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Endometriosis and ectopic pregnancy: A meta-analysis

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Abstract

Objective: To systematically review and perform a meta-analysis of the risk of ectopic pregnancy in endometriosis.

Data sources: MEDLINE (OVID), Embase (OVID), CINAHL (EBSCO) and Cochrane to April 1, 2019. Inclusion criteria: cohort or case-control studies from 1990 onwards. Exclusion criteria: cohort studies without controls, case reports or series, or no English full-text.

Methods of study selection: 1361 titles/abstracts were screened after removal of duplicates, 39 full-texts were requested, and after 14 studies were excluded, there were 15 studies in the meta-analysis.

Tabulation, Integration, and Results: Data was extracted utilizing standardized spreadsheets with two independent reviewers, and conflicts broken by a third reviewer. We performed random effects calculation of weighted estimated average Odds Ratios (OR). Heterogeneity and publication bias were assessed with the I^2 metric and funnel plots/Egger's test, respectively. The Ottawa-Newcastle quality assessment scale was utilized with a cut-off of ≥ 7 for higher quality. There were ten case-control studies (17,972 ectopic pregnancy cases and 485,266 non-ectopic pregnancy controls), and five cohort studies (30,609 women with endometriosis and 107,321 women without endometriosis). For case-control studies, endometriosis was associated with increased risk of ectopic pregnancy with an OR of 2.66 (95%CI=1.14-6.21, p=.02). For cohort studies, the OR was 0.95 (95%CI=0.29-3.11, p=.94), but after post-hoc analysis of the studies with Ottawa-Newcastle score ≥ 7, the OR was 2.16 (95%CI=1.67-2.79, p<.001). For both case-control and cohort studies, there was high heterogeneity among studies (I^2 = 93.9% and I^2 = 96.6%, Q test p < .001), but no obvious evidence of systematic bias in the funnel plot and Egger's test was not significant (p = .35, p = .70), suggesting no strong publication bias. There was insufficient data to make any conclusions with respect to anatomic characteristics of endometriosis (e.g. stage) or mode of conception (e.g. ART vs. spontaneous).

Conclusion: Possible evidence of an association between endometriosis and ectopic pregnancy was observed (OR = 2.16-2.66). However, these results should be considered with caution, due to high heterogeneity between studies. Continued research is needed to delineate the pregnancy implications of endometriosis.

Key words: Ectopic pregnancy, Endometriosis, Meta-analysis, Systematic review

Introduction

Endometriosis' impact on pelvic pain and infertility is well recognized. However, there is increasing evidence for this common condition's implications for other aspects of women's health, including ovarian cancer[1], coronary heart disease[2], autoimmune disease[3], and pregnancy complications[4]. These associations differ in level of evidence; for example a large meta-analysis of 13 studies confirmed the association with ovarian cancer subtypes[1], while the association with coronary heart disease was a recent report from the Nurses Health Study II[2].

Recent meta-analyses have demonstrated evidence for an association between endometriosis and obstetrical outcomes. One meta-analysis showed that endometriosis was associated with later pregnancy complications ranging from placenta previa and cesarean section, to perinatal death and neonatal ICU admission[5]. Also of interest is the impact of endometriosis on early pregnancy, with a previous meta-analysis demonstrating an association between endometriosis and spontaneous abortion[6].

Ectopic pregnancy remains a major cause of morbidity and mortality worldwide[7], and may also be associated with endometriosis due to altered tubo-ovarian anatomy in moderate-to-severe disease. Establishing the risk of ectopic pregnancy in endometriosis is important, so that

women have this knowledge pre-conceptionally and so that clinicians consider endometriosis amongst other ectopic pregnancy risk factors.

Therefore, we conducted a meta-analysis of the association between endometriosis and ectopic pregnancy, given the lack of a such systematic review in the literature. Specifically, we considered both cohort studies and case-control studies. We also planned sub-analyses for ART pregnancies and endometriosis anatomic characteristics (e.g. stage or presence of endometrioma).

Methods

This systematic review was performed according to the PRISMA guidelines[8] and registered on PROSPERO (CRD42019128923) (www.crd.york.ac.uk), and IRB exempt.

Identification of The Literature

A literature search was done using MEDLINE (OVID), Embase (OVID), CINAHL (EBSCO) and Cochrane Library to April 1, 2019 (see Appendix for detailed search strategy). Inclusion criteria: publication from 1990 onwards of a) cohort studies of women with endometriosis vs. women without endometriosis, for the outcome of ectopic pregnancy (retrospective, prospective, and randomized controlled trials); or b) case-control studies. For this systematic review, we considered a cohort study to be one where patients with endometriosis were compared to individuals without endometriosis, for the outcome of ectopic pregnancy ideally through prospective follow-up. We considered a case-control study to be one where ectopic pregnancy cases were compared to controls without ectopic pregnancy, and these cases and controls were examined for a diagnosis of endometriosis as an underlying risk factor. We did not have any a priori restrictions on the diagnosis of endometriosis, recognizing that there was likely to be significant heterogeneity between studies ranging from gold-standard histological confirmation

to use of ICD codes alone. Exclusion criteria: cohort studies without controls, case reports or series, or no English full-text.

Figure 1 shows the PRISMA flow chart. In addition to the literature search, reference lists were searched as well as the grey literature (e.g. Google Scholar). Titles/abstracts were reviewed by two independent reviewers (SM/CB) for full-text review and managed using Rayyan (https://rayyan.qcri.org). If an abstract was not available, the full text was obtained. Duplicates were identified and removed. Conflicts between the two reviewers were broken by a third reviewer (PY). Once full-texts were obtained, they were reviewed by the two independent reviewers (SM/CB) using a standardized data collection spreadsheet, with conflicts decided upon by the third reviewer (PY).

Statistical Analysis

After identification of included studies (see Results and flow chart in Figure 1), a meta-analysis was performed for cohort studies and case-control studies separately. All analyses were carried out in R version 3.5.3 (2019-03-11)[9]. We used a random effects meta-analysis (R package 'metafor'[10]) and calculated estimated average Odds Ratios (OR) and 95% confidence intervals. A random effects model was chosen a priori as we expected differences in the treatment effects among the studies due to clinical heterogeneity of the comparison groups. Forest plots were created, and ORs were weighted by the inverse variance (i.e. weighted towards larger studies). The I^2 metric was calculated to estimate study heterogeneity, prediction intervals were used to assess the impact of this variability on the direction of the estimated average effect, and publication bias assessed by funnel plots and Egger's test[10,11]. The Ottawa-Newcastle quality assessment scale was utilized for each study, with a cut-off of ≥ 7 suggestive of higher quality[12].

Planned a priori sub-analyses for both cohort and case-control studies were for a) ART studies; and b) endometriosis anatomic characteristics (e.g. Stage I/II vs. III/IV, endometrioma presence or characteristics). After inspection of the initial forest plots, we also conducted the following post-hoc sub-analyses: a) histology case-control studies (i.e. where endometriosis was diagnosed on histological examination of salpingectomy specimens); and b) Ottawa-Newcastle score ≥ 7 for cohort studies (due to variation in OR based on study quality).

Results

Inclusion of studies

A total of 1912 studies were identified, 1910 through database searching and 2 through other sources (reference lists and grey literature) (see flow chart in Figure 1). After elimination of 551 duplicates, there were 1361 studies (titles/abstracts) which were screened by the two independent reviewers. Of the 1361 screened studies, 24 studies were included for full-text review, 1179 did not meet inclusion/exclusion criteria, and in 158 there was no consensus between the two reviewers. Among these latter 158 studies, the third reviewer reviewed the full-texts and determined that 15 should be included for full-test review while 143 did not meet inclusion/exclusion criteria. Thus, there were 1322 studies (1179 + 143) excluded and 39 studies (24 + 15) for full-text review. Of the 39, a further 14 studies were excluded for the following reasons: duplicate, non-English, conference abstract only, full-text not available even after contacting authors, and in one study[13], we were unable to calculate the rate of ectopic pregnancy in the non-endometriosis sample. This left 15 studies included in the meta-analysis (Figure 1).

Description of included studies and heterogeneity

Table 1 reflects the main characteristics of each study, including Ottawa-Newcastle scores. There were ten case-control studies (17,972 ectopic pregnancy cases and 485,266 non-ectopic

pregnancy controls)[14-23], and five cohort studies (30,609 women with endometriosis and 107,321 women without endometriosis)[24-28]. There were no randomized controlled trials.

The ten case-control studies (Table 1) varied from high-quality population based studies[20-23], to single institution chart reviews[14]. Eight of the case-control studiesinvolved identification of a previous diagnosis of endometriosis in cases with ectopic pregnancy and controls without ectopic pregnancy. In these studies, the previous diagnosis of endometriosis was based on questionnaires[16-17], on confirmation of a previous surgical diagnosis[18,21], or use of ICD codes[22-23]. Ectopic pregnancy cases were identified either through surgical diagnosis[16-17], ultrasound diagnosis[20-21], or through ICD codes[22-23]. Non-ectopic pregnancy controls ranged from intrauterine pregnancies[14,18,20-22],other women who gave birth within a time interval of the ectopic pregnancy[16-17], or non-pregnant women with no history of ectopic pregnancy[23]. Most studies did not use matched controls, while one matched for age[23]. In contrast to these eight case-control studies, two studies differed substantially in study design: they were “histological” involving comparisons of salpingectomies for ectopic pregnancy and salpingectomies for other reasons and looking for histological endometriosis in the tubal specimen[15,19]. Dates of the study samples ranged from 1983-1989[14] to 2012-2016[22]. Four of the studies involved ART pregnancies only[14, 18, 20, 21], while the remaining were mixed ART and spontaneous or otherwise did not specify mode of conception. Ottawa-Newcastle scores ranged from 3 to 9.

Among the five cohort studies (Table 1), two consisted of high-quality population based cohorts where record linkage was used to follow-up women with endometriosis or without endometriosis (Hjordt-Hansen et al.[25] and Saraswat et al.[28]). In the study of Hjordt-Hansen [25], women from 1977-1982 were included, with the endometriosis group defined by ICD code compared to women without endometriosis who were age-matched. The cohort was followed for 15 years for pregnancy outcomes, and included both ART and spontaneous pregnancies. In the study of

Saraswat et al. [28], women with a first-time surgical diagnosis of endometriosis 1981-2009 using ICD codes were compared to a random sample with no prior diagnosis of endometriosis, who were followed up to 30 years for pregnancy outcomes. One other study was a retrospective cohort comparing women with a surgical diagnosis of endometriosis compared to those without endometriosis at surgery (who had male factor or tubal infertility), with patients then being asked retrospectively about their pregnancy history[24]. The two remaining studies were significantly different[26-27], in that they were small retrospective studies of patients who underwent cystectomy for ovarian endometrioma compared to those with cystectomy for non-endometrioma cyst[27] or those with idiopathic reduced ovarian reserve[26]. Sample sizes varied from <200 for these small retrospective studies, to >100,000 for the population based study of Hjordt-Hansen et al[25]. Ottawa-Newcastle scores ranged from 8-9 for the two population based cohorts[25,28], to 3-4 for the retrospective cohorts[24,26-27].

Case-control studies

The random effects model showed a significant association between ectopic pregnancy and endometriosis (estimated average OR = 2.66, 95% CI = 1.14 to 6.21, p = .02) suggesting that there was higher odds of endometriosis in the ectopic pregnancy group compared to the control group (Figure 2a). There was a large amount of heterogeneity among studies (I^2 = 93.9%, Q test p < .001) (Figure 2a). The 95% prediction intervals were very wide (0.25 to 28.17) suggesting that while the overall average effect was estimated as above one, this may not be true in all settings. Therefore, the true differences in effects among studies may be due to variability in underlying clinical factors between the studies. There was no obvious evidence of systematic bias in the funnel plot, and Egger's test was not significant (p = .35), suggesting no strong publication bias (Figure 3a).

Planned sub-analysis was performed for the four ART studies[14,18,20,21], with estimated average OR = 1.96 (95% CI = 0.45 to 8.62, p = .37) (Figure 2b). However, caution is required because there were only four studies with high heterogeneity (I^2 = 87%, Q test p < .001) (Figure 2b), and the 95% prediction intervals were extremely wide (0.09 to 41.57). Sub-analysis by endometriosis characteristics (e.g. stage or endometrioma) was not possible due to lack of data.

A post-hoc analysis was done for the two studies involving histological examination of salpingectomies[15,19]; there were very low rates of endometriosis in both cases and controls (Figure 2c).

Cohort studies

The random effects model showed no significant association between endometriosis and risk of ectopic pregnancy (estimated average OR = 0.95, 95% CI = 0.29 to 3.11, p = .94) (Figure 4a). There was a large amount of heterogeneity among studies (I^2 = 96.6%, Q test p < .001) (Figure 4a). The 95% prediction intervals were wide (0.07 to 12.78) emphasizing that the specific effects varied widely in both direction and size among the studies. There was no obvious evidence of systematic bias in the funnel plot, and Egger's test was not significant (p = .70), suggesting no strong publication bias, although with only five studies this is difficult to assess (Figure 3b).

Planned sub-analysis by ART was not possible due to only one such study[26]. Similarly, sub-analysis by endometriosis characteristics could not be done due to only one study reporting stage (though without any sub-analysis of ectopic risk by stage)[24], and one study including only patients with stage III-IV endometriosis[27].

Inspection of the forest plot for cohort studies (Figure 4a) revealed that the two large population based cohorts with long-term follow-up and utilization of record linkage (i.e. with higher quality

score ≥ 7 on the Ottawa-Newcastle scale) [25,28] showed significant associations between endometriosis and ectopic pregnancy. Thus a post-hoc analysis was done for these studies with Ottawa-Newcastle score ≥ 7, and the estimated average OR was 2.16 (95% CI 1.67-2.79, p < .001) (Figure 4b). Prediction intervals could not be calculated in this case due to only two studies. The three lower quality cohort studies (excluded from the sub-analysis), which did not show an association between endometriosis and ectopic pregnancy, involved the following: a retrospective chart review where the control group included patients with tubal factor infertility[24]; and two small retrospective studies of the specific subgroup of patients post-cystectomy for ovarian endometriomas[26,27].

Discussion

We found evidence that endometriosis was more common in women with ectopic pregnancy (OR = 2.16), and in a post-hoc analysis, endometriosis was associated with an increased risk of ectopic pregnancy in cohort studies with Ottawa-Newcastle score ≥ 7 (OR = 2.66). There was insufficient data to make any conclusions for risk of ectopic pregnancy in women with endometriosis and ART pregnancies, or in women with Stage I-II vs. III-IV endometriosis or with or without endometriomas. One issue with the ART sub-analysis is that this population is at increased risk of ectopic pregnancy, regardless of presence/absence of endometriosis, which may dilute any associations. For anatomic characteristics of endometriosis, it would have been ideal to be able to do sub-analyses by not only Stage and presence of endometrioma, but also factors such as location of disease (tubal vs. non-tubal), deep vs. superficial, degree of tubo-ovarian adhesions, and the procedure that was done at the time of the index surgery (e.g. excision vs. ablation, and completeness of treatment). Unfortunately, this detailed phenotyping was simply not available in the reviewed studies.

It is important to emphasize that the statistical association observed in this meta-analysis does not necessarily imply causation. It is possible that endometriosis and ectopic pregnancy may share underlying risk factors (whether genetic or environmental), which can explain their association. In addition, there may be confounding demographic factors not controlled in these studies (e.g. age, parity), which may explain the observed associations. However, there are also several possible etiological mechanisms for the association between endometriosis and ectopic pregnancy. Some factors may be tubo-ovarian adhesions, tubal endometriosis lesions, or ovarian endometriomas that alter tubo-ovarian relationships. However, future studies taking into account endometriosis anatomic factors are necessary to test these hypotheses. There may also be alterations in tubal physiology in endometriosis, similar to those seen in uterine eutopic endometrium[29], perhaps related to the peritoneal inflammation seen in endometriosis[30]. In addition, one study showed an association between pelvic inflammatory disease and subsequent risk of endometriosis, which suggests salpingitis (whether diagnosed or subclinical) as a potential factor in endometriosis-associated ectopic pregnancy[31].

Given the evidence for an association between endometriosis and ectopic pregnancy, patients with endometriosis should be counseled about the possible increased risk of extrauterine implantation. Although it is not possible to infer the specifics of this counseling based on this review alone, we speculate that this may be particularly important in those with other risk factors, such as previous ectopic or pelvic inflammatory disease. We also hypothesize that early ultrasound to locate the pregnancy may be indicated in some patients with endometriosis, depending on their profile of risk factors. Moreover, it is possible that in patients with ectopic pregnancy who have been managed medically – particularly those with recurrence – there may be a role for laparoscopy to investigate endometriosis-associated anatomic abnormalities as a risk factor. However, it remains to be seen whether excision/ablation of disease and lysis of

associated adhesions reduces risk of future ectopic pregnancy, either in general or in specific cases that alter tubo-ovarian anatomy.

Strengths of the study include analysis of both cohort and case-control studies, and an apparent lack of publication bias. Amongst limitations was heterogeneity in study design (cohort or case-control), dates of study samples (ranging from 1977-2016), sample sizes (from <20 to >100,000), how endometriosis was diagnosed (gold standard histopathological confirmation vs. ICD coding alone), and in ascertainment of the sample (ranging from single center to population based studies) (Table 1). There was also insufficient data to perform sub-analyses based on anatomic characteristics of endometriosis, including stage, anatomic subtype, location of disease, or type of surgical procedure (ablation vs. excision). In addition, the studies in this review would primarily involve tubal ectopic pregnancies, and it is not certain that the findings could be generalized to the rarer ectopic pregnancies such as interstitial, cervical, cesarean, or ovarian.

In summary, endometriosis may be associated with ectopic pregnancy, as it is for spontaneous abortion[6] and later perinatal complications[5]. A very recent analysis of the Nurses' Health Study II, which was published after the dates of this systematic review, confirmed an association between endometriosis and ectopic pregnancy, spontaneous abortion, and gestational diabetes and hypertension[32]. As the evidence for the importance of endometriosis in pregnancy becomes more apparent, guidelines may be needed for the obstetrical care of patients with endometriosis.

References

1. Pearce CL, Templeman C, Rossing MA, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol.* 2012;13:385-94.

2. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and Risk of Coronary Heart Disease. *Circ Cardiovasc Qual Outcomes*. 2016;9:257-64.

3. Kvaskoff M, Mu F, Terry KL, et al. Endometriosis: a high-risk population for major chronic diseases? *Hum Reprod Update.* 2015;21:500-16.

4. Chen I, Lalani S, Xie RH, Shen M, Singh SS, Wen SW. Association between surgically diagnosed endometriosis and adverse pregnancy outcomes. *Fertil Steril*. 2018;109:142-7.

5. Lalani S, Choudhry AJ, Firth B, et al. Endometriosis and adverse maternal, fetal and neonatal outcomes, a systematic review and meta-analysis. *Hum Reprod.* 2018;33:1854-65.

6. Zullo F, Spagnolo E, Saccone G, et al. Endometriosis and obstetrics complications: a systematic review and meta-analysis. *Fertil Steril.* 2017;108:667-72 e5.

7. Committee on Practice Bulletins - Gynecology. ACOG Practice Bulletin No. 191: Tubal Ectopic Pregnancy. *Obstet Gynecol.* 2018;131:e65-e77.

8. Moher D LA, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6:e1000097.

9. Team RC. *R: A language and environment for statistical computing.* Vienna: R Foundation for Statistical Computing; 2019.

10. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Software.* 2010;36:1-48.

11. Sterne JAC E, M. Regression methods to detect publication and other bias in meta-analysis. In: Rothstein HR SA, Borenstein M, eds. *Publication bias in meta-analysis: prevention, assessment, and adjustments*. New York: Wiley; 2005:99-110.

12. Bae JM. A suggestion for quality assessment in systematic reviews of observational studies in nutritional epidemiology. *Epidemiol Health*. 2016;38:e2016014.

13. Clayton HB, Schieve LA, Peterson HB, Jamieson DJ, Reynolds MA, Wright VC. Ectopic pregnancy risk with assisted reproductive technology procedures. *Obstet Gynecol.* 2006;107:595-604.

14. Dubuisson JB, Aubriot FX, Mathieu L, Foulot H, Mandelbrot L, de Joliere JB. Risk factors for ectopic pregnancy in 556 pregnancies after in vitro fertilization: implications for preventive management. *Fertil Steril.* 1991;56:686-90.

15. Kutluay L, Vicdan K, Turan C, Batioglu S, Oguz S, Gokmen O. Tubal histopathology in ectopic pregnancies. *Eur J Obstet Gynecol Reprod Biol*. 1994;57:91-4.

16. Coste J, Bouyer J, Job-Spira N. Construction of composite scales for risk assessment in epidemiology: an application to ectopic pregnancy. *Am J Epidemiol*. 1997;145:278-89.

17. Bunyavejchevin S, Havanond P, Wisawasukmongchol W. Risk factors of ectopic pregnancy. *J Med Assoc Thai*. 2003;86 Suppl 2:S417-21.

18. Malak M, Tawfeeq T, Holzer H, Tulandi T. Risk factors for ectopic pregnancy after in vitro fertilization treatment. *J Obstet Gynecol Can.* 2011;33:617-9.

19. Dahiya N, Singh A, Kalra R, Sen R, Kumar S. Histopathological changes associated with ectopic tubal pregnancy. *IJPSR.* 2011;2:929-33.

20. Perkins KM, Boulet SL, Kissin DM, Jamieson DJ, National ARTSG. Risk of ectopic pregnancy associated with assisted reproductive technology in the United States, 2001-2011. *Obstet Gynecol.* 2015;125:70-8.

21. Weiss A, Beck-Fruchter R, Golan J, Lavee M, Geslevich Y, Shalev E. Ectopic pregnancy risk factors for ART patients undergoing the GnRH antagonist protocol: a retrospective study. *Reprod Biol Endocrinol.* 2016;14:12.

22. Jacob L, Kalder M, Kostev K. Risk factors for ectopic pregnancy in Germany: a retrospective study of 100,197 patients. *Ger Med Sci.* 2017;15:Doc19.

23. Hwang A, Chou L, Islam MM, Li YC, Syed-Abdul S. Risk factors for ectopic pregnancy in the Taiwanese population: a retrospective observational study. Archives of gynecology and obstetrics 2016;294:779-83.

24. Matalliotakis IM, Cakmak H, Fragouli YG, Goumenou AG, Mahutte NG, Arici A. Epidemiological characteristics in women with and without endometriosis in the Yale series. *Arch Gynecol Obstet.* 2008;277:389-93.

25. Hjordt Hansen MV, Dalsgaard T, Hartwell D, Skovlund CW, Lidegaard O. Reproductive prognosis in endometriosis. A national cohort study. *Acta Obstet Gynecol Scand.* 2014;93:483-9.

26. Roustan A, Perrin J, Debals-Gonthier M, Paulmyer-Lacroix O, Agostini A, Courbiere B. Surgical diminished ovarian reserve after endometrioma cystectomy versus idiopathic DOR: comparison of in vitro fertilization outcome. *Hum Reprod.* 2015;30:840-7.

27. Kostrzewa M, Stachowiak G, Zyla M, et al. Women's fertility after laparoscopic cystectomy of endometrioma and other benign ovarian tumors - a 24-month follow-up retrospective study. *Neuro Endocrinol Lett.* 2016;37:295-300.

28. Saraswat L, Ayansina DT, Cooper KG, et al. Pregnancy outcomes in women with endometriosis: a national record linkage study. *BJOG*. 2017;124:444-52.

29. Bulun SE. Endometriosis. *N Engl J Med.* 2009;360:268-79.

30. Morotti M, Vincent K, Brawn J, Zondervan KT, Becker CM. Peripheral changes in endometriosis-associated pain. *Hum Reprod Update.* 2014;20:717-36.

31. Tai FW, Chang CY, Chiang JH, Lin WC, Wan L. Association of pelvic inflammatory disease with risk of endometriosis: a nationwide cohort study involving 141, 460 individuals. *J Clin Med.* 2018;24:E379.

32. Farland LV, Prescott J, Sasamoto N, et al. Endometriosis and risk of adverse pregnancy outcomes. *Obstet Gynecol*. 2019;134:527-536.

Figure legends

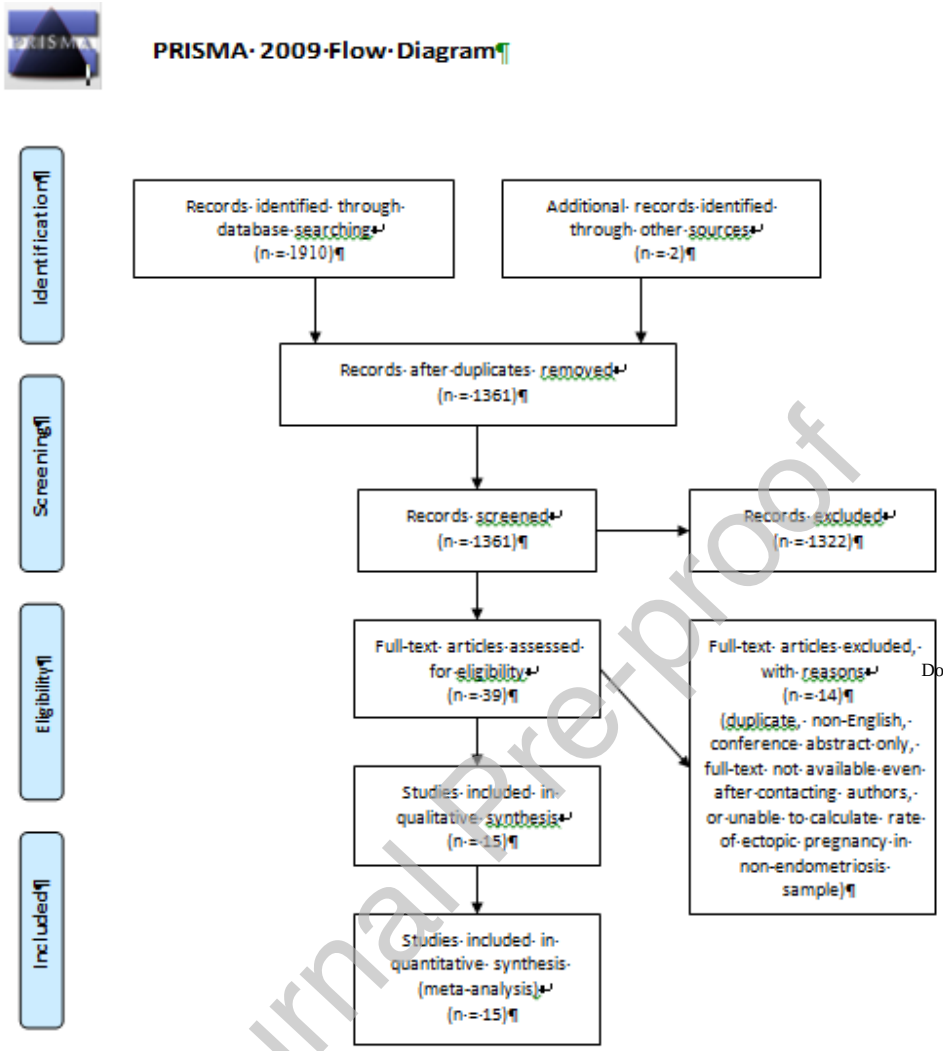

Figure 1. PRISMA diagram

Flow chart of included and excluded studies

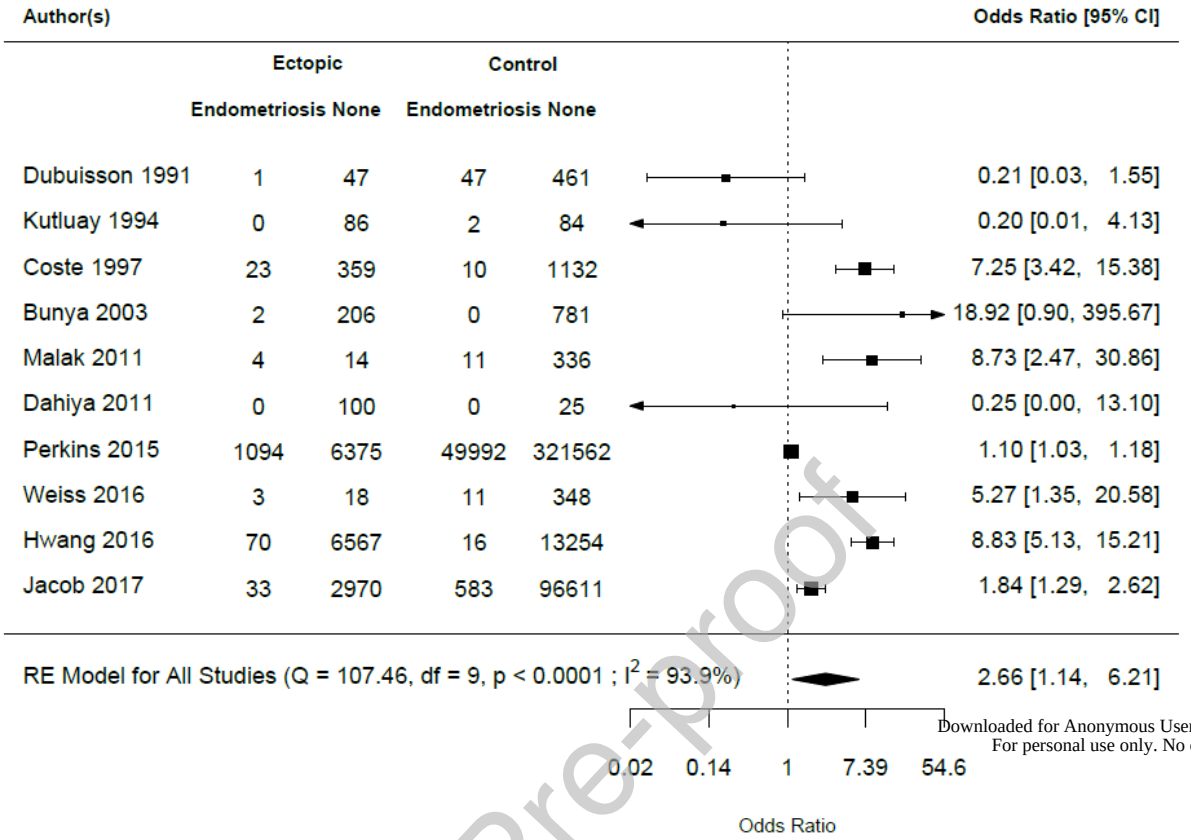

Figure 2a. Forest plot for case-control studies

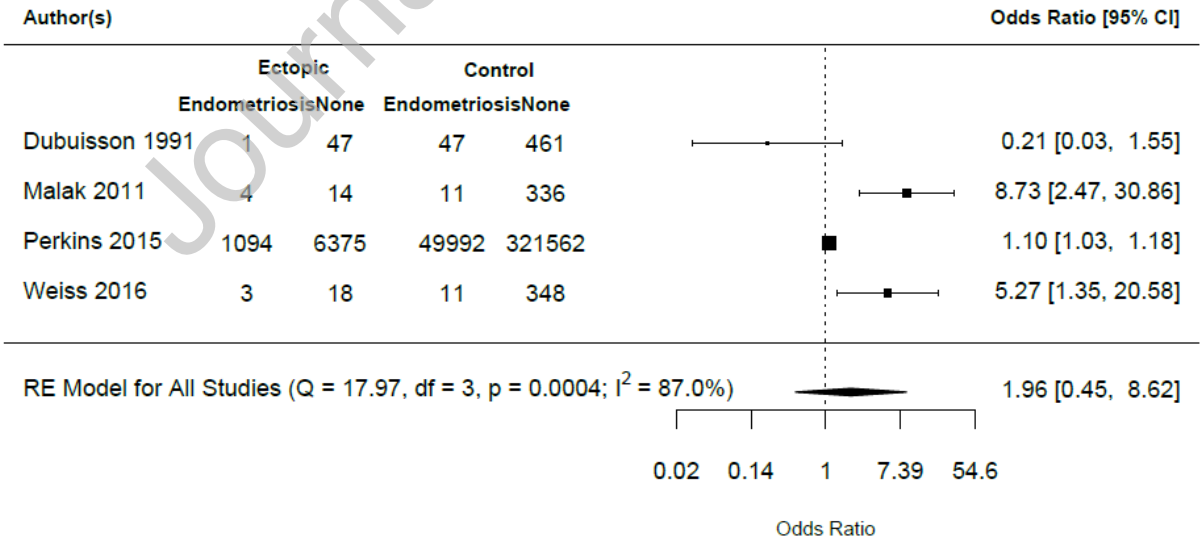

Figure 2b. Sub-analysis for ART case-control studies

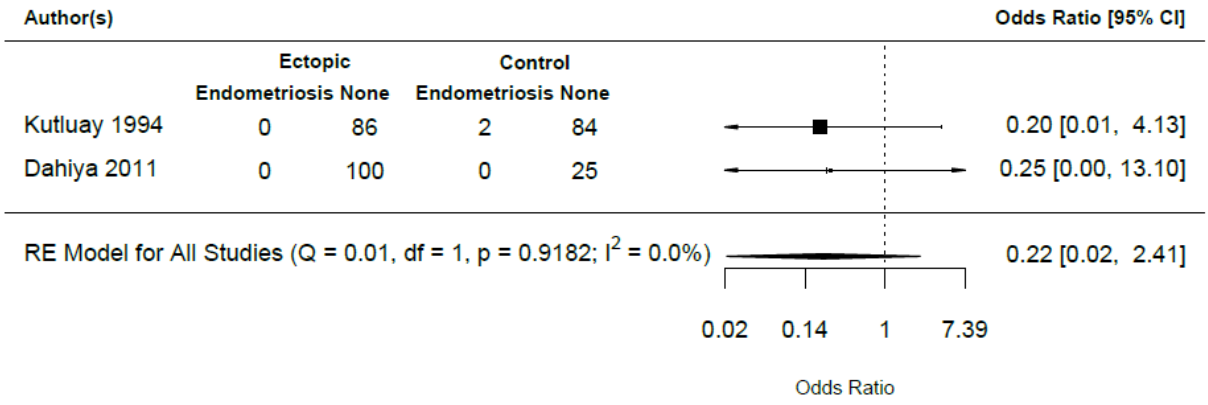

Figure 2c. Sub-analysis for histology case-control studies (post-hoc)

Forest plots for a) all case-control studies; b) sub-analysis of case-control studies involving only ART pregnancies; c) sub-analysis of case-control studies involving pathological exam of salpingectomy specimens (for ectopic pregnancy vs. other indications for salpingectomy).

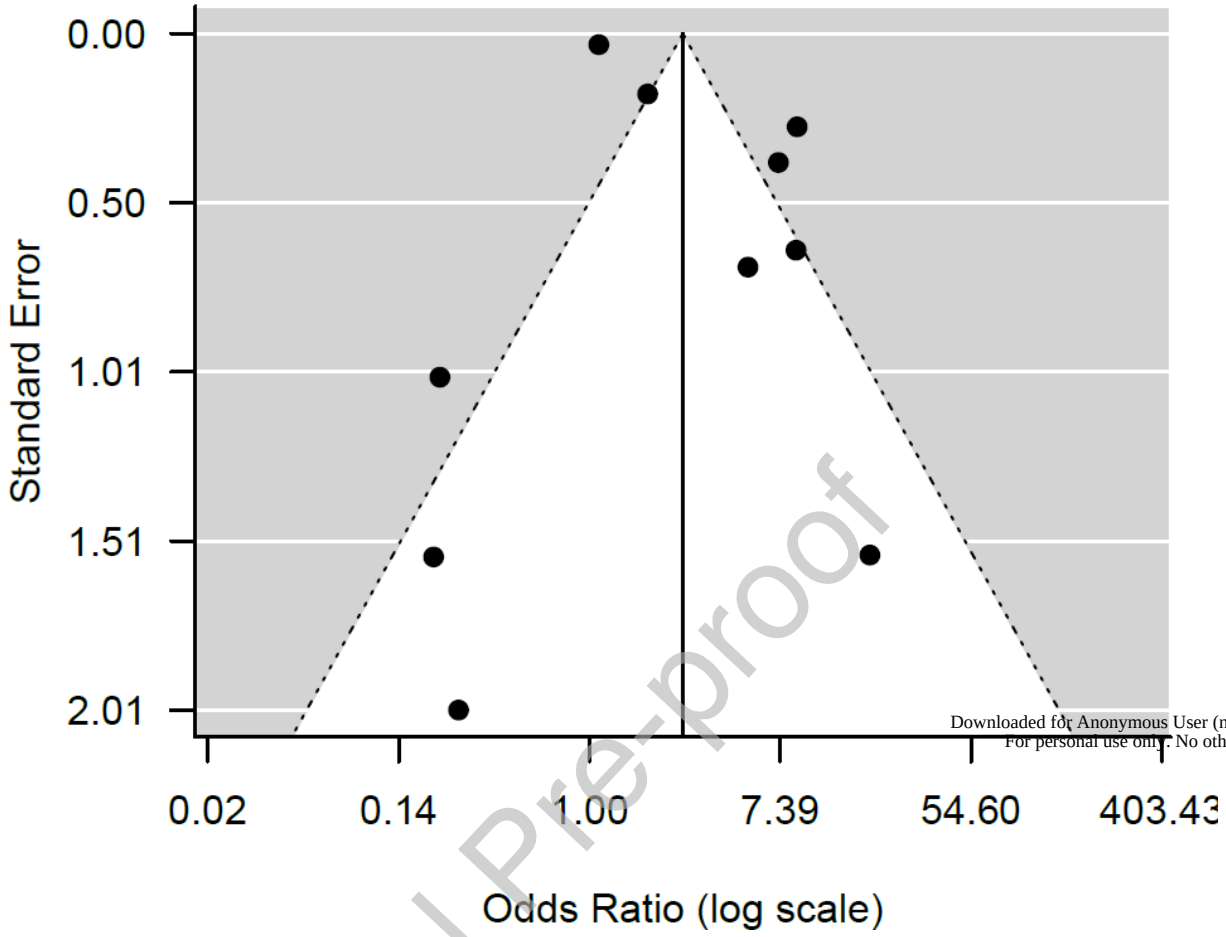

Figure 3a. Funnel plot for case-control studies

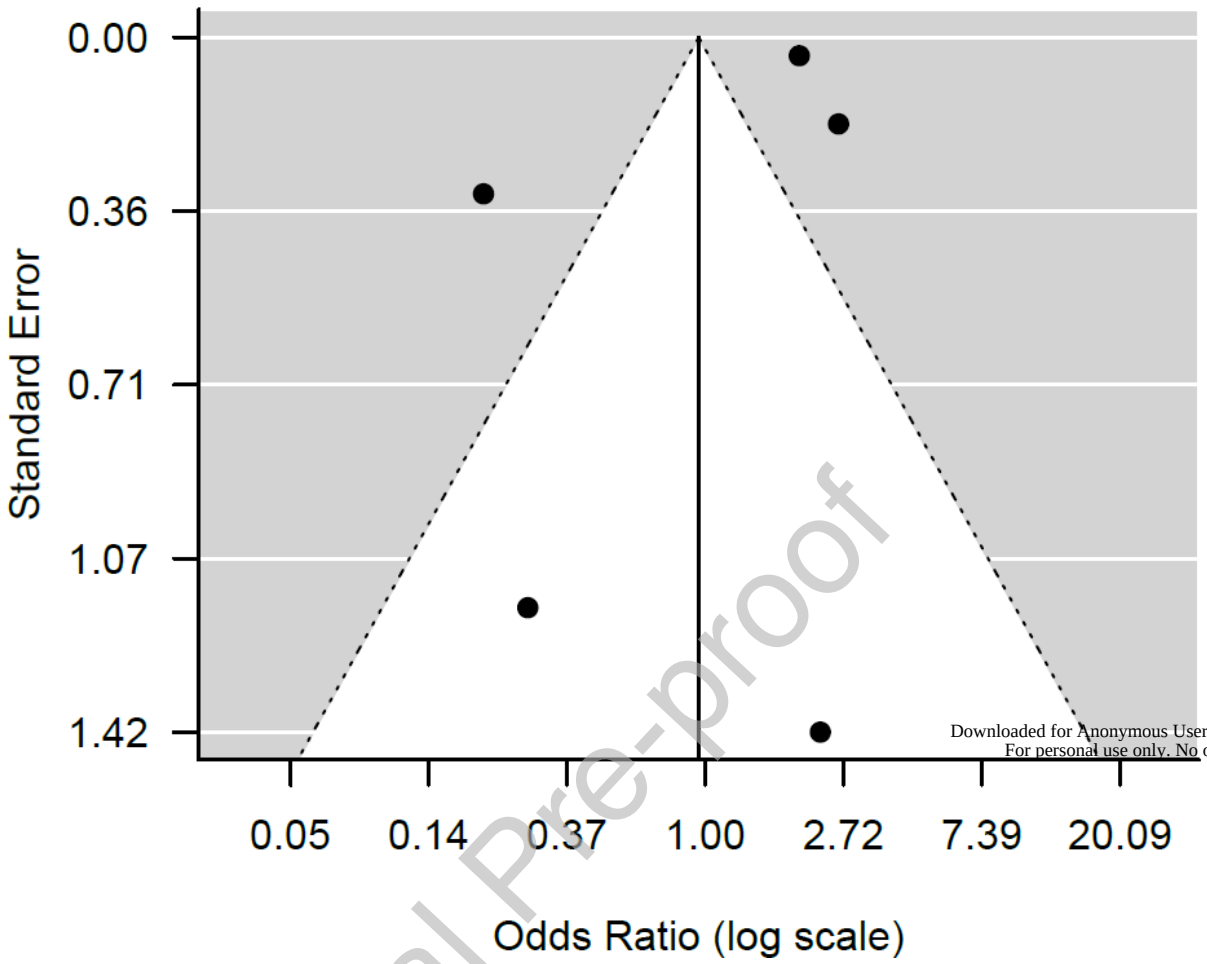

Figure 3b. Funnel plot for cohort studies

Funnel plot for a) all case-control studies; and b) all cohort studies.

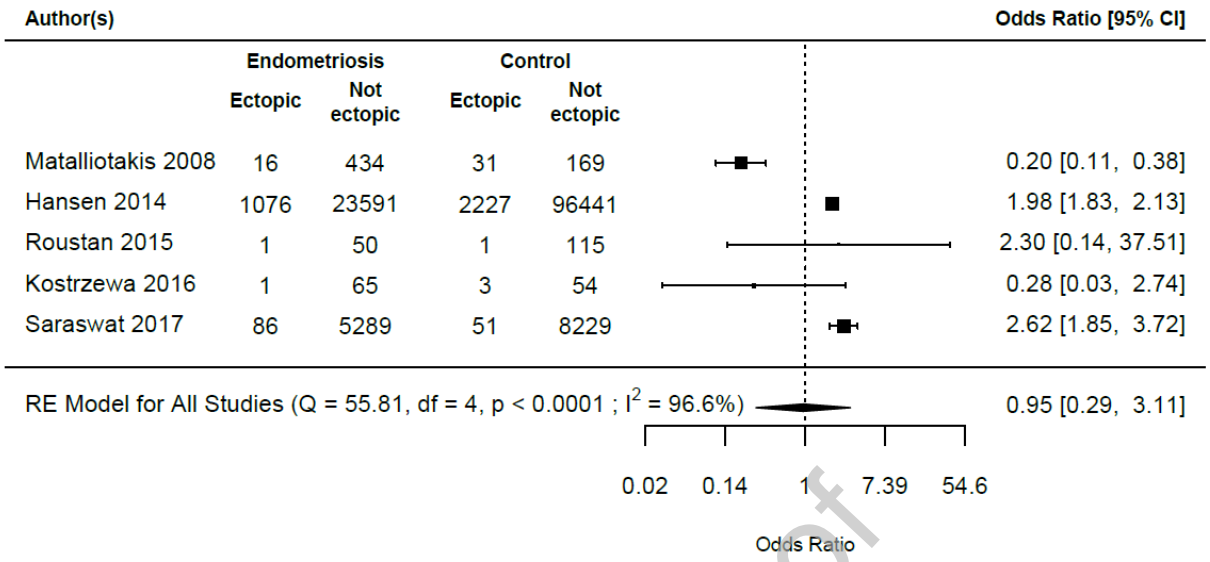

Figure 4a. Forest plot for cohort studies

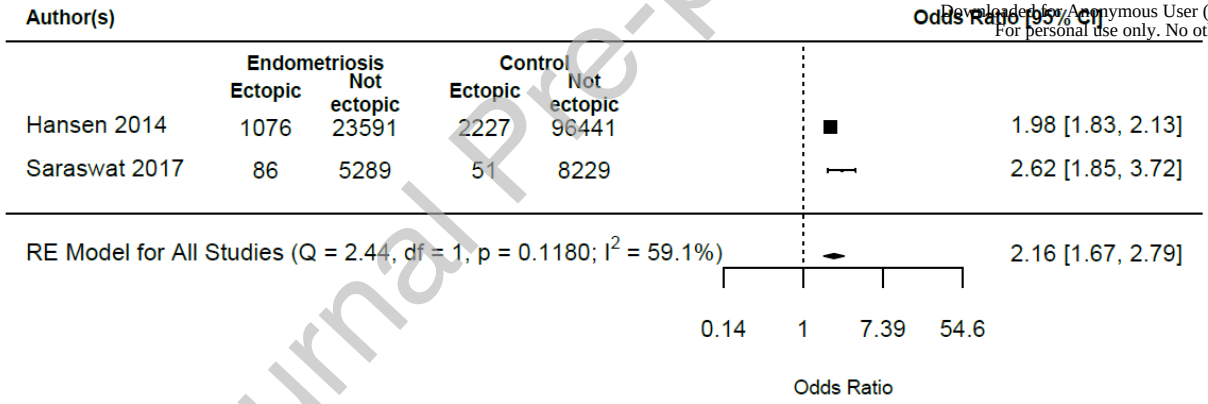

Figure 4b. Sub-analysis for cohort studies with Ottawa Newcastle score ≥ 7 (post-hoc)

Forest plots for a) all cohort studies; b) sub-analysis of cohort studies with Ottawa-Newcastle score ≥ 7 (i.e. population database studies involving record linkage and long-term follow-up of participants).

Table 1 Characteristics of selected studies (n = 15)

Study	Study Design	Inclusion Criteria	Exclusion Criteria	Endometriosis group	Non-endometriosis group	Types of pregnancies	Ottawa-Newcastle
COHORT STUDIES							
Matalliotakis et al. (2008)	Retrospective cohort, with chart review of prior reproductive history at time of surgery	Women of reproductive-age, with laparoscopy or laparotomy for pain or infertility between 1996-2002	Former smokers	Pelvic endometriosis diagnosed at surgery, "married" (n = 450 women)	No endometriosis at surgery, male factor or tubal infertility (n = 200 women)	Not specified *	3
Hjordt Hansen et al. (2014)	Population based cohort, follow-up of pregnancies over 15 years	Women 15-49 years old at any time during 1977-1982	N/A	Discharge diagnosis of endometriosis through ICD-8 or ICD-10 codes (n = 24667 women)	No endometriosis, age-matched 4:1 (n = 98668 women)	Spontaneous + ART	8
Roustan et al. (2015)	Retrospective cohort, with follow-up of IVF cycles	Age ≤ 40 years, seen 2010-2014, with AMH < 2.0 ng/mL who underwent IVF	Lack of patient consent, donor oocyte, or chromosomal abnormality	Infertility related to decreased ovarian reserve for least 12 months with history of unilateral or bilateral	Idiopathic decreased ovarian reserve: no prior ovarian surgery and no ultrasound evidence of endometrioma, matched 2:1	ART	3

				ovarian cystectomy(s) for endometrioma via laparoscopy or laparotomy with histopathological confirmation (n = 51 women)	by AMH level (n = 116 women)		
Kostrezewa et al. 2016	Retrospective study, follow-up 2 years after cystectomy	Women 18–40 years, laparoscopic cystectomy involving excision and "careful electrocoagulation" between 2009-2012, who reported effort to become pregnant at 2 years	Previous adnexal surgery, unable to contact at 2 years	Endometrioma (n = 66 women)	Non-endometrioma cyst (n = 57 women)	Not specified	4
Saraswat et al. (2017)	Population based cohort, follow-up of pregnancies between 1 and 30 years	1981-2010	Multiple births, clinical diagnosis of endometriosis without surgery	First-time surgical diagnosis of endometriosis from 1981-2009, using ICD codes, with subsequent pregnancy	Random sample with no prior diagnosis of endometriosis, who had pregnancy during study period, 1:1 ratio (n = 8280	Not specified	9

				until 2010 (n = 5375 women with a pregnancy)	women with a pregnancy)		
CASE CONTROL STUDIES				**Cases (ectopic pregnancy)**	**Controls (non-ectopic pregnancy)**		
Dubuisson et al. (1991)	Retrospective study at single center, endometriosis defined as indication for IVF	1983-1989	N/A	Consecutive ectopic pregnancies after IVF (n = 48)	Intrauterine pregnancies after IVF (n = 508)	ART	3
Kutluay et al. (1994)	Salpingectomies, fallopian tubes examined histologically for endometriosis	1991-1992	N/A	Salpingectomy for ectopic pregnancy, with extensive tubal damage or desire for definitive contraception (n = 86)	Salpingectomy for reasons other than ectopic pregnancy, matched for age and parity (n = 86)	Not specified	5
Coste et al. 1997)	Seven hospitals, endometriosis diagnosis based on questionnaires collected by physicians or midwives	1988-1994, aged 15-44 years, married or living as married	Using contraception at time of conception	Women with ectopic pregnancy diagnosed by laparoscopy or laparotomy)	Women giving birth immediately after case surgery, 2:1 (n = 1142)	Spontaneous and ART	4

				(n = 382)			
Bunyavejchevin et al. (2003)	Single hospital, endometriosis diagnosed and treated by physician as determined by trained interviewers and standardized questionnaire	1999-2000	N/A	Ectopic pregnancy diagnosed by laparoscopy or laparotomy and pathology confirmed (n = 208)	Women who gave birth at term to healthy neonates on randomly selected days, within 1 week of case, 1:4 (n = 781)	Not specified	2
Malak et al. (2011)	Consecutive women who conceived following IVF at fertility center, chart review with endometriosis diagnosed at previous surgery	2003-2008	N/A	Ectopic pregnancy (n = 18)	Intrauterine pregnancy (n = 347)	ART	3
Dahiya et al. (2011)	Prospective study of salpingectomies, fallopian tubes examined histologically for endometriosis	N/A	N/A	Salpingectomy for ectopic pregnancy (n = 100)	Salpingectomy for sterilization (n = 25)	Not specified	3
Perkins et al. (2015)	Population based study of ART clinics, endometriosis diagnosis from database	Transcervical embryo transfer from 2001-2011 resulting in clinical intrauterine, ectopic, or heterotopic	N/A	Ectopic pregnancy diagnosed when gestational sac confirmed outside of	Intrauterine pregnancy diagnosed when ultrasound confirmed gestational sac in uterus (n =	ART	7

		pregnancy		uterus by ultrasound or high b-hCG in absence of intrauterine pregnancy on ultrasound, plus heterotopic pregnancies (n = 7469 where endometriosis could be diagnosed or excluded)	371554 where endometriosis could be diagnosed or excluded)		
Weiss et al. (2016)	Database of IVF cycles, endometriosis previously surgically diagnosed	Last menstrual period 2010-2015, GnRH antagonist ART cycle with sonographically identifiable intrauterine or ectopic pregnancy	Biochemical pregnancies or pregnancies of unknown location	Ectopic pregnancy diagnosed by non-homogenous adnexal mass adjacent to ovary, a mass with an echoic ring around gestational sac, or a gestational sac with fetal pole (n = 21)	Intrauterine pregnancy diagnosed by gestational sac with echoic ring on ultrasound (n = 359)	ART	7
Hwang et al. (2016)	Population based, with endometriosis	2003-2011	N/A	Aged 15-60 years with at	Age matched with no history	Not specified	6

	identified using ICD codes for 5 years prior to initial ectopic pregnancy diagnosis			least two ectopic pregnancies using ICD codes (n = 6637)	of ectopic pregnancy, 2:1 (n = 13270)		
Jacob et al. (2017)	Population based, 262 gynecologic practices, endometriosis diagnosed using ICD codes	Aged 16-45 years, 2012-2016, followed for at least 365 days prior to index date	N/A	Pregnant women diagnosed with ectopic pregnancy using ICD codes (n = 3003)	Pregnant women without ectopic pregnancy (n = 97194)	Not specified	9

*Not specified = likely reflects both spontaneous and ART pregnancies

Search documentation

Summary

Total	1910
Duplicates removed	494
Deduplicated total	1416
Further duplicates removed manually	57
Final Total	1359 (+ 2 from other sources = 1361)

Databases

Database	Ovid Medline
Database time coverage	1946-present
Date searched	1 April 2019
Number of records before deduplication	593
Number of records after deduplication	589

Database	Ovid Embase
Database time coverage	1947-present
Date searched	1 April 2019
Number of records before deduplication	1178
Number of records after deduplication	736

Database	Cochrane Library (Wiley interface)
Database time coverage	1995-present
Date searched	1 April 2019
Number of records before deduplication	82 (14 reviews, 67 trials, 1 protocol – didn't include)
Number of records after deduplication	61

Database	CINAHL Plus
Database time coverage	1937-present
Date searched	1 April 2019
Number of records before deduplication	58
Number of records after deduplication	30

Search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily <1946 to Present> # Search Statement Results Annotation

1 exp Endometriosis/ 20614

2 endometrio*.tw,kf. 28331

3 1 or 2 31645

4 exp Pregnancy, Ectopic/ 14295

5 ((ectopic or abdominal or angular or cornual or heterotopic or ovar* or tubal or interstitial or uter* tube or extrauterine or extra uterine or oviduct* or fallopian) adj2 (pregnan* or fertili#ation)).tw,kf. 16808

6 4 or 5 19762

7 3 and 6 593

Embase Classic+Embase <1947 to 2019 March 29> # Search Statement Results Annotation

1 endometriosis/ 36851

2 endometrio*.tw,kw. 43658

3 1 or 2 50144

4 exp ectopic pregnancy/ 22171

5 ((ectopic or abdominal or angular or cornual or heterotopic or ovar* or tubal or interstitial or uter* tube or extrauterine or extra uterine or oviduct* or fallopian) adj2 (pregnan* or fertili#ation)).tw,kw. 21236

6 4 or 5 26645

7 3 and 6 1178

Cochrane

#1 MeSH descriptor: [Endometriosis] explode all trees 742

#2 (endometrio*):ti,ab,kw 2575

#3 #1 or #2 2575

#4 MeSH descriptor: [Pregnancy, Ectopic] explode all trees 162

#5 ((ectopic or abdominal or angular or cornual or heterotopic or ovar* or tubal or interstitial or "uter* tube" or extrauterine or "extra uterine" or oviduct* or fallopian) NEAR/2 (pregnan* or fertilization or fertilisation)) 1584

#6 #4 or #5 1584

#7 #3 and #6 82

CINAHL

#	Query	Limiters/Expanders	Last Run Via	Results
S7	S3 AND S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	58
S6	S4 OR S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	3,425
S5	TI ((ectopic or abdominal or angular or cornual or heterotopic or ovar* or tubal or interstitial or "uter* tube" or extrauterine or "extra uterine" or oviduct* or fallopian) N2 (pregnan* or fertilization or fertilisation)) OR AB ((ectopic or abdominal or angular or cornual or heterotopic or ovar* or tubal or interstitial or "uter* tube" or extrauterine or "extra uterine" or oviduct* or fallopian) N2 (pregnan* or fertilization or fertilisation))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	2,767
S4	(MH "Pregnancy, Ectopic")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen	2,195

			- Advanced Search Database - CINAHL Plus with Full Text	
S3	S1 OR S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	5,033
S2	TI endometrio*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	4,086
S1	(MH "Endometriosis")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	3,710