td>
<td>Male Factor</td>
<td>Male offspring born to parents who underwent ICSI Vs. Male offspring born to parents who conceived spontaneously</td>
<td>Birthweight</td>
<td>Poor</td>
</tr>
<tr>
<td>Author, Year</td>
<td>ACRONYM</td>
<td>Study Design</td>
<td>Geographic Location</td>
<td>N Enrolled N Completed Underlying Diagnosis</td>
<td>Interventions</td>
<td>Outcomes (Subgroups analyzed)</td>
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<tr>
<td>Bhattacharya, 2008</td>
<td>SUIT</td>
<td>RCT</td>
<td>UK/Europe</td>
<td>580 576 Unknown</td>
<td>Expectant Management Vs. CC 50 mg days 2-6 of cycle Vs. IUI</td>
<td>Live Birth (Diagnostic Criteria) Time to Pregnancy Ectopic Pregnancy Miscarriage Patient Costs</td>
<td>Good</td>
<td></td>
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<tr>
<td>Bodri, 2009</td>
<td>KQ 6</td>
<td>Observational</td>
<td>UK/Europe</td>
<td>1171? 1171 Donor</td>
<td>Triggering with recombinant hCG Vs. Triggering with GnRH</td>
<td>OHSS</td>
<td>Fair</td>
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<tr>
<td>Bodri, 2008</td>
<td>KQ 6</td>
<td>Observational</td>
<td>UK/Europe</td>
<td>2653 2653 Donor</td>
<td>Ovarian stimulation with GnRH agonist Vs. Ovarian stimulation with GnRH antagonist/hCG Vs. Ovarian stimulation with GnRH antagonist/GnRH agonist Vs. A control group was created by taking into account all IVF cycles reaching oocyte retrieval performed during the same period</td>
<td>OHSS</td>
<td>Fair</td>
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<tr>
<td>Boulet, 2015</td>
<td>NASS</td>
<td>Observational</td>
<td>US</td>
<td>499,135 cycles NA Male Factor</td>
<td>Conventional IVF Vs. ICSI</td>
<td>Live Birth Miscarriage Multiple Pregnancies Birthweight</td>
<td>Fair</td>
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<tr>
<td>Brinton, 2015</td>
<td>KQ 2, 4, 5</td>
<td>Observational</td>
<td>US</td>
<td>9892 9892 Endometriosis, Tubal Factor, Male Factor</td>
<td>Control Vs. CC Vs. Gonadotropins</td>
<td>Maternal Cancer</td>
<td>Good</td>
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<tr>
<td>Butts, 2014</td>
<td>NASS</td>
<td>Observational</td>
<td>US</td>
<td>38,926 38,926 Unknown</td>
<td>ICSI Vs. IVF Vs. Assisted hatching Vs. No assisted hatching</td>
<td>Live Birth (Ovarian Reserve)</td>
<td>Fair</td>
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<tr>
<td>Author, Year ACRONYM KQs</td>
<td>Study Design Geographic Location</td>
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<td>Interventions</td>
<td>Outcomes (Subgroups analyzed)</td>
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<tr>
<td>Choi, 2012(^{130}) KQ 1</td>
<td>RCT Asia</td>
<td>61 61 PCOS</td>
<td>IVM/IVF with FSH and hCG priming protocol Vs. GnRH agonist long protocol group Vs. GnRH antagonist multi-dose flexible protocol</td>
<td>Live Birth</td>
<td>Poor</td>
<td></td>
<td></td>
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<tr>
<td>Custers, 2012(^{184}) KQ 3</td>
<td>RCT UK/Europe</td>
<td>253 253 Unknown</td>
<td>Expectant Management for 6 months, followed by six cycles of IUI-COS, followed by 3 cycles of IVF Vs. IUI with controlled ovarian stimulation (IUI-COS) for 6 months followed by 3 cycles of IVF</td>
<td>Miscarriage Ectopic Pregnancy Multiple Birth Health System Costs</td>
<td>Good</td>
<td></td>
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<tr>
<td>Demirol, 2007(^{197}) KQ 3</td>
<td>RCT UK/Europe</td>
<td>241 241 Unknown</td>
<td>IUI following: Group I (Gonal-F, Serono, Turkey), 81 Follitropin alpha Vs. Group II (Metrodin-HP, Serono), highly-purified uFSH Vs. Group III (Pergonal, Serono), hMG</td>
<td>Miscarriage OHSS</td>
<td>Good</td>
<td></td>
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<tr>
<td>Dhillon, 2015(^{165}) CARE Consortium KQ 2, 3, 4, 5</td>
<td>Observational UK/Europe</td>
<td>13,473 13,473 Endometriosis, Unknown, Tubal Factor, Male Factor</td>
<td>IVF in White Women Vs. IVF in Black Women Vs. IVF in South Asian Women Vs. IVF in Chinese Women</td>
<td>Live Birth</td>
<td>Good</td>
<td></td>
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<tr>
<td>Ebrahimi, 2010(^{196}) KQ 3</td>
<td>RCT Middle East</td>
<td>200 179 Unknown</td>
<td>CC 50 mg BID on cycle days 3 – 7 followed by 75 IU hMG on cycle days 7-9 and adjusted thereafter. IUI performed following triggered ovulation. Cyclogest vaginal pessaries 400 mg/daily through the tenth week of pregnancy Vs. No luteal phase support</td>
<td>Live Birth Multiple Births</td>
<td>Good</td>
<td></td>
<td></td>
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<tr>
<td>Erdem, 2009(^{192}) KQ 3</td>
<td>RCT UK/Europe</td>
<td>214 214 Unknown</td>
<td>Gonadotropin IUI followed by luteal support with crinone once a day beginning 2 days after insemination until pregnancy testing. Vs. Gonadotropin IUI without luteal support.</td>
<td>Live Birth</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Author, Year</td>
<td>Study Design</td>
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<td>Interventions</td>
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<td>Quality</td>
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<tr>
<td>Erdem, 2015</td>
<td>RCT</td>
<td>Middle East</td>
<td>219</td>
<td>Unknown, Male Factor</td>
<td>rFSH followed by triggered ovulation Vs. CC 100 mg/d on days 3-7 of cycle followed by triggered ovulation</td>
<td>Live Birth</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Ge, 2008</td>
<td>RCT</td>
<td>Asia</td>
<td>62</td>
<td>PCOS</td>
<td>IVF using oocytes cultured in media containing hCG, rFSH, and rhCG Vs. hCG-free media with rFSH for the first 10 hours, then were transferred to the same medium the group above Vs. hCG-free media only</td>
<td>Live Birth Miscarriage</td>
<td>Good</td>
<td></td>
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<tr>
<td>Ghanem, 2013</td>
<td>RCT</td>
<td>Middle East</td>
<td>174</td>
<td>PCOS</td>
<td>CC 100 mg/d for 5 days plus uFSH 37.5 IU/d. Vs. uFSH 37.5 IU/d only</td>
<td>Live Birth</td>
<td>Good</td>
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<tr>
<td>Gibreel, 2013</td>
<td>RCT</td>
<td>Africa</td>
<td>105</td>
<td>Unknown</td>
<td>Endometrial scratching using a pipelle biopsy catheter with biopsies obtained Vs. Sham procedure using uterine sound only</td>
<td>Miscarriage Multiple Births</td>
<td>Good</td>
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<tr>
<td>Goldman, 2014</td>
<td>RCT</td>
<td>US</td>
<td>154</td>
<td>Unknown</td>
<td>CC 100 mg/d for 5 days followed by IUI, maximum 2 cycles after which patients proceeded to IVF up to 6 cycles Vs. rFSH followed by IUI, maximum 2 cycles after which patients proceeded to IVF up to 6 cycles Vs. Immediate IVF up to 6 cycles.</td>
<td>Live Birth Time to Pregnancy Ectopic Pregnancy Miscarriage Multiple Births Birthweight Neonatal Death OHSS</td>
<td>Good</td>
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<td>Gregoriou, 2008</td>
<td>RCT</td>
<td>UK/Europe</td>
<td>50</td>
<td>Unknown</td>
<td>rFSH beginning on cycle day 3 Vs. Letrozole 5 mg/d on cycle day 3</td>
<td>Live Birth (Prior Treatments)</td>
<td>Good</td>
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<tr>
<td>Homburg, 2012</td>
<td>RCT</td>
<td>UK/Europe/Latin America</td>
<td>302 255</td>
<td>PCOS</td>
<td>CC 50 – 150 mg/d for 5 days, triggered ovulation Vs. rhFSH, triggered ovulation</td>
<td>Live Birth Ectopic Pregnancy Miscarriage Multiple Births</td>
<td>Good</td>
<td></td>
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<tr>
<td>Author, Year</td>
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<td>Hosseini, 2010</td>
<td>RCT</td>
<td>Middle East</td>
<td>NR 150</td>
<td>NR 112</td>
<td>PCOS</td>
<td>Long-term desensitization protocol using GnRH agonist buserelin 500 mcg SQ. Gonal F started on day 3, replaced by hMG after 7th day of stimulation. Vs. Gonal F for ovarian stimulation. Cetrorelix (GnRH antagonist) 0.35 mg/d injected SQ for 3 days. hMG prescribed after 7th day of stimulation. Fertilization via ICSI. 3 good quality embryos transferred 3 days later.</td>
<td>Miscarriage OHSS</td>
<td>Fair</td>
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<tr>
<td>Kansal Kaira, 2008</td>
<td>RCT</td>
<td>US</td>
<td>18</td>
<td>18</td>
<td>Unknown</td>
<td>Follicular arm - rFSH on cycle day 1 or 2 of the oocyte retrieval cycle. Vs. Luteal phase arm - rFSH 9 days after spontaneous LH surge of the menstrual cycle preceding oocyte retrieval</td>
<td>Live Birth (Ovarian Reserve)</td>
<td>Fair</td>
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<tr>
<td>Kawwass, 2012</td>
<td>Observational</td>
<td>US</td>
<td>111,354 cycles</td>
<td>118,354 cycles</td>
<td>Tubal Factor, Male Factor</td>
<td>All fresh, frozen, donor and non-donor ART cycles performed in the US between 2000 and 2010 that did not use a gestational carrier and had the diagnosis consistent with tubal factor infertility Vs. All fresh, donor, and non-donor ART cycles performed in the US between 2000 and 2010 that did not use a gestational carrier and had the diagnosis consistent with male factor infertility</td>
<td>Miscarriage Birthweight</td>
<td>Good</td>
</tr>
<tr>
<td>Kim, 2011</td>
<td>RCT</td>
<td>Asia</td>
<td>110</td>
<td>110</td>
<td>Unknown</td>
<td>IVF/ICSI with testosterone gel pretreatment (12.5 mg/d) starting on cycle day 6 of the estrogen-progesterone pretreatment. Vs. 21 days pretreatment with estradiol valerate and norethindrone</td>
<td>Live Birth (Ovarian Reserve) Miscarriage (Ovarian Reserve)</td>
<td>Fair</td>
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<tr>
<td>Author, Year ACRONYM KQs</td>
<td>Study Design Geographic Location</td>
<td>N Enrolled N Completed Underlying Diagnosis</td>
<td>Interventions</td>
<td>Outcomes (Subgroups analyzed)</td>
<td>Quality</td>
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<tr>
<td>Kim, 2012142 KQ 1</td>
<td>RCT Asia</td>
<td>211 208 PCOS</td>
<td>Ovarian stimulation using 50 - 150 IU of rhFSH after establishing ovarian and uterine quiescence using vaginal ultrasound. GnRH antagonist, cetrorelix (Cetrotide) 0.125 mg/d was administered in the morning of stimulation day 1 and 2. When the mean diameter of lead follicle reached 13 mm, cetrorelix at a dose of 0.25 mg/d was started again and continued daily up to the day of rhCG (injection). Vs. GnRH agonist, triptorelin (Decapeptyl) at a dose of 0.1 mg/d was initiated from day 18 of oral contraceptive pretreatment cycle. All patients had withdrawal bleeding after discontinuation of oral contraceptive. When pituitary desensitization was achieved, ovarian stimulation was started and the dose of triptorelin was reduced to 0.05 mg daily and continues up to day of rhCG administration. Ovarian stimulation was performed in the same manner.</td>
<td>Live Birth</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Kjotrod, 2011147 KQ 1</td>
<td>RCT UK/Europe</td>
<td>150 149 PCOS</td>
<td>Metform prior to, and during, AFT Vs. Placebo prior to, and during, AFT</td>
<td>Live Birth</td>
<td>Fair (ITT results) Poor (non-ITT results)</td>
<td></td>
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<tr>
<td>Kramer, 2009212 KQ 6</td>
<td>Observational US</td>
<td>287 155 Donor</td>
<td>All respondents were egg donors Vs. No comparator</td>
<td>Adverse effects of treatments OHSS Downstream fertility</td>
<td>Poor</td>
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<tr>
<td>Author, Year ACRONYM KQs</td>
<td>Study Design Geographic Location</td>
<td>N Enrolled N Completed Underlying Diagnosis</td>
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<tr>
<td>Kurzawa, 2008&lt;sup&gt;156&lt;/sup&gt; KQ 1</td>
<td>RCT UK/Europe</td>
<td>74 70 PCOS</td>
<td>All patients received oral contraceptives pills x 1 month before starting controlled ovarian hyperstimulation. None of the patients used oral antidiabetic medications (biguanides or thiazolidinediones). rhFSH started on cycle day 2 at 150 IU/d and adjusted depending on an ovarian response. A GnRH antagonist - cetrorelix 0.25 mg subcutaneous injections were given until the criteria for recombinant hCG administration were met Vs. During oral contraception on days 16–18 of the preceding cycle, after transvaginal ultrasonographic screening of ovaries, an intramuscular injection of GnRH agonist triptorelin (Diphereline SR 3.75; Boufor Ibsen Pharma, France) was given. After confirmation of pituitary desensitization (LH &lt;2 mIU/mL and estradiol &lt;40 pg/mL) the administration of FSH was commenced. rFSH and hCG administered as above</td>
<td>Live Birth Miscarriage Multiple Births OHSS</td>
<td>Fair</td>
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<tr>
<td>Kuzmin, 2014&lt;sup&gt;198&lt;/sup&gt; KQ 4</td>
<td>RCT Asia</td>
<td>468 468 Tubal Factor</td>
<td>Laparoscopy, salpingolysis, salpingostomy, and transcervical falloposcopy tubal dilatation (TFTD) Vs. Laparoscopy, salpingolysis, salpingostomy</td>
<td>Ectopic Pregnancy</td>
<td>Poor</td>
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<tr>
<td>La Sala, 2015&lt;sup&gt;200&lt;/sup&gt; KQ 5</td>
<td>RCT UK/Europe</td>
<td>242 242 Male Factor</td>
<td>IMSI Vs. ICSI</td>
<td>Live Birth Miscarriage Multiple Births Birthweight Congenital Anomalies</td>
<td>Poor</td>
<td></td>
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<tr>
<td>Leandri, 2013&lt;sup&gt;203&lt;/sup&gt; KQ 5</td>
<td>RCT UK/Europe</td>
<td>255 255 Male Factor</td>
<td>Conventional ICSI Vs. IMSI</td>
<td>Live Birth</td>
<td>Fair</td>
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<tr>
<td>Legro, 2007&lt;sup&gt;124&lt;/sup&gt; PPCOS KQ 1</td>
<td>RCT US</td>
<td>626 450 PCOS</td>
<td>CC initial dose of 50 mg of CC on days 3–7 of each treatment cycle on-study Vs. Metformin 500 mg/d, increased to 2000 mg/d Vs. Combination of CC and metformin</td>
<td>Live Birth (Obesity/BMI) Ectopic Pregnancy Miscarriage Multiple Births Congenital Anomalies</td>
<td>Good</td>
<td></td>
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<td>Author, Year</td>
<td>Study Design</td>
<td>Geographic Location</td>
<td>N Enrolled</td>
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<td>Underlying Diagnosis</td>
<td>Interventions</td>
<td>Outcomes (Subgroups analyzed)</td>
<td>Quality</td>
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<tr>
<td>Legro, 2014&lt;sup&gt;26&lt;/sup&gt;</td>
<td>RCT</td>
<td>US</td>
<td>750</td>
<td>750</td>
<td>PCOS</td>
<td>CC 50 mg daily starting on cycle day 3 for 5 days Vs. Letrozole 2.5 mg daily starting on cycle day 3 for 5 days</td>
<td>Live Birth Time to Pregnancy Ectopic Pregnancy Miscarriage Birthweight Congenital Anomalies Neonatal Death</td>
<td>Good</td>
</tr>
<tr>
<td>PPCOS 2</td>
<td>KQ 1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Luke, 2010&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Observational</td>
<td>US</td>
<td>69,028 cycles (69,028 cycles Endometriosis, Unknown, Tubal Factor, Male Factor)</td>
<td>69,028 cycles</td>
<td>69,028 cycles</td>
<td>Elective single embryo transfer (eSET)--1 embryo Vs. eSET--2 embryos Vs. eSET--3 embryos Vs. eSET--4 or more embryos</td>
<td>Live Birth</td>
<td>Fair</td>
</tr>
<tr>
<td>NASS</td>
<td>KQ 2, 3, 4, 5</td>
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<tr>
<td>Majumdar, 2013&lt;sup&gt;79&lt;/sup&gt;</td>
<td>RCT</td>
<td>Asia</td>
<td>156</td>
<td>151</td>
<td>Unknown</td>
<td>ICSI with sperm selection based on visual assessment Vs. ICSI with sperm selection based on ability to bind hyaluronic acid</td>
<td>Live Birth Miscarriage</td>
<td>Fair</td>
</tr>
<tr>
<td>KQ 3</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Maxwell, 2008&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Observational</td>
<td>US</td>
<td>587</td>
<td>587</td>
<td>Donor</td>
<td>Oocyte Donors Vs. No comparison</td>
<td>Adverse effects of treatments OHSS</td>
<td>Fair</td>
</tr>
<tr>
<td>KQ 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mehrabian, 2012&lt;sup&gt;140&lt;/sup&gt;</td>
<td>RCT</td>
<td>Middle East</td>
<td>104</td>
<td>Unclear</td>
<td>PCOS</td>
<td>hMG followed by triggered ovulation Vs. Laparoscopic ovarian drilling If after 3 cycles anovulation persisted, CC was prescribed and gonadotropin was administered if anovulation persisted after CC.</td>
<td>OHSS</td>
<td>Fair</td>
</tr>
<tr>
<td>KQ 1</td>
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<tr>
<td>Morad, 2012&lt;sup&gt;194&lt;/sup&gt;</td>
<td>RCT</td>
<td>Africa</td>
<td>234</td>
<td>231</td>
<td>Unknown</td>
<td>Hydrotubation performed one day before IUI using: 20 mL of saline Vs. 20 mL of 0.1 mg Lidocaine/mL saline mixed with 19.9 cc of saline</td>
<td>Ectopic Pregnancy Miscarriage Multiple Births OHSS</td>
<td>Good</td>
</tr>
<tr>
<td>KQ 3</td>
<td></td>
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<td>Author, Year</td>
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<td>Outcomes (Subgroups analyzed)</td>
<td>Quality</td>
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<tr>
<td>Morin-Papunen, 2012(^{[143]})</td>
<td>RCT</td>
<td>320</td>
<td>Metformin (500 mg) was initiated at a dose of one tablet once a day for the first week and increased thereafter by one tablet daily in weekly steps up to three tablets (one + two daily) in nonobese women and to four tablets (two + two daily) in obese women and was continued up to a maximum of 9 months. If pregnancy occurred, metformin was continued up to the 12th week. The women used metformin or placebo alone for at least 3 months. If pregnancy did not occur, ovulation induction was commenced: if the woman ovulated after CC, she continued metformin/placebo with the same dose of clomiphene for four to six cycles or until the 12th week of pregnancy. After four to six unsuccessful cycles with metformin/placebo and CC, either gonadotrophins or aromatase inhibitors were used. Vs. Placebo with all other management the same as above.</td>
<td>Live Birth (Obesity/BMI) Time to Pregnancy</td>
<td>Good</td>
<td></td>
<td></td>
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<tr>
<td>Nahuis, 2011(^{[33]})</td>
<td>RCT</td>
<td>168</td>
<td>Laparoscopic electrocautery (LEC). LEC followed by clomiphene citrate and then rFSH if still anovulatory. Vs. rFSH</td>
<td>Live Birth Patient Costs</td>
<td>Fair</td>
<td></td>
<td></td>
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<tr>
<td>Nangia, 2011(^{[21]})</td>
<td>Observational</td>
<td>272,526</td>
<td>IVF w/o ICSI, male factor only Vs. IVF w/o ICSI, tubal ligation only Vs. ICSI, male factor only Vs. ICSI, tubal ligation only</td>
<td>Live Birth Birthweight</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Oyesanya 2009(^{[19]})</td>
<td>RCT</td>
<td>353</td>
<td>Provided that 6 or more oocytes were retrieved from the prospective donor, half were given to the recipient and half were given to another recipient. Vs. Recipients received all retrieved oocytes from their altruistic donor.</td>
<td>Ectopic Pregnancy (Diagnostic Criteria)</td>
<td>Fair</td>
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<tr>
<td>Author, Year</td>
<td>Study Design</td>
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<td>Outcomes (Subgroups analyzed)</td>
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<tr>
<td>Palomba, 2010</td>
<td>RCT</td>
<td>50 47</td>
<td>PCOS</td>
<td>Laparoscopic ovarian diathermy. No drugs to trigger ovulation. Vs. CC for up to 6 cycles plus metformin 500 mg tapered upwards. No drugs to trigger ovulation.</td>
<td>Live Birth Surgical Complications</td>
<td>Good</td>
<td></td>
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<tr>
<td>Palombia, 2011</td>
<td>RCT</td>
<td>120 120</td>
<td>PCOS</td>
<td>Metformin 500 mg three times daily Vs. Placebo Metformin and placebo treatments started on the same day of GnRH-a administration (pretreatment) and were continued during the gonadotropin ovarian stimulation (cotreatment), treatment that started at least 14 days later. Both active drug and placebo were stopped when a positive pregnancy test or menstrual bleeding appeared.</td>
<td>Live Birth OHSS</td>
<td>Good</td>
<td></td>
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<tr>
<td>Ragni, 2012</td>
<td>RCT</td>
<td>304 249</td>
<td>Unknown</td>
<td>CC oral tablets at dose of 150 mg/d from day 3 to day 7 Vs. Daily SQ injections of triptoreline started on day one or two of the menstrual cycle and 450 IU of SQ rFSH from day 3 of the cycle.</td>
<td>Live Birth (Ovarian reserve) Patient Costs</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Rashidi, 2013</td>
<td>RCT</td>
<td>280 259</td>
<td>Unknown</td>
<td>Induction of ovulation with CC 100 mg/d on cycle days 3 –7, followed by 75 IU/d hMG on cycle days 7–9, followed by triggered ovulation and IUI Vs. Same protocol except hMG replaced by 75 IU rFSH.</td>
<td>Live Birth Miscarriage OHSS</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Rashidi, 2015</td>
<td>RCT</td>
<td>276 276</td>
<td>PCOS</td>
<td>Ovulation induction with CC day 3-7 followed by: 75 IU of rFSH day 7-9 and IUI Vs. 75 IU of hMG day 7-9 and IUI</td>
<td>Live Birth Miscarriage Multiple Births OHSS</td>
<td>Fair</td>
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<tr>
<td>Razi, 2013</td>
<td>RCT</td>
<td>182 182</td>
<td>Male Factor</td>
<td>Laser Assisted Hatching (LAH) following ICSI Vs. Control group. Intact transferred embryos without LAH</td>
<td>Live Birth Multiple Births Congenital Anomalies</td>
<td>Poor</td>
<td></td>
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<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Geographic Location</td>
<td>N Enrolled</td>
<td>Interventions</td>
<td>Outcomes (Subgroups analyzed)</td>
<td>Quality</td>
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<td>Reindollar, 2010</td>
<td>RCT US</td>
<td>US</td>
<td>503</td>
<td>CC/IUI x 3 cycles followed by up to 3 cycles gonadotropin/IUI followed by 6 cycles of IVF (of which 2 could be frozen cycles) Vs. CC/IUI x 3 cycles followed by 6 cycles of IVF (of which 2 could be frozen cycles)</td>
<td>Live Birth Ectopic Pregnancy Miscarriage Multiple Births Time to Pregnancy OHSS Birthweight Neonatal Death Health System Costs</td>
<td>Good</td>
<td></td>
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<tr>
<td>Rubio, 2013</td>
<td>RCT UK/Europe</td>
<td>Unknown</td>
<td>274</td>
<td>IVF with day-5 blastocyst transfer (no PGD) Vs. IVF, embryo biopsy and FISH for 9 chromosomes on day 3, transfer on day 5</td>
<td>Live Birth Miscarriage Multiple Births (RIF and AMA)</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Schendelaar, 2011</td>
<td>Observational UK/Europe</td>
<td>Groningen</td>
<td>310</td>
<td>Children who were not born to sub-fertile parents Vs. Children born to sub-fertile parents who received IVF (either COH-IVF or MNC-IVF)</td>
<td>Neurodevelopmental Issues</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Seckin, 2014</td>
<td>RCT UK/Europe</td>
<td>Unknown</td>
<td>149</td>
<td>Luteal phase support with 90 mg/d vaginal 8% progesterone gel starting on the day of IUI until pregnancy testing Vs. No drug for luteal phase support</td>
<td>Live Birth</td>
<td>Good</td>
<td></td>
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<tr>
<td>Sismanoglu, 2009</td>
<td>RCT UK/Europe</td>
<td>Unknown</td>
<td>50</td>
<td>Donor triggering with hCG Vs. Donor triggering with GnRH agonist</td>
<td>OHSS</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Spaan, 2015</td>
<td>Observational UK/Europe</td>
<td>Unknown</td>
<td>25,108</td>
<td>Received at least one IVF cycle with ovarian stimulation Vs. Subfertile women with other treatments including tubal surgery, IUI, or hormonal treatment OR withdrew from IVF waiting list</td>
<td>Maternal Cancer</td>
<td>Good</td>
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<tr>
<td>Author, Year, ACRONYM</td>
<td>Study Design</td>
<td>Geographic Location</td>
<td>N Enrolled &amp; N Completed</td>
<td>Underlying Diagnosis</td>
<td>Interventions</td>
<td>Outcomes (Subgroups analyzed)</td>
<td>Quality</td>
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<tr>
<td>Stadtmauer, 2011¹⁵¹</td>
<td>RCT</td>
<td>US</td>
<td>98 98</td>
<td>NR PCOS</td>
<td>rFSH Follistim starting on cycle day 3 until the appropriate follicle size was reached. Vs. Ganirelix 0.25 mg SQ/d added to rFSH in a flexible protocol when the leading follicle diameter reached R13 mm. Vs. rFSH and Ganirelix</td>
<td>Live Birth Miscarriage Multiple Births</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Stern, 2015²¹⁸</td>
<td>Observational</td>
<td>US</td>
<td>NA 28</td>
<td>NA Endometriosis, Tubal Factor</td>
<td>Deliveries to fertile women (without diagnosis associated with infertility) Vs. Deliveries to women with diagnosis of male factor infertility, treated with ART, are identified from the NASS database Vs. Deliveries to women with diagnosis of endometriosis, treated with ART, are identified from the NASS database Vs. Deliveries to women with diagnosis of endometriosis, identified from Massachusetts (PELL) data system who did not have ART according to NASS</td>
<td>Multiple Births Birthweight</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>NASS MOSART KQ 2, 4</td>
<td></td>
<td></td>
<td>22,045 21,646</td>
<td>Endometriosis</td>
<td>Women receiving infertility treatment but not IVF Vs. Women receiving IVF</td>
<td>Maternal Cancer (Parity)</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Stewart, 2013¹⁶⁸</td>
<td>Observational</td>
<td>Australia/NZ</td>
<td>109 109</td>
<td>Endometriosis</td>
<td>IVF with DHEA 75 mg/d for 8 weeks pre-treatment Vs. Placebo</td>
<td>Live Birth Miscarriage</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Tartagni, 2015¹⁷²</td>
<td>RCT</td>
<td>UK/Europe</td>
<td>95 109</td>
<td>Endometriosis</td>
<td>Pretreatment with OCP for 21 days, controlled ovarian stim started on day 2-3. Cetrolix (antagonist) 0.25 mg SQ started when follicles 12-14 mm. Vs. Control group. Pretreatment with OCP for 21 days, along with buserelin (agonist) 500 mcg/d SQ. Buserelin then reduced to 250 mcg/d. Controlled ovarian stimulation with hMG.</td>
<td>OHSS</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Tehraninejad, 2010¹⁵³</td>
<td>RCT</td>
<td>Middle East</td>
<td>95 90</td>
<td>PCOS</td>
<td>Testicular sperm extraction (TESE) via biopsy in men w/ azoospermia Vs. Fresh ejaculated sperm from men with extreme severe oligo-astheno-teratozoospermia (OAT) sperm</td>
<td>Live Birth Miscarriage Birthweight Congenital Anomalies</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Tsai, 2011²⁰⁴</td>
<td>Observational</td>
<td>Asia</td>
<td>NA 191 cycles</td>
<td>Male Factor</td>
<td>Testicular sperm extraction (TESE) via biopsy in men w/ azoospermia Vs. Fresh ejaculated sperm from men with extreme severe oligo-astheno-teratozoospermia (OAT) sperm</td>
<td>Live Birth Miscarriage Birthweight Congenital Anomalies</td>
<td>Poor</td>
<td></td>
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<tr>
<td>Author, Year ACRONYM KQs</td>
<td>Study Design Geographic Location</td>
<td>N Enrolled N Completed Underlying Diagnosis</td>
<td>Interventions</td>
<td>Outcomes (Subgroups analyzed)</td>
<td>Quality</td>
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<td>van Rumste, 2014&lt;sup&gt;177&lt;/sup&gt; KQ 3</td>
<td>RCT UK/Europe</td>
<td>116 116 Unknown</td>
<td>IVF elective single embryo transfer Vs. COH/IUI, maximum treatment duration 3 cycles</td>
<td>Live Birth Health System Costs</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Verhoeve, 2013&lt;sup&gt;199&lt;/sup&gt; KQ 4</td>
<td>Observational UK/Europe</td>
<td>5000 5000 Tubal Factor</td>
<td>No diagnostics and no treatment Vs. No diagnostics and immediate treatment (up to 3 IVF treatments) Vs. No diagnostics and delayed treatment (no treatment for 1 yr, then up to 3 IVF treatments) Vs. Hysterosalpingogram followed by tailored treatment (delayed or immediate IVF)</td>
<td>Live Birth Patient Costs</td>
<td>Good</td>
<td></td>
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<tr>
<td>Vitek, 2013&lt;sup&gt;180&lt;/sup&gt; KQ 3</td>
<td>Observational US</td>
<td>154 154 Unknown</td>
<td>Split IVF/ICSI Vs. Computer simulated- all IVF Vs. Computer simulated- all ICSI</td>
<td>Patient Costs</td>
<td>Good</td>
<td></td>
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<tr>
<td>Williams, 2013&lt;sup&gt;178&lt;/sup&gt; KQ 3, 5</td>
<td>Observational UK/Europe</td>
<td>106,013 NA Unknown, Male Factor</td>
<td>Assisted Reproduction Vs. General Population</td>
<td>Child Cancer</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Wiser, 2010&lt;sup&gt;187&lt;/sup&gt; KQ 3</td>
<td>RCT Middle East</td>
<td>33 33 Unknown</td>
<td>Long-stimulation protocol IVF with 75 mg DHEA orally, once a day, at least 6 weeks before starting the first cycle of ovulation induction. Patients who did not conceive and continued to the second cycle took DHEA for at least 16–18 weeks. Vs. Standard long-stimulation protocol IVF</td>
<td>Live Birth (Ovarian Reserve)</td>
<td>Fair</td>
<td></td>
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<tr>
<td>Yapca, 2015&lt;sup&gt;171&lt;/sup&gt; KQ 3</td>
<td>RCT UK/Europe</td>
<td>80 80 Unknown</td>
<td>CC 100 mg/d on cycle days 3 - 7 followed by time-limited hydrotubation performed after detection of the dominant follicle and then timed intercourse Vs. No hydrotubation</td>
<td>Live Birth Miscarriage</td>
<td>Fair</td>
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<td>Author, Year</td>
<td>ACRONYM</td>
<td>KQs</td>
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<td>N Completed</td>
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<td>Interventions</td>
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<td>Yazici, 2014</td>
<td>KQ 1</td>
<td>RCT</td>
<td>UK/Europe</td>
<td></td>
<td>110</td>
<td>56</td>
<td>PCOS</td>
<td>Ovarian stimulation using rFSH followed by IUI and luteal support with vaginal micronized progesterone 300 mg/d Vs. No luteal support</td>
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<tr>
<td>Yildiz, 2014</td>
<td>KQ 3</td>
<td>RCT</td>
<td>UK/Europe</td>
<td></td>
<td>180</td>
<td>180</td>
<td>Unknown</td>
<td>Follitropin alpha, follitropin beta, uhMG and urofolitropin were used for ovarian stimulation. Ovulation induction was started between 2-5 days of menstruation on patients who had no residual cysts larger than 15 mm as visualized with basal transvaginal USG (ultrasound). All patients had 75-150 IU/d drug as an initial dose. On cycle day 5-6, stimulated follicles were measured ultrasonographically. Induction doses were increased or decreased between 37.5-75 IU/d according to follicle size. When 1-2 follicles reached a mean diameter of 17 mm, 250 mcg of rhCG was administered to trigger ovulation. Uterine washing was accomplished by introducing a silicone catheter through the internal cervical os, after which 20 cc saline and 1 cc jetocain were slowly injected. The speculum was removed and the procedure completed after the injection. At 35-36 hours after the hCG injection, IUI was performed. Vs. Same procedures except no uterine washing performed</td>
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<td>Author, Year</td>
<td>Study Design</td>
<td>Geographic Location</td>
<td>N Enrolled</td>
<td>Underlying Diagnosis</td>
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<td>Outcomes (Subgroups analyzed)</td>
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<td>Zain, 2009</td>
<td>RCT</td>
<td>Asia</td>
<td>124</td>
<td>PCOS</td>
<td>Metformin tablets at the initial dose of 500 mg and increased in a step-wise fashion during the first 3 weeks to a total dose of 1,500 mg/d. The patients were then asked to make a telephone call once they had a menstrual period and a transvaginal ultrasound (TVS) and follicular tracking was done to document evidence of follicular growth and ovulation on days 2, 8, 12, and 16. A menstrual calendar chart recorded menses cycles monthly. Vs. CC at a dose of 50 mg on days 2–6. The TVS and follicular tracking were done to document follicular growth and ovulation on days 2, 8, 12, and 16. If there was absence of ovulation, the CC dose was increased stepwise on a treatment cycle basis after a P withdrawal bleed to a maximum of 200 mg. If there was evidence of ovulation but the patient did not get pregnant, the same dosage was continued for a maximum of six cycles. Vs. Metformin was given in a similar manner to the metformin only group. CC was given at a dose of 50 mg on days 2–6. The TVS and follicular tracking were done to document evidence of follicular growth and ovulation on days 2, 8, 12, and 16. If there was absence of ovulation, the CC dose was increased stepwise on a treatment cycle basis after a P withdrawal bleed to a maximum of 200 mg. If there was evidence of ovulation but patient did not get pregnant, a similar dosage was continued for a maximum of six cycles.</td>
<td>Live Birth  Ectopic Pregnancy  Miscarriage  Multiple Births</td>
<td>Fair</td>
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<tr>
<td>Zakherah, 2010</td>
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<td>Africa</td>
<td>150</td>
<td>PCOS</td>
<td>CC 150 mg + Tamoxifen 40 mg from cycle days 3 to 7, maximum treatment duration 6 cycles. Vs. Laparoscopic ovarian drilling (LOD) performed through triple-puncture laparoscopy followed by timed intercourse.</td>
<td>Live Birth  Miscarriage</td>
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<td>Zheng, 2012</td>
<td>RCT</td>
<td>Asia</td>
<td>82</td>
<td>74</td>
<td>PCOS</td>
<td>Primed with 10,000 IU hCG after progesterone induced withdrawal bleeding. Immature oocytes were collected 36-38 hours after hCG priming. IVM and ICSI were done. Vs. No priming after progesterone induced withdrawal bleeding. Immature oocytes were collected directly after allocation to non-priming group. IVM and ICSI were done.</td>
<td>Live Birth</td>
<td>Fair</td>
</tr>
<tr>
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<td>RCT</td>
<td>Asia</td>
<td>163</td>
<td>156</td>
<td>Endometriosis</td>
<td>Oral contraceptive for 63 days, every 3 month visits for 14 months, if no pregnancy within 12 months of stopping OCP, advised to undergo IVF Vs. Oral contraceptive for 33 days, followed by a combination of oral contraceptive and 30 g/d Dan'e mixture for 30 days; every 3 month visits for 14 months, if no pregnancy within 12 months of stopping OCP, advised to undergo IVF Vs. No treatment; q3month visits for 12 months, if no pregnancy within 12 months, advised to undergo IVF</td>
<td>Live Birth Ectopic Pregnancy Miscarriage Neonatal Death</td>
<td>Fair</td>
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</table>

Abbreviations: ART=assisted reproductive technology; BID=two times per day; BMI=body mass index; CARE Consortium=Centres for Assisted Reproduction; CC=clomiphene citrate; COH=controlled ovarian hyperstimulation; COS=controlled ovarian stimulation; DHEA=dehydroepiandrosterone; FASTT=Fast Track and Standard Treatment Trial; FISH=fluorescence in situ hybridization; FORT-T=Forty and Over Treatment Trial; FSH=follicle stimulating hormone; GnRH=gonadotropin-releasing hormone; hCG=human chorionic gonadotropin; hMG=human menopausal gonadotropin; ICSI=intracytoplasmic sperm injection; IMSI=intracytoplasmic morphologically selected sperm injection; ITT=intention-to-treat; IU=international units; IUI=intrauterine insemination; IVF=in vitro fertilization; IVM=in vitro maturation; KQ=key question; mcg=mcgrom; MNC=modified natural cycle; MOSART=Massachusetts Outcomes Study of Assisted Reproductive Technologies; NA=not applicable; NASS=National Artificial Reproductive Technology Surveillance System; NR=Not Reported; OCP=oral contraceptive pill; OHSS=Ovarian Hyperstimulation Syndrome; PCOS=Polycystic Ovary Syndrome; PGD=preamplantation genetic diagnosis; PPCOS=Pregnancy in Polycystic Ovary Syndrome; RCT=Randomized Controlled Trial; rhFSH=recombinant human follicle stimulating hormone; SQ=subcutaneous; SUIT=Scottish Unexplained Infertility Trial; TVS=transvaginal ultrasound; uFSH=urinary follicle stimulating hormone; uhMG=urinary human menopausal gonadotropin
Appendix F. AMSTAR Quality Assessment for Systematic Reviews

Table F-1 shows the AMSTAR (A Measurement Tool to Assess Systematic Reviews) quality assessment for the included systematic reviews. For full study citations, please refer to the report’s main reference list.

### Table F-1. AMSTAR assessment for included systematic reviews

<table>
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<tr>
<th>Study</th>
<th>&quot;A Priori&quot; design provided?</th>
<th>Duplicate study selection and data abstraction?</th>
<th>Comprehensive literature search performed?</th>
<th>Status of publication (i.e., grey literature) used as an inclusion criterion?</th>
<th>List of studies (included and excluded) provided?</th>
<th>Characteristics of included studies provided?</th>
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<th>Scientific quality of the included studies used appropriately in formulating conclusions?</th>
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<td>Comprehensive literature search performed?</td>
<td>Status of publication (i.e. grey literature used as an inclusion criterion)?</td>
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Abbreviations: C=Can’t answer; N=No; Y=Yes
Figure F-1. Summary of AMSTAR quality assessment for systematic reviews

- "A Priori" design provided?
- Duplicate study selection and data abstraction?
- Comprehensive literature search performed?
- Status of publication (i.e. grey literature) used as an inclusion criterion?
- List of studies (included and excluded) provided?
- Characteristics of included studies provided?
- Scientific quality of included studies assessed and documented?
- Scientific quality of the included studies used appropriately in formulating conclusions?
- Methods used to combine the findings of studies appropriate?
- Likelihood of publication bias assessed?
- Conflict of interest included?

Percent of studies with low, high, or unclear risk of bias

Yes  No  Can't Answer
# Appendix G. Risk of Bias Assessment for Included Studies

Table G-1 shows the risk of bias quality assessment for the included cohort studies. For full study citations, please refer to the report’s main reference list.

## Table G-1. Risk of bias assessment for included cohort studies

<p>| Study          | Were participants analyzed within the groups they were originally assigned to? (selection bias) | Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (selection bias) | Did the strategy for recruiting participants differ across study groups? (selection bias) | Did the design or analysis account for confounding and modifying variables through matching, stratification, multivariable analysis or other approaches? (selection bias) | Did researchers rule out any impact from concurrent intervention or unintended exposure that might bias results? (performance bias) | Did the study maintain fidelity to the intervention protocol? (performance bias) | If attrition was a concern, were missing data handled appropriately? (attrition bias) | Was the length of follow-up the same between the groups? (detection bias) | Were the outcome assessors blinded to the status of participants? (detection bias) | Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were outcomes assessed, implemented consistently across all study participants? (detection bias) | Were confounding variables implemented consistently across all study participants? (detection bias) | Were potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias) |
|----------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|
| Brinton, 2015  | Y                                                                                           | Y                                                                                              | N                                                                                         | Y                                                                                                                      | Y                                                                                                                                       | Y                                                                                                                                       | Y                                                                                                                                           | Y                                                                                          | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Bedaiwy, 2009  | Y                                                                                           | N                                                                                              | U                                                                                         | N                                                                                                                      | N                                                                                                                                       | Y                                                                                                                                       | Y                                                                                                                                           | Y                                                                                          | N                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Belva, 2011    | N                                                                                           | N                                                                                              | U                                                                                         | N                                                                                                                      | N                                                                                                                                       | N                                                                                                                                       | Y                                                                                                                                           | Y                                                                                          | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | N                                                                 |
| Bodri, 2008    | N                                                                                           | Y                                                                                              | U                                                                                         | N                                                                                                                      | N                                                                                                                                       | U                                                                                                                                       | U                                                                                                                                           | Y                                                                                          | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Bodri, 2009    | Y                                                                                           | Y                                                                                              | U                                                                                         | N                                                                                                                      | N                                                                                                                                       | U                                                                                                                                       | U                                                                                                                                           | Y                                                                                          | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | N                                                                 |
| Boulet, 2015   | N                                                                                           | N                                                                                              | U                                                                                         | Y                                                                                                                      | N                                                                                                                                       | U                                                                                                                                       | U                                                                                                                                           | U                                                                                          | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Boulet, 2016   | Y                                                                                           | Y                                                                                              | N                                                                                         | Y                                                                                                                      | Y                                                                                                                                       | U                                                                                                                                       | U                                                                                                                                           | Y                                                                                          | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Butts, 2014    | Y                                                                                           | Y                                                                                              | N                                                                                         | Y                                                                                                                      | U                                                                                                                                       | Y                                                                                                                                       | Y                                                                                                                                           | Y                                                                                          | N                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Chang, 2016    | Y                                                                                           | Y                                                                                              | N                                                                                         | Y                                                                                                                      | Y                                                                                                                                       | U                                                                                                                                       | U                                                                                                                                           | Y                                                                                          | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Study                  | Were participants analyzed within the groups they were originally assigned to? | Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? | Did the participants differ across study groups? (selection bias) | Does the design or analysis account for confounding and modifying variables through matching, stratification, or other approaches? (selection bias) | Did researchers rule out any impact from concurrent intervention or unintended exposure that might bias results? (performance bias) | Did the study maintain fidelity to the intervention protocol? (performance bias) | If attrition was a concern, were missing data handled appropriately? (attrition bias) | Was the length of follow-up the same between the groups? (detection bias) | Were the outcome assessors blinded to the status of the participants? (detection bias) | Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias) |
|-----------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dhalwani, 2016(^{243}) | Y                                                                               | Y                                                                               | N                                                                                                  | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                     | Y                                                                                                                                   | Y                                                                                                                                   | N                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                 |
| Dhillon, 2015(^{245}) | Y                                                                               | Y                                                                               | N                                                                                                  | Y                                                                                                                                   | U                                                                                                                                   | Y                                                                                                                                     | Y                                                                                                                                   | U                                                                                                                                   | Y                                                                                                                                   | U                                                                                                                                   | Y                                                                                                                                 |
| Hershko-Klement, 2016(^{246}) | U                                                                               | Y                                                                               | U                                                                                                  | N                                                                                                                                   | U                                                                                                                                   | U                                                                                                                                     | U                                                                                                                                   | U                                                                                                                                   | U                                                                                                                                   | U                                                                                                                                   | U                                                                                                                                 |
| Kawwass, 2013(^{247}) | Y                                                                               | Y                                                                               | N                                                                                                  | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                     | MYS                                                                                                                  | Y                                                                                                                                   | U                                                                                                                                   | U                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                 |
| Kawwass, 2016(^{248}) | Y                                                                               | Y                                                                               | Y                                                                                                  | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                     | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                 |
| Kissin, 2015(^{249}) | Y                                                                               | Y                                                                               | Y                                                                                                  | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                     | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                 |
| Luke, 2010(^{250})   | N                                                                               | Y                                                                               | U                                                                                                  | N                                                                                                                                   | N                                                                                                                                   | N                                                                                                                                     | N                                                                                                                                   | N                                                                                                                                   | U                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                 |
| Luke, 2015(^{251})   | Y                                                                               | Y                                                                               | N                                                                                                  | Y                                                                                                                                   | U                                                                                                                                   | Y                                                                                                                                     | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                 |
| Maxwell, 2008(^{252}) | N                                                                               | Y                                                                               | N                                                                                                  | N                                                                                                                                   | N                                                                                                                                   | N                                                                                                                                     | U                                                                                                                                   | Y                                                                                                                                   | N                                                                                                                                   | Y                                                                                                                                   | N                                                                                                                                   | N                                                                                                                                 |
| Nangia, 2011(^{253})  | U                                                                               | Y                                                                               | U                                                                                                  | Y                                                                                                                                   | N                                                                                                                                   | U                                                                                                                                     | U                                                                                                                                   | U                                                                                                                                   | N                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                 |
| Oyesanya, 2009(^{254}) | Y                                                                               | Y                                                                               | N                                                                                                  | N                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                     | Y                                                                                                                                   | N                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                 |
| Provost, 2016(^{255}) | Y                                                                               | Y                                                                               | N                                                                                                  | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                     | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                   | Y                                                                                                                                 |
| Study               | Were participants analyzed within the groups they were originally assigned to? | Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (selection bias) | Did the strategy for recruiting participants differ across study groups? (selection bias) | Does the design or analysis account for confounding and modifying variables through statistical or other approaches? (selection bias) | Did researchers rule out any impact from concurrent interventions that might bias results? (performance bias) | Did the study maintain fidelity to the intervention protocol? (performance bias) | If attrition was a concern, were missing data handled appropriately? (attrition bias) | Was the length of follow-up the same between the groups? (detection bias) | Did the study assess the status of participants? (detection bias) | Were confounding variables implemented consistently across all study participants? (detection bias) | Were potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias) |
|--------------------|------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Purcell, 2007&lt;sup&gt;249&lt;/sup&gt; | Y                                                               | Y                                                                                           | U                                                                                           | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |
| Santos-Ribeiro, 2016&lt;sup&gt;250&lt;/sup&gt; | Y                                                               | Y                                                                                           | N                                                                                           | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | N                                                                                                                                  | N                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |
| Sarais, 2016&lt;sup&gt;251&lt;/sup&gt; | Y                                                               | Y                                                                                           | N                                                                                           | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | U                                                                                                                                  | N                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |
| Schendelaar, 2011&lt;sup&gt;185&lt;/sup&gt; | Y                                                               | Y                                                                                           | Y                                                                                           | U                                                                                                                                  | U                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | N                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  |
| Seifer, 2016&lt;sup&gt;252&lt;/sup&gt; | Y                                                               | Y                                                                                           | N                                                                                           | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | N                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |
| Senapati, 2016&lt;sup&gt;253&lt;/sup&gt; | Y                                                               | Y                                                                                           | U                                                                                           | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | Y                                                                                                                                  |
| Spaan, 2015&lt;sup&gt;122&lt;/sup&gt; | N                                                               | Y                                                                                           | N                                                                                           | Y                                                                                                                                  | Y                                                                                                                                  | U                                                                                                                                  | Y                                                                                                                                  | U                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | U                                                                                                                                  |
| Stern, 2015&lt;sup&gt;28&lt;/sup&gt; | Y                                                               | Y                                                                                           | Y                                                                                           | N                                                                                                                                  | Y                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | N                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |
| Stewart, 2013&lt;sup&gt;168&lt;/sup&gt; | Y                                                               | Y                                                                                           | N                                                                                           | N                                                                                                                                  | U                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | N                                                                                                                                  | Y                                                                                                                                  |
| Tsai, 2011&lt;sup&gt;204&lt;/sup&gt; | N                                                               | N                                                                                           | Y                                                                                           | N                                                                                                                                  | N                                                                                                                                  | U                                                                                                                                  | N                                                                                                                                  | N                                                                                                                                  | N                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | N                                                                                                                                  |
| Verhoeve, 2013&lt;sup&gt;190&lt;/sup&gt; | U                                                               | U                                                                                           | U                                                                                           | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  | U                                                                                                                                  |
| Vitek, 2013&lt;sup&gt;160&lt;/sup&gt; | Y                                                               | Y                                                                                           | N                                                                                           | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | U                                                                                                                                  |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Were participants analyzed within the groups they were originally assigned to? (selection bias)</th>
<th>Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (selection bias)</th>
<th>Did the study identify potential confounders and assess their effects? (selection bias)</th>
<th>Did the strategy for recruiting participants differ across study groups? (selection bias)</th>
<th>Did researchers rule out any impact from concurrent interventions or exposure that might bias results? (performance bias)</th>
<th>Did the study maintain fidelity to the intervention protocol? (performance bias)</th>
<th>If attrition was a concern, were missing data handled appropriately? (attrition bias)</th>
<th>Was the length of follow-up the same between the groups? (detection bias)</th>
<th>Were the outcome assessors blinded to the status of participants? (detection bias)</th>
<th>Were outcomes assessed, implemented consistently across all study participants? (detection bias)</th>
<th>Were confounding variables implemented consistently across all study participants? (selection bias)</th>
<th>Were potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias)</th>
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<td>Williams, 2013™</td>
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</tr>
</tbody>
</table>

Abbreviations: N=No; U=Unclear; Y=Yes
Figure G-1. Summary of risk of bias assessment for included cohort studies

- Were participants analyzed within the groups they were originally assigned to? (selection bias)
- Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (selection bias)
- Did the strategy for recruiting participants into the study differ across study groups? (selection bias)
- Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or... (detection bias)
- Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (performance bias)
- Did the study maintain fidelity to the intervention protocol? (performance bias)
- If attrition was a concern, were missing data handled appropriately? (attrition bias)
- In prospective studies, was the length of follow-up the same between the groups, or in case-control studies, was the time period between the... (detection bias)
- Were the outcome assessors blinded to the intervention or exposure status of participants? (detection bias)
- Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias)
- Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias)
- Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? (detection bias)
- Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias)
Table G-2 shows the risk of bias quality assessment for the included cross-sectional studies. For full study citations, please refer to the report’s main reference list.

<table>
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<tr>
<th>Study</th>
<th>Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (selection bias)</th>
<th>Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (selection bias)</th>
<th>Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (performance bias)</th>
<th>If attrition was a concern, were missing data handled appropriately? (attrition bias)</th>
<th>Were the outcome assessors blinded to the intervention or exposure status of participants? (detection bias)</th>
<th>Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias)</th>
<th>Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias)</th>
<th>Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? (detection bias)</th>
<th>Were outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias)</th>
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<tr>
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</tr>
</tbody>
</table>

Abbreviations: N=No; U=Unclear; Y=Yes
Figure G-2. Summary of risk of bias assessment for included cross-sectional studies

1. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (selection bias)
   - Yes (Black)
   - No (Gray)
   - Unclear (Light Gray)

2. Does the design or analysis control for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (selection bias)
   - Yes (Black)
   - No (Gray)
   - Unclear (Light Gray)

3. Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (performance bias)
   - Yes (Black)
   - No (Gray)
   - Unclear (Light Gray)

4. If attrition was a concern, were missing data handled appropriately? (attrition bias)
   - Yes (Black)
   - No (Gray)
   - Unclear (Light Gray)

5. Were the outcome assessors blinded to the intervention or exposure status of participants? (detection bias)
   - Yes (Black)
   - No (Gray)
   - Unclear (Light Gray)

6. Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias)
   - Yes (Black)
   - No (Gray)
   - Unclear (Light Gray)

7. Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias)
   - Yes (Black)
   - No (Gray)
   - Unclear (Light Gray)

8. Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? (detection bias)
   - Yes (Black)
   - No (Gray)
   - Unclear (Light Gray)

9. Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias)
   - Yes (Black)
   - No (Gray)
   - Unclear (Light Gray)
Table G-3 shows the risk of bias quality assessment for the included RCTs. For full study citations, please refer to the report’s main reference list.

### Table G-3. Risk of bias assessment for included RCTs

<p>| Study               | Was the allocation sequence generated adequately? (selection bias) | Was the allocation of treatment adequately concealed? (selection bias) | Were participants analyzed within the groups they were originally assigned to? (selection bias) | Was the design or analysis control accounting for important confounding and modifying variables through matching, stratification, or other approaches? (selection bias) | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (performance bias) | Did the study maintain fidelity to the intervention protocol? (performance bias) | If attrition was a concern, were missing data handled appropriately? (attrition bias) | Were participants克斯, were the intervention exposed and the outcome assessed the same for cases and controls? (detection bias) | Were the outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias) |
|---------------------|---------------------------------------------------------------|---------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------|---------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| Abdellah 2011        | Y                                                             | Y                                                                   | Y                                                                                | Y                                                                                | N                                                                                | Y                                                               | Y                                                              | Y                                                              | Y                                                              | Y                                                              | Y                                                              |
| Aboulghar 2010       | Y                                                             | Y                                                                   | Y                                                                                | Y                                                                                | Y                                                                                | Y                                                               | Y                                                              | Y                                                              | Y                                                              | Y                                                              | Y                                                              |
| Abu Hashim 2012      | Y                                                             | Y                                                                   | Y                                                                                | Y                                                                                | Y                                                                                | Y                                                               | Y                                                              | Y                                                              | Y                                                              | Y                                                              | Y                                                              |
| Abu Hashim 2011      | Y                                                             | Y                                                                   | Y                                                                                | Y                                                                                | Y                                                                                | Y                                                               | Y                                                              | Y                                                              | Y                                                              | Y                                                              | Y                                                              |
| Abu Hashim 2010      | Y                                                             | Y                                                                   | Y                                                                                | Y                                                                                | Y                                                                                | Y                                                               | Y                                                              | Y                                                              | Y                                                              | Y                                                              | Y                                                              |
| Abu Hashim 2011      | Y                                                             | Y                                                                   | Y                                                                                | Y                                                                                | Y                                                                                | Y                                                               | Y                                                              | Y                                                              | Y                                                              | Y                                                              | Y                                                              |
| Amer 2009            | Y                                                             | Y                                                                   | N                                                                                | N                                                                                | N                                                                                | Y                                                               | Y                                                              | Y                                                              | Y                                                              | Y                                                              | N                                                              |
| An 2014              | Y                                                             | Y                                                                   | Y                                                                                | Y                                                                                | Y                                                                                | Y                                                               | Y                                                              | Y                                                              | Y                                                              | Y                                                              | Y                                                              |
| Study               | Was the allocation sequence generated adequately? (selection bias) | Was the allocation of treatment adequately concealed? (selection bias) | Were participants analyzed within the groups they were originally assigned to? (selection bias) | Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (selection bias) | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (performance bias) | Did the study maintain fidelity to the intervention protocol? (performance bias) | If attrition was a concern, were missing data handled appropriately? (attrition bias) | In prospective studies, was the length of follow-up the same between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls? (detection bias) | Were the outcome assessors blinded to the intervention or exposure status of participants? (detection bias) | Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias) |
|--------------------|---------------------------------------------------|---------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Badawy 2009&lt;sup&gt;99&lt;/sup&gt; | N                                                 | N                                                 | Y                                                                                             | N                                                                                             | U                                                                                             | Y                                                                                             | U                                                                                             | N                                                                                             | N                                                                                             | Y                                                                                             | U                                                                                             | U                                                                                             |
| Bagis 2010&lt;sup&gt;18&lt;/sup&gt;  | Y                                                 | Y                                                 | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | U                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             |
| Balaban 2011&lt;sup&gt;205&lt;/sup&gt; | U                                                 | U                                                 | Y                                                                                             | N                                                                                             | N                                                                                             | U                                                                                             | U                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             |
| Bhattacharya 2008&lt;sup&gt;226&lt;/sup&gt; | Y                                                 | U                                                 | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | N                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             |
| Boostanfar 2016&lt;sup&gt;299&lt;/sup&gt; | U                                                 | U                                                 | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | U                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | U                                                                                             |
| Chen 2016&lt;sup&gt;299&lt;/sup&gt; | Y                                                 | Y                                                 | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             |
| Choi 2012&lt;sup&gt;139&lt;/sup&gt; | U                                                 | U                                                 | Y                                                                                             | U                                                                                             | U                                                                                             | U                                                                                             | U                                                                                             | U                                                                                             | U                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             |
| Custers 2012&lt;sup&gt;254&lt;/sup&gt; | Y                                                 | Y                                                 | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | U                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             |
| Demirol 2007&lt;sup&gt;197&lt;/sup&gt; | Y                                                 | Y                                                 | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | N                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             | Y                                                                                             |
| Study                | Was the allocation sequence generated adequately? | Was the allocation of treatment adequately concealed? | Were participants analyzed within the groups they were originally assigned to? | Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? | Did the study maintain fidelity to the intervention protocol? | If attrition was a concern, were missing data handled appropriately? | In prospective studies, was the length of follow-up the same between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls? | Were the outcome assessors blinded to the intervention or exposure status of participants? | Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? | Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? |
|---------------------|-------------------------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Diamond 2015        | Y                                               | Y                                                  | Y                                                                               | Y                                                                               | Y                                                                                | Y                                                                                     | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                     |
| Dreyer 2016         | Y                                               | Y                                                  | N                                                                               | Y                                                                               | Y                                                                                | Y                                                                                     | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                     |
| Ebrahimi 2010       | Y                                               | Y                                                  | Y                                                                               | Y                                                                               | Y                                                                                | Y                                                                                     | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                     |
| Erdem 2009          | Y                                               | N                                                  | Y                                                                               | Y                                                                               | U                                                                                | Y                                                                                     | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                     |
| Erdem 2015          | Y                                               | Y                                                  | Y                                                                               | Y                                                                               | Y                                                                                | Y                                                                                     | Y                                                                                                                  | U                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                     |
| Ge 2008             | Y                                               | Y                                                  | Y                                                                               | Y                                                                               | Y                                                                                | Y                                                                                     | Y                                                                                                                  | U                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                     |
| Ghahir 2016         | Y                                               | Y                                                  | Y                                                                               | Y                                                                               | N                                                                                | U                                                                                     | Y                                                                                                                  | U                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | U                                                                                     |
| Ghanem 2013         | Y                                               | N                                                  | Y                                                                               | Y                                                                               | Y                                                                                | U                                                                                     | N                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                     |
| Gibreel 2013        | Y                                               | Y                                                  | Y                                                                               | Y                                                                               | Y                                                                                | Y                                                                                     | Y                                                                                                                  | N                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                                                  | Y                                                                                     |
| Study               | Was the allocation sequence generated adequately? | Was the allocation of treatment adequately concealed? | Were participants analyzed within the groups they were originally assigned to? | Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? | Did the study maintain fidelity to the intervention protocol? | If attrition was a concern, were missing data handled appropriately? | In prospective studies, was the length of follow-up the same between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls? | Were the outcome assessors blinded to the intervention or exposure status of participants? | Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? | Did the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? |
|---------------------|--------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Goldman 2014(^175) | Y                                                | Y                                                   | Y                                                                           |                                  | Y                                                                           | Y                                                                            | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           |
| Gregoriou 2008(^193) | Y                                                | Y                                                   | Y                                                                           |                                  | Y                                                                           | Y                                                                            | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           |
| Homburg 2012(^144) | Y                                                | Y                                                   | Y                                                                           |                                  | Y                                                                           | Y                                                                            | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           |
| Hosseini 2010(^150) | U                                                | U                                                   | U                                                                           | N                                | N                                                                           | U                                                                            | U                                                                           | U                                                                           | U                                                                           | N                                                                           | Y                                                                           | Y                                                                           | U                                                                           |
| Hossein-Rashidi 2016(^264) | Y                                                | U                                                   | U                                                                           | Y                                | Y                                                                           | Y                                                                            | N                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           |
| Johnson 2010(^152) | Y                                                | Y                                                   | Y                                                                           | N                                | Y                                                                           | Y                                                                            | Y                                                                           | Y                                                                           | Y                                                                           | U                                                                           | Y                                                                           | Y                                                                           | Y                                                                           |
| Kansal Kalra 2008(^190) | Y                                                | Y                                                   | Y                                                                           | N                                | U                                                                           | Y                                                                            | Y                                                                           | Y                                                                           | N                                                                           | Y                                                                           | Y                                                                           | Y                                                                           | Y                                                                           |
| Kar 2015(^236)     | N                                                | Y                                                   | Y                                                                           | Y                                | Y                                                                           | Y                                                                            | Y                                                                           | N                                                                           | Y                                                                           | Y                                                                           | N                                                                           | Y                                                                           | Y                                                                           |
| Study            | Was the allocation sequence generated adequately? (selection bias) | Was the allocation of treatment adequately concealed? (selection bias) | Were participants analyzed within the groups they were originally assigned to? (selection bias) | Does the design or analysis control for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (selection bias) | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (performance bias) | Did the study maintain fidelity to the intervention protocol? (performance bias) | Did attrition was a concern, were missing data handled appropriately? (attrition bias) | In prospective studies, was the length of follow-up the same between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls? (detection bias) | Were the outcome assessors blinded to the intervention or exposure status of participants? (detection bias) | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias) |
|-----------------|------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Khosravi 2015   | Y                                                               | Y                                                                   | Y                                                                                            |                                                                                               |                                                                                                                                |                                                                                                                                | Y                                                                                                                                   |                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |
| Kim 2011       | U                                                               | U                                                                   | Y                                                                                            | N                                                                                              | U                                                                   | Y                                                                   | U                                                                                                                                   |                                                                                                                                  | U                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |                                                                                                                                  |
| Kim 2012       | Y                                                               | Y                                                                   | Y                                                                                            | Y                                                                                              | Y                                                                   | Y                                                                   | Y                                                                                                                                   |                                                                                                                                  | U                                                                   | Y                                                                                                                                  | Y                                                                                                                                  |                                                                                                                                  |
| Kjotrod 2011    | Y                                                               | Y                                                                   | Y                                                                                            | N                                                                                              | Y                                                                   | Y                                                                   | Y                                                                                                                                   |                                                                                                                                  | Y                                                                   | Y                                                                                                                                  | Y                                                                                                                                  |                                                                                                                                  |
| Kurzawa 2008    | Y                                                               | N                                                                   | Y                                                                                            | Y                                                                                              | Y                                                                   | Y                                                                   | U                                                                                                                                   | Y                                                                                                                                  | N                                                                   | Y                                                                                                                                  | U                                                                                                                                  | Y                                                                                                                                  |
| Kuzmin 2014     | U                                                               | U                                                                   | U                                                                                            | U                                                                                              | U                                                                   | U                                                                   | U                                                                                                                                   | N                                                                   | U                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |
| La Sala 2015    | N                                                               | N                                                                   | U                                                                                            | Y                                                                                              | N                                                                   | U                                                                   | Y                                                                                                                                   | Y                                                                                                                                  | Y                                                                   | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |
| Leandri 2013    | Y                                                               | Y                                                                   | U                                                                                            | Y                                                                                              | Y                                                                   | U                                                                   | Y                                                                                                                                   | Y                                                                                                                                  | Y                                                                   | Y                                                                                                                                  | Y                                                                                                                                  | Y                                                                                                                                  |
| Legro 2007      | Y                                                               | Y                                                                   | Y                                                                                            | Y                                                                                              | Y                                                                   | Y                                                                   | Y                                                                                                                                   | Y                                                                                                                                  | Y                                                                   | Y                                                                                                                                  | Y                                                                                                                                  | N                                                                                                                                  |
| Study               | Was the allocation sequence generated adequately? (selection bias) | Was the allocation of treatment adequately concealed? (selection bias) | Were participants analyzed within the groups they were originally assigned to? (selection bias) | Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (selection bias) | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (performance bias) | Did the study maintain fidelity to the intervention protocol? (performance bias) | If attrition was a concern, were missing data handled appropriately? (attrition bias) | In prospective studies, was the length of follow-up the same between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls? (detection bias) | Were the outcome assessors blinded to the intervention or exposure status of participants? (detection bias) | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias) |
|--------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------|
| Legro 2014(^{126}) | Y                                               | Y                                               | Y                                               | Y                                                               | Y                                                               | Y                                               | Y                                               | Y                                                               | Y                                               | Y                                                               | Y                                               | Y                                                               | Y                                               |
| Legro 2015(^{267}) | Y                                               | Y                                               | Y                                               | Y                                                               | Y                                                               | Y                                               | Y                                               | Y                                                               | Y                                               | Y                                                               | Y                                               | Y                                                               | Y                                               |
| Majumdar 2013(^{179}) | Y                                               | U                                               | N                                               | N                                                               | U                                                               | U                                               | N                                               | Y                                                               | U                                               | Y                                                               | Y                                               | Y                                                               | U                                               |
| Mehrabian 2012(^{180}) | Y                                               | U                                               | Y                                               | Y                                                               | U                                                               | Y                                               | U                                               | U                                                               | U                                               | Y                                                               | Y                                               | Y                                                               | Y                                               |
| Morad 2012(^{194})  | Y                                               | Y                                               | Y                                               | Y                                                               | Y                                                               | Y                                               | Y                                               | Y                                                               | N                                               | Y                                                               | Y                                               | Y                                                               | Y                                               |
| Morin-Papunen 2012(^{143}) | Y                                               | Y                                               | Y                                               | Y                                                               | Y                                                               | Y                                               | Y                                               | U                                                               | Y                                               | Y                                                               | Y                                               | Y                                                               | Y                                               |
| Mutsaerts 2016(^{268}) | Y                                               | Y                                               | Y                                               | Y                                                               | Y                                                               | Y                                               | Y                                                               | Y                                                               | N                                               | Y                                                               | Y                                               | Y                                                               | Y                                               |
| Nada 2016(^{189})   | Y                                               | Y                                               | Y                                               | Y                                                               | Y                                                               | Y                                               | Y                                                               | U                                                               | Y                                               | Y                                                               | Y                                               | Y                                                               | Y                                               |
| Study         | Was the allocation sequence generated adequately? | Was the allocation of treatment adequately concealed? | Were participants analyzed within the groups they were originally assigned to? | Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? | Did the study maintain fidelity to the intervention protocol? | If attrition was a concern, were missing data handled appropriately? | In prospective studies, was the length of follow-up the same between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls? | Were the outcome assessors blinded to the intervention or exposure status of participants? | Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? | Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? |
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| Nahuis 2011  | U                                              | U                                             | Y                                                                              | Y                                                                              | Y                                                                | Y                                                              | Y                                                        | Y                                                                        | Y                                                                                                                                           | Y                                                                                                                                       | Y                                                                                                                                       | U                                                                                                                                       |
| Palomba 2010 | Y                                              | Y                                             | Y                                                                              | N                                                                              | N                                                                | Y                                                              | Y                                                        | Y                                                                        | Y                                                                                                                                           | Y                                                                                                                                       | Y                                                                                                                                       | Y                                                                                                                                       |
| Palomba 2011 | Y                                              | Y                                             | Y                                                                              | Y                                                                              | Y                                                                | Y                                                              | U                                                        | Y                                                                        | Y                                                                                                                                           | Y                                                                                                                                       | Y                                                                                                                                       | Y                                                                                                                                       |
| Ragni 2012   | Y                                              | Y                                             | Y                                                                              | N                                                                              | U                                                                | Y                                                              | Y                                                        | N                                                                        | Y                                                                                                                                           | U                                                                                                                                       | Y                                                                                                                                       | Y                                                                                                                                       |
| Rashidi 2013 | U                                              | U                                             | Y                                                                              | N                                                                              | U                                                                | Y                                                              | N                                                        | Y                                                                        | Y                                                                                                                                           | U                                                                                                                                       | U                                                                                                                                       | U                                                                                                                                       |
| Rashidi 2015 | U                                              | U                                             | Y                                                                              | U                                                                              | U                                                                | Y                                                              | Y                                                        | Y                                                                        | Y                                                                                                                                           | Y                                                                                                                                       | Y                                                                                                                                       | Y                                                                                                                                       |
| Razi 2013    | N                                              | N                                             | U                                                                              | N                                                                              | N                                                                | U                                                              | Y                                                        | Y                                                                        | U                                                                                                                                           | Y                                                                                                                                       | Y                                                                                                                                       | U                                                                                                                                       |
| Reindollar   | Y                                              | Y                                             | Y                                                                              | Y                                                                              | Y                                                                | Y                                                              | Y                                                        | Y                                                                        | Y                                                                                                                                           | Y                                                                                                                                       | Y                                                                                                                                       | Y                                                                                                                                       |
| Rubio 2013   | Y                                              | N                                             | Y                                                                              | N                                                                              | U                                                                | Y                                                              | U                                                        | Y                                                                        | Y                                                                                                                                           | N                                                                                                                                       | N                                                                                                                                       | U                                                                                                                                       |
| Study                | Was the allocation sequence generated adequately? (selection bias) | Was the allocation of treatment adequately concealed? (selection bias) | Were participants analyzed within the groups they were originally assigned to? (selection bias) | Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? (selection bias) | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (performance bias) | Did the study maintain fidelity to the intervention protocol? (performance bias) | Did attrition was a concern, were missing data handled appropriately? (attrition bias) | In prospective studies, was the length of follow-up the same between the groups or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls? (detection bias) | Were the outcome assessors blinded to the intervention or exposure status of participants? (detection bias) | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? (detection bias) | Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? (reporting bias) |
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| Saharkhiz 2016[20] | Y                                                             | Y                                                             | Y                                                                 | Y                                                                                                                             | Y                                                                                                                             | Y                                                                                                                             | N                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Seckin 2014[14]    | Y                                                             | U                                                             | Y                                                                 | Y                                                                                                                             | Y                                                                                                                             | Y                                                                                                                             | Y                                                                 | N                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Selman 2016[71]    | Y                                                             | Y                                                             | Y                                                                 | Y                                                                                                                             | Y                                                                                                                             | Y                                                                                                                             | Y                                                                 | N                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Singh 2015[72]     | Y                                                             | Y                                                             | Y                                                                 | Y                                                                                                                             | Y                                                                                                                             | Y                                                                                                                             | Y                                                                 | N                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Sismanglu 2009[106]| Y                                                             | N                                                             | N                                                                 | Y                                                                                                                             | N                                                                                                                             | Y                                                                                                                             | Y                                                                 | Y                                                                 | Y                                                                 | U                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Smit 2016[73]      | Y                                                             | N                                                             | Y                                                                 | Y                                                                                                                             | Y                                                                                                                             | Y                                                                                                                             | Y                                                                 | N                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Stadtmauer 2011[151]| Y                                                             | Y                                                             | Y                                                                 | N                                                                                                                             | U                                                                                                                             | Y                                                                                                                             | Y                                                                 | N                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Tartagni 2015[72]  | Y                                                             | U                                                             | Y                                                                 | N                                                                                                                             | U                                                                                                                             | Y                                                                                                                             | Y                                                                 | Y                                                                 | N                                                                 | U                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |
| Tehraninejad 2010[83]| Y                                                             | Y                                                             | Y                                                                 | N                                                                                                                             | Y                                                                                                                             | N                                                                                                                             | Y                                                                 | N                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 | Y                                                                 |</p>
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Abbreviations: N=No; U=Unclear; Y=Yes
Figure G-3 Summary of risk of bias assessment for included RCTs

- Was the allocation sequence generated adequately? (selection bias)
- Was the allocation of treatment adequately concealed? (selection bias)
- Were participants analyzed within the groups they were originally assigned to? (selection bias)
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Appendix H. Supplemental Project to Assess the Transparency of Reporting for Trials Evaluating Treatment for Infertility

Authors: Williams JW Jr., Eaton JL, Gierisch JM, Masilamani V, von Isenburg M, Chobot MM

Background and Objectives

Selective reporting can bias estimates of effect, yet methods to detect such biases are limited.\textsuperscript{1,2} Statistical methods for detecting publication bias (e.g., funnel plots, Beggs rank correlation) are underpowered.\textsuperscript{3} Comparing outcomes listed under Methods versus those reported under Results in published manuscripts is an expedient but crude method for detecting reporting bias.\textsuperscript{4} Another method is to search ClinicalTrials.gov (CT.gov) and (a) compare studies identified there to published studies (to detect publication bias) and (b) compare planned analyses and outcomes reported in CT.gov to those reported in the final publication (to detect reporting bias).\textsuperscript{4,5} The EPC guidance recommends this approach.\textsuperscript{6} While conceptually sound, this approach may be labor-intensive, and its utility uncertain.

The overall goal of this project was to evaluate the utility of CT.gov for detecting selective reporting, and to determine the impact of selective reporting on the estimates of treatment effect. A secondary goal was to estimate the person-hours required to complete these analyses.

To accomplish these goals, we used an ongoing review, Management of Infertility, to explore differences between information from published sources included in the review and CT.gov.

Methods

Scope and General Approach

We adopted a pragmatic approach, using methods that could be readily incorporated into future systematic reviews. To maintain feasibility while still applying our methods to a range of interventions, we included KQ 1, KQ 2, and KQ 4 from the Management of Infertility review in this analysis. The KQs are listed below:

**KQ 1:** What are the comparative safety and effectiveness of available treatment strategies for women with polycystic ovary syndrome (PCOS) who are subfertile/infertile and who wish to become pregnant?

**KQ 2:** What are the comparative safety and effectiveness of available treatment strategies for women with endometriosis who are subfertile/infertile and who wish to become pregnant?

**KQ 4:** What are the comparative safety and effectiveness of available treatments for women with tubal or peritoneal factors (e.g., pelvic adhesions) who are subfertile/infertile and who wish to become pregnant?
Searching CT.gov

We searched CT.gov for trials potentially applicable to the KQs with the assistance of our search librarian. Because CT.gov does not use MeSH-based search terms, we adapted the search strategies developed for the Management of Infertility review to language appropriate for CT.gov. We conducted two searches, a broad search using the basic interface and a more specific search using the advanced interface in CT.gov. For the broad search, we searched for synonyms for infertility (infertility OR infertile OR subfertility OR subfertile OR sub-fertility OR sub-fertile) in the conditions field and limited our results to interventional studies. For the narrow search, we searched for the same synonyms for infertility in the broader search terms field and combined this with multiple, separate searches for each of the conditions of interest. This narrower search was also limited to interventional studies. Exact search strings used in both searches are given in Appendix A.

Results of the two searches were imported into Excel.

Matching Studies

We matched randomized controlled trials (RCTs) identified in CT.gov with those identified for the Management of Infertility review at several levels.

First, we determined whether RCTs reporting a live birth outcome that were included in the Management of Infertility review had a matching record in CT.gov. Matching was performed initially using the NCT identifier (NCTID). Our intention was to conduct this matching using a semi-automated process within EndNote. This approach proved infeasible due to inconsistent assignment of NCTIDs to EndNote fields. Thus, all matching was accomplished by manual review. For unmatched studies, we conducted a secondary match using other trial registration numbers and then trial characteristics, including: condition, intervention, sample size, and author/investigator. Matching was performed initially for the broad CT.gov search. We then determined the proportion of matched studies that were not identified by the narrow CT.gov search.

Second, for matched studies (i.e., studies included in the Management of Infertility review with a CT.gov record), we abstracted selected variables from the CT.gov record to determine whether key study design variables and reported outcomes matched information in the published manuscript. Variables abstracted were:

- Date of completion
- Number of study arms
- Intervention description
- Study design
- Outcomes measures and results prioritized in the Management of Infertility review
- Analysis approach
- Subgroup analyses

Data from CT.gov were compared to published data. For each variable, the result was classified as: matching, discrepant, or possibly discrepant. Discrepant data were defined as cases where information was absent in one source but reported in another, or when the information given in the two sources was contradictory. Discrepancies were summarized narratively.

Third, we screened the unmatched CT.gov citations for potentially eligible completed trials. Eligibility criteria for each KQ are given in Table 1 of the Methods chapter of the main
Management of Infertility review. For potentially eligible studies identified from CT.gov, we used author names and intervention terms to search for a matching publication in PubMed. We classified studies into two groups: (1) potentially eligible completed study without a published manuscript; and (2) potentially eligible completed study with a matching published manuscript that was not identified in the systematic review search.

All matching was limited to studies published since the 2005 International Committee of Medical Journal Editors (ICMJE) policy requiring trial registration. Matching was performed initially by a research assistant, and reviewed by a study investigator. Team members involved in matching piloted the data collection forms and procedures to refine them before full use.

Estimate of Person-Hours Required to Complete the Project

EPC staff routinely log the time spent working on projects using project-specific codes. Co-investigators do not log project time routinely. Therefore, our project coordinator sent regular queries to co-investigators asking for estimates of time spent (to nearest 15 minutes) completing project-specific tasks. These estimates were tracked in an Excel spreadsheet. We used the staff logs and co-investigator reports to estimate the total staff time and co-investigator time dedicated to completing project-related activities.

Impact on Systematic Review Conclusions

Study conclusions will flow from the strength of evidence (SOE). We used the GRADE framework for evaluating SOE, a framework that includes assessment of risk of bias, consistency, precision, directness, and publication bias. The EPC risk of bias tool explicitly considers reporting bias. Therefore, risk of bias and publication bias are the domains most likely to be affected by supplemental data from CT.gov. In collaboration with authors of the Management of Infertility review, we reviewed the SOE table to determine qualitatively whether study conclusions would change.

Results

Results are presented in five sections: 1) concordance between RCTs included in the Management of Infertility review and in CT.gov; 2) studies identified from CT.gov as potentially eligible but not included in the Management of Infertility review; 3) concordance between data from CT.gov and published studies for studies present in both sources; 4) effects of CT.gov results on SOE and review conclusions; and 5) person-hours required to generate these results.

Concordance between RCTs Included in the Management of Infertility Review and in CT.gov

Twenty-four unique RCTs reported live birth as an outcome and were included for KQs 1, 2, and 4 in the Management of Infertility review. The majority of these trials (n=22) were applicable to KQ 1. Of the 24 trials:

- 8 were matched to a CT.gov record by NCTID
- 3 were matched by other trial ID number
- 1 was matched by other criteria (i.e., study characteristics)
- 12 were not matched
All matched studies were confirmed by an investigator. Three preliminary matches based on “other criteria” were not confirmed by study investigators and are included in the 12 unmatched studies above.

Only one-third of the included trials were matched to a CT.gov record using the NCTID, the most reliable and readily applied matching variable. When using all available data, 50% (95% CI, 30 to 50%) of the eligible studies were matched to a CT.gov record.

Studies Identified from CT.gov as Potentially Eligible but Not Included in the Management of Infertility Review

Using broad search criteria, we searched CT.gov for potentially eligible studies. The search yielded 858 registered studies. Of those, 376 were classified as “completed.” The 355 studies published from 2005 forward were reviewed by two study staff, and 94 were flagged as potentially eligible for the Management of Infertility review, with relevance to KQs as follows: KQ1 = 14, KQ 2 = 1, KQ 3 = 69, KQ 4 = 1, KQ 5 = 3, KQ 6 = 1, and multiple KQs = 5.

Of the 16 studies potentially relevant to KQs 1, 2, or 4, 11 had been identified in the Management of Infertility search and included in the review. The other 5 studies were reviewed by an investigator; details are reported in the Table H-1.

<table>
<thead>
<tr>
<th>NCTID</th>
<th>Search Strategy</th>
<th>Identifying Trial</th>
<th>CT.gov Completion Date</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01675843</td>
<td>Both</td>
<td>Both</td>
<td>March 2012</td>
<td>Potentially eligible; no citation in PubMed</td>
</tr>
<tr>
<td>NCT01679574</td>
<td>Both</td>
<td>Both</td>
<td>January 2012</td>
<td>Potentially eligible; no citation in PubMed</td>
</tr>
<tr>
<td>NCT01894074</td>
<td>Both</td>
<td>Broad</td>
<td>July 2015</td>
<td>Potentially eligible, no citation in PubMed</td>
</tr>
<tr>
<td>NCT00220545</td>
<td>Both</td>
<td>Both</td>
<td>March 2006</td>
<td>Identified in original review search but excluded at title-and-abstract screening stage. Full text reviewed and study included in Management of Infertility review</td>
</tr>
<tr>
<td>NCT01581359</td>
<td>Both</td>
<td>Both</td>
<td>May 2015</td>
<td>Potentially eligible, no citation in PubMed</td>
</tr>
</tbody>
</table>

Only 5 potentially eligible studies were identified across the 3 KQs. Of these, 2 are recently completed trials (2015) and no journal publication was expected. Two trials with a combined sample size of 340 patients were completed more than 3 years ago, indicating potential publication bias. Both of these trials were applicable to KQ 1. One trial was excluded at the title-and-abstract screening phase of the review; upon review of the full text, the study was reclassified as eligible and included in the review.

Concordance between Data from CT.gov and Published Studies for Studies Present in Both Sources

Study investigators participating in the transparency project abstracted data independently from CT.gov for the 8 studies matched by the NCTID. These data were compared to data abstracted from published data by the Management of Infertility investigators.

Overall, there were no important differences in the study characteristic descriptions between the two sources. Details are described below:

- The KQ classification matched for all 8 studies.
- The study design and number of study arms matched for all 8 studies.
• Of 5 studies reporting the enrolled “n,” 4 were exact matches and 1 had a discrepancy in the estimated enrollment (326) vs. the number enrolled (320). Three studies did not report the sample size in CT.gov and thus were classified as discrepant.
• Intervention descriptions were substantially concordant for all 8 studies and thus were classified as matching.
• The analytic approach and any plans for subgroup analyses were not addressed in CT.gov for any of the studies. However, subgroup analyses were not reported in the published manuscripts for any of these trials.
• The funding sources was classified as matched for 6 studies. Two studies were classified as discrepant: 1 of these was classified as non-government/non-industry from CT.gov and as “not reported” from manuscript, and 1 was classified as non-government/non-industry from CT.gov and as government from the published manuscript.

Outcomes were compared at 2 levels: the outcomes planned from CT.gov to those reported in published manuscripts, and the results reported in CT.gov to those reported in published manuscripts.
• Planned outcomes: 11 outcomes were reported in both sources and classified as matched. Three outcomes reported as planned in CT.gov were not abstracted from manuscripts: quality of life, miscarriage, and live birth. In 4 studies, outcomes reported in published manuscripts were not described in CT.gov: live birth, miscarriage, multiple births, and surgical complications.
• Only 1 of the 8 trials reported results in CT.gov, and these results matched those reported in the manuscript for the single outcome present in both sources.

Effects of CT.gov Results on Strength of Evidence

Overall, data from CT.gov had little impact on the SOE ratings. Using a threshold of 3 years since reported completion, only 2 completed trials were identified from CT.gov that did not have a matching journal publication. Both trials were applicable to KQ 1 and had a combined sample size of 340 patients. Thirty trials (10,718 patients) were included in the SOE rating for KQ 1, and thus these 2 “missing” trials are unlikely to have had a meaningful impact on study results. Similarly, there was little evidence of reporting bias, with only single mismatches for 3 different outcomes between planned outcomes in CT.gov and reported outcomes in published manuscripts.

Person-Hours Required for Data Collection and Analysis

Overall, the project team devoted an estimated 74.5 hours to planning and conducting this study. Data by investigator vs. staff are given in Table H-2.

<table>
<thead>
<tr>
<th>Name</th>
<th>Administrative (meetings, etc.)</th>
<th>Planning/designing</th>
<th>Running searches/abstracting data</th>
<th>Synthesizing data/writing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>7</td>
<td>9</td>
<td>10.75</td>
<td>7.75</td>
<td>34.5</td>
</tr>
<tr>
<td>EPC Staff</td>
<td>23</td>
<td>0</td>
<td>14</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Totals</td>
<td>30</td>
<td>9</td>
<td>24.75</td>
<td>10.75</td>
<td>74.5</td>
</tr>
</tbody>
</table>
Discussion

This substudy found that CT.gov has important limitations for identifying selective reporting. Only one-third of the studies included in the Management of Infertility review were matched to a CT.gov record based on NCTID, and only 1 of those studies reported results in CT.gov. In addition, there were few discrepancies between planned outcomes reported in CT.gov and those reported in published manuscripts. A careful search and inspection of CT.gov for potentially eligible studies not identified by the review team yielded only 2 studies without a publication and 1 study incorrectly excluded at the title-and-abstract screening stage. These data had no impact on the SOE ratings or study conclusions, but required substantial person-hours to generate.

It is possible that CT.gov will mature into a more useful resource for the purpose of identifying selective reporting. Using data from CT.gov for the dates of trial registration compared to conduct of the study, it is clear that some studies were registered retrospectively. Prospective registration may yield more complete records and more informative data. However, it is likely that changes to CT.gov will be required for this database to serve as a useful source for identifying selective reporting.

At present, these results do not support the routine use of CT.gov to evaluate selective reporting. However, our study examined a small set of interventions for a single condition (infertility) and included a relatively small set of trials. Additional studies are needed before definitive conclusions can be drawn about the utility of CT.gov for detecting selective reporting. If changes to CT.gov were made to facilitate its use for this purpose, other resources could improve efficiency, including: a customized EndNote filter for importing CT.gov results, a standard methodology to guide investigators, and additional data on the activities that can be reliably completed by study staff versus investigators.

References to Appendix H


