Human Reproduction, Vol.33, No.10 pp. 1854–1865, 2018
Advanced Access publication on September 17, 2018 doi:10.1093/humrep/dey269

human reproduction

META-ANALYSIS ***Gynaecology***

Endometriosis and adverse maternal, fetal and neonatal outcomes, a systematic review and meta-analysis

S. Lalani[1], A.J. Choudhry[2], B. Firth[2], V. Bacal[1,2], Mark Walker[1,2], S.W. Wen[1,2], S. Singh[1,2], A. Amath[2], M. Hodge[2], and I. Chen[1,2,*]

[1]Department of Obstetrics and Gynecology, University of Ottawa/The Ottawa Hospital, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada
[2]Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada

*Correspondence address.1967 Riverside Drive, Rm 7236-3, Ottawa, Ontario, Canada K1H 7W9. Tel. +1-613-738-8400x81740; E-mail: ichen@toh.on.ca

Submitted on April 7, 2018; resubmitted on June 4, 2018; accepted on September 4, 2018

STUDY QUESTION: How is endometriosis associated with adverse maternal, fetal and neonatal outcomes of pregnancy?

SUMMARY ANSWER: Women with endometriosis are at elevated risk for serious and important adverse maternal (pre-eclampsia, gestational diabetes, placenta praevia and Cesarean section) and fetal or neonatal outcomes (preterm birth, PPROM, small for gestational age, stillbirth and neonatal death).

WHAT IS KNOWN ALREADY: A number of studies have shown an association between endometriosis and certain adverse maternal and fetal outcomes, but the results have been conflicting with potential for confounding by the use of assisted reproductive technology.

STUDY DESIGN, SIZE, DURATION: A systematic review and meta-analysis of observational studies (1 January 1990–31 December 2017) that evaluated the effect of endometriosis on maternal, fetal and neonatal outcomes was conducted.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Studies were considered for inclusion if they were prospective or retrospective cohort or case–control studies; included women greater than 20 weeks gestational age with endometriosis; included a control group of gravid women without endometriosis; and, reported at least one of the outcomes of interest. Each study was reviewed for inclusion, data were extracted and risk of bias was assessed by two independent reviewers.

MAIN RESULTS AND THE ROLE OF CHANCE: The search strategy identified 33 studies (sample size, $n = 3\,280\,488$) for inclusion. Compared with women without endometriosis, women with endometriosis had higher odds of pre-eclampsia (odds ratio [OR] = 1.18 [1.01–1.39]), gestational hypertension and/or pre-eclampsia (OR = 1.21 [1.05–1.39]), gestational diabetes (OR = 1.26 [1.03–1.55]), gestational cholestasis (OR = 4.87 [1.85–12.83]), placenta praevia (OR = 3.31 [2.37, 4.63]), antepartum hemorrhage (OR = 1.69 [1.38–2.07]), antepartum hospital admissions (OR = 3.18 [2.60–3.87]), malpresentation (OR = 1.71 [1.34, 2.18]), labor dystocia (OR = 1.45 [1.04–2.01]) and cesarean section (OR = 1.86 [1.51–2.29]). Fetuses and neonates of women with endometriosis were also more likely to have preterm premature rupture of membranes (OR = 2.33 [1.39–3.90]), preterm birth (OR = 1.70 [1.40–2.06]), small for gestational age <10th% (OR = 1.28 [1.11–1.49]), NICU admission (OR = 1.39 [1.08–1.78]), stillbirth (OR = 1.29 [1.10, 1.52]) and neonatal death (MOR = 1.78 [1.46–2.16]). Among the subgroup of women who conceived spontaneously, endometriosis was found to be associated with placenta praevia, cesarean section, preterm birth and low birth weight. Among the subgroup of women who conceived with the use of assisted reproductive technology, endometriosis was found to be associated with placenta praevia and preterm birth.

LIMITATIONS, REASONS FOR CAUTION: As with any systematic review, the review is limited by the quality of the included studies. The diagnosis for endometriosis and the selection of comparison groups were not uniform across studies. However, the effect of potential misclassification would be bias towards the null hypothesis.

WIDER IMPLICATIONS OF THE FINDINGS: The association between endometriosis with the important and serious pregnancy outcomes observed in our meta-analysis, in particular stillbirth and neonatal death, is concerning and warrants further studies to elucidate the mechanisms for the observed findings.

STUDY FUNDING/COMPETING INTEREST(S): Dr Shifana Lalani is supported by a Physicians' Services Incorporated Foundation Research Grant, and Dr Innie Chen is supported by a University of Ottawa Clinical Research Chair in Reproductive Population Health and Health Services. Dr Singh declares conflicts of interests with Bayer, Abvie, Allergan and Cooper Surgical. All other authors have no conflicts of interests to declare.

REGISTRATION NUMBER: PROSPERO CRD42015013911.

Key words: endometriosis / pregnancy outcomes / assisted reproduction / stillbirth / meta-analysis

Introduction

Endometriosis is a chronic inflammatory condition characterized by the presence of endometrial glands and stroma outside of the uterine cavity and diagnosed by surgery (Leyland *et al.*, 2010; Acién and Velasco, 2013). It affects 10–15% of reproductive age women (Missmer and Cramer, 2003; Macer and Taylor, 2012), and may cause dyspareunia, dysmenorrhea and infertility. As 30–50% of women with endometriosis may have difficulty conceiving (Macer and Taylor, 2012), more women with endometriosis are achieving pregnancy through ART (Stephansson *et al.*, 2009).

Endometriosis may be associated with altered ovulation and oocyte production, increased inflammatory cells in the peritoneal fluid, ovarian endometriomata, and disruption of normal endometrium all of which alter the uterine environment and may compromise normal embryonic development (Koch *et al.*, 2012; Macer and Taylor, 2012; Harb *et al.*, 2013). It is possible that such disturbances in the peri-implantation period may perpetuate throughout the later stages in pregnancy resulting in adverse maternal and fetal outcomes (Maggiore *et al.*, 2016).

There have been many studies in the literature, especially in more recent years, showing an association between endometriosis and certain adverse maternal and fetal outcomes such as preterm birth, pre-eclampsia, placenta praevia and postpartum hemorrhage (Hadfield *et al.*, 2009; Healy *et al.*, 2010; Kuivasaari-Pirinen *et al.*, 2012; Aris, 2014; Stern *et al.*, 2015; Berlac *et al.*, 2017; Glavind *et al.*, 2017; Saraswat *et al.*, 2017; Chen *et al.*, 2018). However, the reported findings are conflicting, as some studies have shown a positive association while others have not. Further, given that many studies include women conceiving with the use of assisted reproduction, the relationship between endometriosis and adverse perinatal outcomes may be confounded by the higher rates of endometriosis among women requiring fertility treatment (Stephansson *et al.*, 2009; Benaglia *et al.*, 2016).

Given the prevalence of endometriosis and the clinical significance of adverse pregnancy outcomes, we conducted a systematic review of the literature to investigate the association between endometriosis and maternal, fetal and neonatal outcomes. In addition to reviewing the outcomes frequently reported in the literature, we also performed an extensive review for less commonly reported but important fetal and neonatal outcomes, such as stillbirth and neonatal death. Where appropriate, we performed a meta-analysis to provide an estimate of the effect for each outcome. To remove the effect of potential confounding with assisted reproduction, we performed a stratified analysis, where possible, to determine the effect of endometriosis on pregnancy outcomes in the subgroup of women with spontaneous conception and the subgroup of women with assisted reproduction.

Materials and Methods

The methods for this review were developed in accordance with the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup *et al.*, 2000), and registered *a priori* in the International Prospective Register of Systematic Reviews (PROSPERO registration no. CRD42015013911). Two independent reviewers were available at all stages of the study, including study selection, data extraction and assessment of risk of bias, with a third reviewer available to resolve any discrepancies.

Search strategy and selection criteria

The search protocol was developed by an experienced university librarian to identify studies investigating endometriosis and various adverse maternal, fetal and neonatal outcomes (Supplementary Data). The electronic bibliographic databases Embase and Medline were searched for publications 1 January 1990–31 December 2017, and reference lists of identified articles were hand-searched for additional studies (Supplementary Data).

Study selection

Studies were included if they (i) were prospective or retrospective cohort or case–control studies, (ii) included women >20 weeks gestational age with endometriosis and (iii) included a control group of gravid women without endometriosis. Studies needed to clearly describe case ascertainment for endometriosis and report at least one of the outcomes of interest. The primary outcomes of this study were determined *a priori* and included maternal (pre-eclampsia, placenta previa, antepartum hemorrhage, placental abruption, malpresentation, labor dystocia, cesarean section, postpartum hemorrhage), fetal and neonatal (preterm birth, preterm premature rupture of membranes, intrauterine growth restriction, neonatal compromise, APGAR and fetal/neonatal death) outcomes. The secondary outcomes were to assess for the presence of any other clinically important adverse pregnancy outcomes reported in the literature. Studies were excluded from the review if the data were not extractable. Abstracts, reviews, letters to the editor, case reports and case series were also excluded.

Data extraction

A standardized data extraction form was used to extract information on study design; patient characteristics (age, gravidity, parity, body mass index, race); the diagnosis of endometriosis (mode of diagnosis, severity);

use of assisted reproductive technology; and details regarding any reported adverse pregnancy outcomes.

Data analysis

Data for adverse outcomes were collected as dichotomous data, and the results were given as odds ratios (OR) with 95% CI. Where appropriate, study results were combined in meta-analysis using a random-effects model for a pooled OR and 95% CI. Where possible, subgroup analyses were performed for women who conceived spontaneously and for women who conceived by assisted reproduction. Forest plots and I^2 statistic were calculated for each study outcome for each group. All analyses were performed using RevMan 5.3.

Risk of bias

The risk of bias was assessed for each study using the Newcastle–Ottawa Scale (NOS) for the selection of study groups (up to 4 stars/points); comparability of groups (up to 2 stars/points); and, the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively (up to 3 stars/points) (Wells et al., 2014).

Results

The electronic search strategy identified 3925 records, and 2794 studies were identified following the removal of duplicates. Following title and abstract screen, 117 studies were included for full text review, and 33 studies (sample size, n = 3 280 488) were included in the meta-analysis (Fig. 1) (Kortelahti et al., 2003; Omland et al., 2005; Brosens et al., 2007; Fernando et al., 2009; Hadfield et al., 2009; Healy et al., 2010; Kuivasaari-Pirinen et al., 2012; Takemura et al., 2013; Aris, 2014; Conti et al., 2014; Mekaru et al., 2014; Rombauts et al., 2014; Baggio et al., 2015; Lin et al., 2015; Messerlian et al., 2015; Stern et al., 2013, 2015; Benaglia et al., 2012, 2016; Exacoustos et al., 2016; Fujii et al., 2016; Guo et al., 2016; Harada et al., 2016; Jacques et al., 2016; Morassutto et al., 2016; Berlac et al., 2017; Glavind et al., 2017; Li et al., 2017; Mannini et al., 2017; Pan et al., 2017; Saraswat et al., 2017; Tzur et al., 2018; Chen et al., 2018).

Of the included studies, thirteen studies (n = 70 306) only included women who conceived by ART, and two studies (n = 586) only included women who conceived spontaneously. Five studies (n = 1 735 474) included women stratified by spontaneous and assisted reproduction. Overall, 12 studies (n = 1 473 747) did not identify or separate patients according to the method of conception. The remaining one study (n = 375) had two subsets of analyses whereas one was for women without identification of method of conception and another with documented ART and no-ART (Table I).

All included women

Compared with women without endometriosis, women with endometriosis had higher odds of pre-eclampsia (13 studies; OR = 1.18 [1.01–1.39]), gestational hypertension and/or pre-eclampsia (24 studies; OR = 1.21 [1.05, 1.39]), gestational diabetes (12 studies; OR = 1.26 [1.03–1.55]), gestational cholestasis (1 study; OR = 4.87 [1.85–12.83]), placenta praevia (18 studies; OR = 3.31 [2.37, 4.63]) (Fig. 2), antepartum hemorrhage (5 studies; OR = 1.69 [1.38–2.07]), antepartum hospital admissions (1 study; OR = 3.18 [2.60–3.87]), malpresentation (1 study; OR = 1.71 [1.34, 2.18]), labor dystocia (1 study; OR = 1.45 [1.04–2.01]) and cesarean section (20 studies; OR = 1.86 [1.51–2.29]) (Fig. 3 and Table II).

Fetuses and neonates of women with endometriosis were also more likely to have preterm premature rupture of membranes (PPROM) (7 studies; OR = 2.33 [1.39–3.90]), preterm birth (23 studies; OR = 1.70 [1.40–2.06]) (Fig. 4), small for gestational age < 10th percentile (19 studies; OR = 1.28 [1.11–1.49]), NICU admission (7 studies; OR = 1.39 [1.08–1.78]), stillbirth (7 studies; OR = 1.29 [1.10, 1.52]) (Fig. 5) and neonatal death (3 studies; OR = 1.78 [1.46–2.16]). Maternal endometriosis had borderline association with infant low birth weight <2500 g (12 studies; OR = 1.13 [1.00–1.27]) (Table III).

Endometriosis was not found to be associated with subchorionic hematoma (1 study; OR = 2.47 [0.22–28.33]), placental abruption (12 studies; OR = 1.46 [0.98–2.19]), induction of labor (2 studies; OR = 1.23 [0.44–3.44]), operative vaginal delivery (5 studies; OR = 1.05 [-0.70–1.57]), postpartum hemorrhage (10 studies; OR = 1.19 [0.89–-1.59]), APGAR <7 at 5 min (4 studies; OR = 0.65 [0.20–2.11]), APGAR <7 at 1 min (2 studies; OR = 0.75 [0.34–1.68]) and low venous pH <7.15 (1 study; OR = 2.01 [0.18–22.48]) (Tables II and III).

Subgroup of women with known spontaneous conception

Among the subgroup of women who conceived spontaneously, the presence of endometriosis was found to be associated with placenta praevia (3 studies; OR = 6.83 [2.10–22.24]) (Fig. 2), cesarean section (6 studies; OR = 1.76 [1.51–2.06]) (Fig. 3), preterm birth (7 studies; OR = 1.70 [1.38–2.10]) (Fig. 4) and low birth weight <2500 g (3 studies; OR = 1.52 [1.13, 2.05]) (Tables II and III).

For women who conceived spontaneously, endometriosis was not found to be associated with pre-eclampsia (2 studies; OR = 1.21 [0.94, 1.56]), gestational hypertension and/or pre-eclampsia (5 studies; OR = 1.12 [0.90, 1.39]), gestational diabetes (2 studies; OR = 1.30 [0.85, 1.98]), placental abruption (2 studies; OR = 2.53 [0.08, 79.34]), postpartum hemorrhage (2 studies; OR = 0.85 [0.70, 1.04]), small for gestational age <10th percentile (6 studies; OR = 1.13 [0.92, 1.40]) and NICU admission (1 studies; OR = 0.81 [0.28, 2.36]) (Tables II and III).

Subgroup of women with known assisted reproduction

Among the subgroup of women who conceived with the use of assisted reproductive technology, the presence of endometriosis was found to be associated with placenta praevia (8 studies; OR = 3.33 [1.52–7.30]) (Fig. 2) and preterm birth (10 studies; OR = 1.27 [1.04–1.55]) (Fig. 4) (Tables II and III).

For women with assisted reproduction, endometriosis was not found to be associated with pre-eclampsia (7 studies; OR = 0.89 [0.48–1.67]), gestational hypertension and/or pre-eclampsia (5 studies; OR = 0.79 [0.56, 1.11]), gestational diabetes (5 studies; OR = 1.08 [0.73–1.60]), gestational cholestasis (2 studies; OR = 1.01 [0.05–21.97]), antepartum hemorrhage (1 studies; OR = 1.21 [0.96–1.52]), placental abruption (3 studies; OR = 0.35 [0.09–1.32]), cesarean section (7 studies; OR = 1.24 [0.89–1.71]) (Fig. 3), postpartum hemorrhage (3 studies; OR = 1.21 [0.86–1.71]), small for gestational age <10th percentile (9 studies; OR = 1.04 [0.83–1.30]), low birthweight <2500 g (6 studies; OR = 0.87 [0.59–1.27]), NICU admission

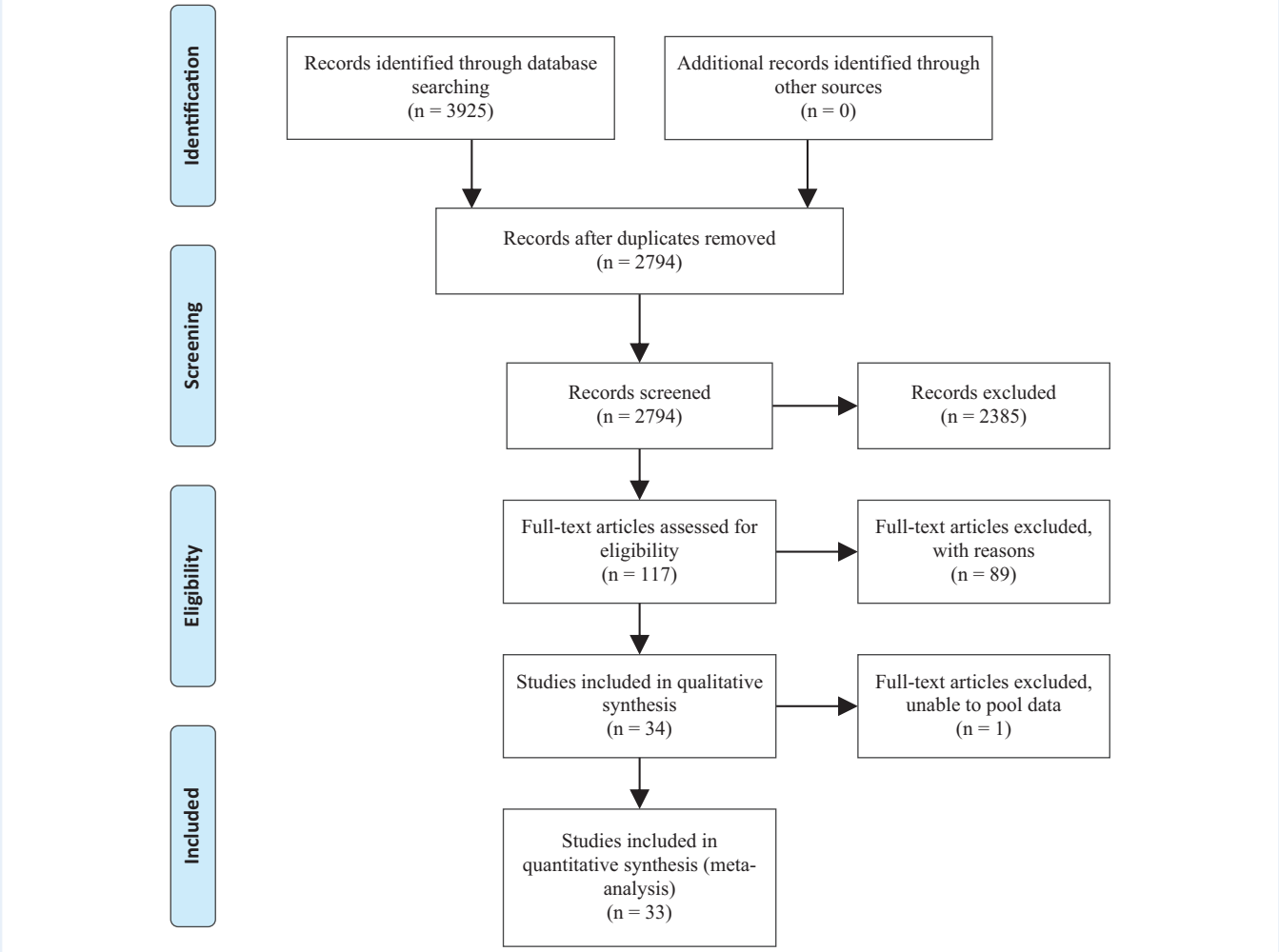

Figure 1 PRISMA diagram for selection of included studies for endometriosis and adverse maternal, fetal and neonatal outcomes—a systematic review and meta-analysis.

(3 studies; OR = 1.58 [0.91–2.75]) and stillbirth (2 studies; OR = 7.16 [0.74–69.57]) (Fig. 5) (Tables II and III).

There was insufficient information specific to either of these subgroups of women to assess the association with antepartum admission, PPROM, malpresentation, labor dystocia, induction of labor, operative vaginal delivery, low APGAR, low venous pH, subchorionic hematoma and neonatal death.

Risk of bias

Following assessment using the NOS, three studies had a medium risk of bias, with stars/scores of NOS 4 (Takemura *et al.*, 2013; Baggio *et al.*, 2015) and NOS 6 (Kuivasaari-Pirinen *et al.*, 2012). The remaining 30 studies had an NOS stars/scores of 7 or greater, indicating low risk of bias (Supplementary Table SI).

Discussion

In our systematic search of the literature, we found that the number of studies investigating the effect of endometriosis on pregnancy outcomes has risen substantially in recent years, verifying the growing relevance of this topic in an era of increasing use of assisted conception.

Maternal outcomes

The relationship between endometriosis and pre-eclampsia has been reported in the literature with conflicting findings, with some studies reporting increased risk (Berlac *et al.*, 2017), no risk (Hadfield *et al.*, 2009; Harada *et al.*, 2016) and even decreased risk (Brosens *et al.*, 2007). Our pooled results suggest that there is an association between endometriosis and pre-eclampsia. Similarly, endometriosis was also found to be associated with gestational diabetes. This stands in contrast to another review specific to this outcome, which did not find an association, possibly due to a smaller number of included studies and smaller sample size (Pérez-López *et al.*, 2017). When subgroup analysis was performed for both of these outcomes, no association was seen in either subgroup. Given the lack of association on subgroup analysis and the modest effect sizes observed, the findings are difficult to interpret in light of the observational nature of the included studies. Only one study

Table I Characteristics of included studies for endometriosis and adverse maternal, fetal and neonatal outcomes—a systematic review and meta-analysis.

Authors(s) (year)	Study design	Endometriosis	Non-endometriosis	Mode of conception	Case ascertainment for endometriosis
Aris (2014)	Retrospective cohort	784	30 284	Combined spontaneous and assisted	Surgical/Histological
Baggio *et al.* (2015)	Retrospective cohort	30	93	Combined spontaneous and assisted	Surgical/Histological
Benaglia *et al.* (2012)	Retrospective cohort	61	130	Assisted reproduction	Clinical
Benaglia *et al.* (2016)	Case–control	239	239	Assisted reproduction	Surgical/Histological or clinical
Berlac *et al.* (2017)	Retrospective cohort	19 331	1 071 920	Combined spontaneous and assisted	Existing database codes
Brosens *et al.* (2007)	Retrospective cohort	245	274	Assisted reproduction	Surgical/Histological or existing record
Chen *et al.* (2018)	Retrospective cohort	469	51 733	Combined spontaneous and assisted	Existing database codes
Conti *et al.* (2014)	Prospective cohort	219	1331	Combined spontaneous and assisted	Surgical/Histological
Exacoustos *et al.* (2016)	Prospective cohort	41	300	Stratified by spontaneous and assisted	Surgical/Histological
Fernando *et al.* (2009)	Retrospective cohort	630	1140	Assisted reproduction	Clinical or existing record
Fuji *et al.* (2016)	Retrospective cohort	92	512	Assisted reproduction	Surgical/Histological
Glavind *et al.* (2017)	Retrospective cohort	1719	81 074	Stratified by spontaneous and assisted	Existing database codes
Guo *et al.* (2016)	Retrospective cohort	129	145	Assisted reproduction	Surgical/Histological
Hadfield *et al.* (2009)	Retrospective cohort	3239	205 640	Stratified by spontaneous and assisted	Existing database codes
Harada *et al.* (2016)	Prospective cohort	330	8856	Combined spontaneous and assisted	Clinical
Healy *et al.* (2010)	Retrospective cohort	1265	5465	Assisted reproduction	Not described
Jacques *et al.* (2016)	Case–control	113	113	Assisted reproduction	Existing record in files
Kortelahti *et al.* (2003)	Case–control	137	137	Combined spontaneous and assisted	Surgical/Histological
Kuivasaari-Pirinen *et al.* (2012)	Retrospective cohort	49	26 870	Assisted reproduction	Surgical/Histological or clinical
Li *et al.* (2017)	Retrospective cohort	75	300	Stratified by spontaneous and assisted	Surgical/Histological
Lin *et al.* (2015)	Retrospective cohort	249	249	Spontaneous	Surgical/Histological
Mannini *et al.* (2017)	Retrospective cohort	262	524	Stratified by spontaneous and assisted	Surgical/Histological
Mekaru *et al.* (2014)	Retrospective cohort	40	48	Spontaneous	Surgical/Histological
Messerlian *et al.* (2015)	Retrospective cohort	269	16 712	Combined spontaneous and assisted	Not described
Omland *et al.* (2005)	Retrospective cohort	212	274	Assisted reproduction	Surgical/Histological
Pan *et al.* (2017)	Retrospective cohort	2578	10 312	Combined spontaneous and assisted	Surgical/Histological
Rombauts *et al.* (2014)	Retrospective cohort	376	4016	Assisted reproduction	Clinical
Saraswat *et al.* (2017)	Retrospective cohort	4232	6707	Combined spontaneous and assisted	Surgical/Histological
Stephansson *et al.* (2009)	Retrospective cohort	13 090	1 429 585	Stratified by spontaneous and assisted	Existing database codes
Stern *et al.* (2013)	Retrospective cohort	7937	19 475	Assisted reproduction	Not described

Continued

Table I *Continued*

Authors(s) (year)	Study design	Endometriosis	Non-endometriosis	Mode of conception	Case ascertainment for endometriosis
Stern *et al.* (2015)	Retrospective cohort	996	297 987	Combined spontaneous and assisted	Existing database codes
Takemura *et al.* (2013)	Case–control	44	261	Assisted reproduction	Surgical/Histological or MRI
Tzur *et al.* (2018)	Retrospective cohort	35	467	Combined spontaneous and assisted	Surgical/Histological

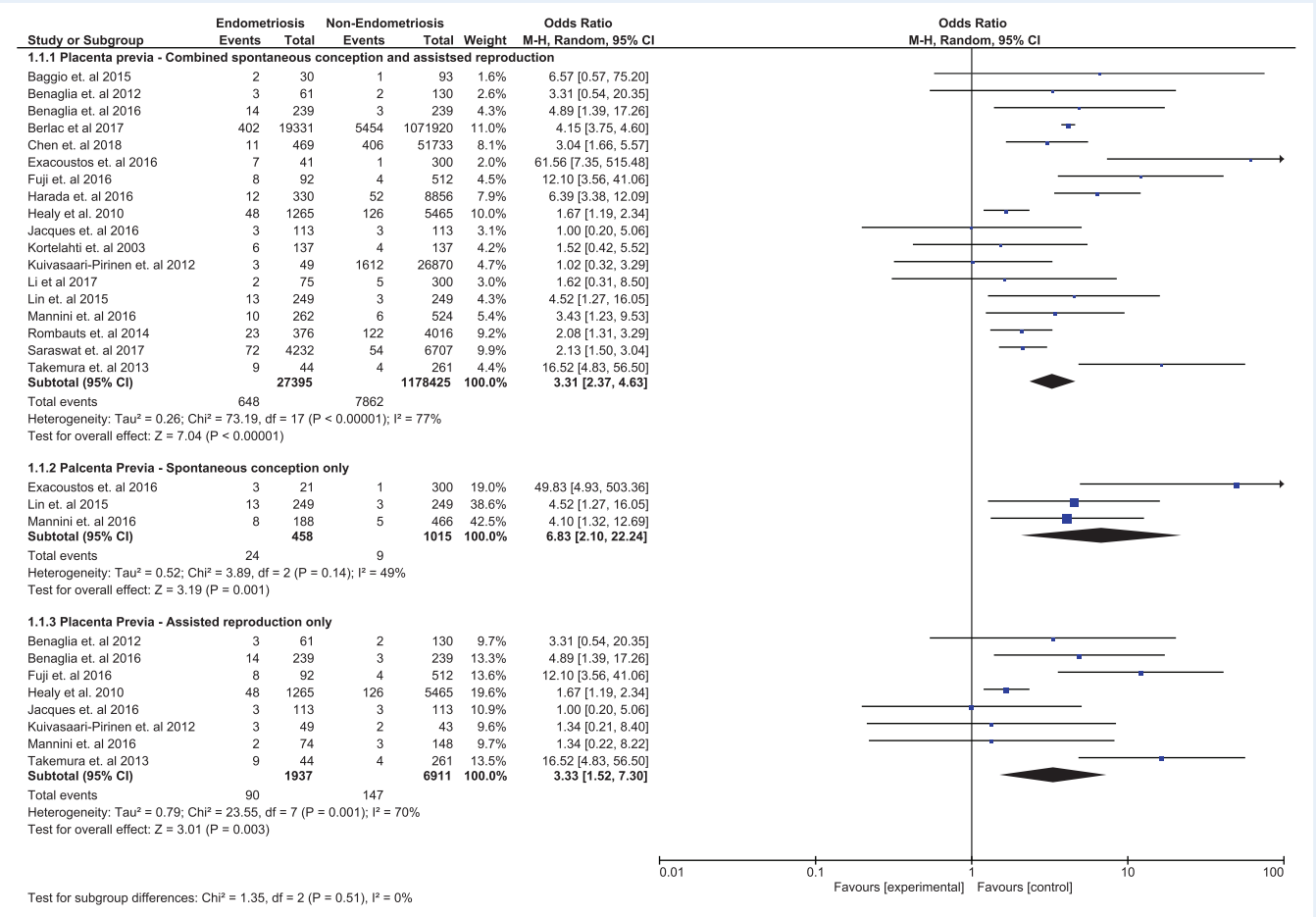

Figure 2 Forest plot for association between endometriosis and placenta praevia by mode of conception.

reported outcomes for gestational cholestasis (Mannini *et al.*, 2017), an interesting finding that warrants further exploration.

The finding of the association between endometriosis and placenta praevia is well-documented (Maggiore *et al.*, 2016) and may explain other less reported findings, such as the increased odds of antepartum hemorrhage and antepartum admission. While it has been suggested that the relationship may be confounded by the increased use of assisted reproduction in women with endometriosis, we found that the association was observed in both women who had spontaneous conception and assisted reproduction.

The findings of malpresentation and cesarean section may be explained in part by the association with placenta praevia, though one study reported increased risk of labor dystocia as well. However, this latter finding may require further corroboration, as pooled results from five studies did not detect increased odds of operative vaginal delivery.

Fetal and neonatal conditions

The association between endometriosis and preterm birth observed in our review is consistent with the literature (Kuivasaari-Pirinen *et al.*, 2012; Conti *et al.*, 2014; Exacoustos *et al.*, 2016; Berlac *et al.*, 2017).

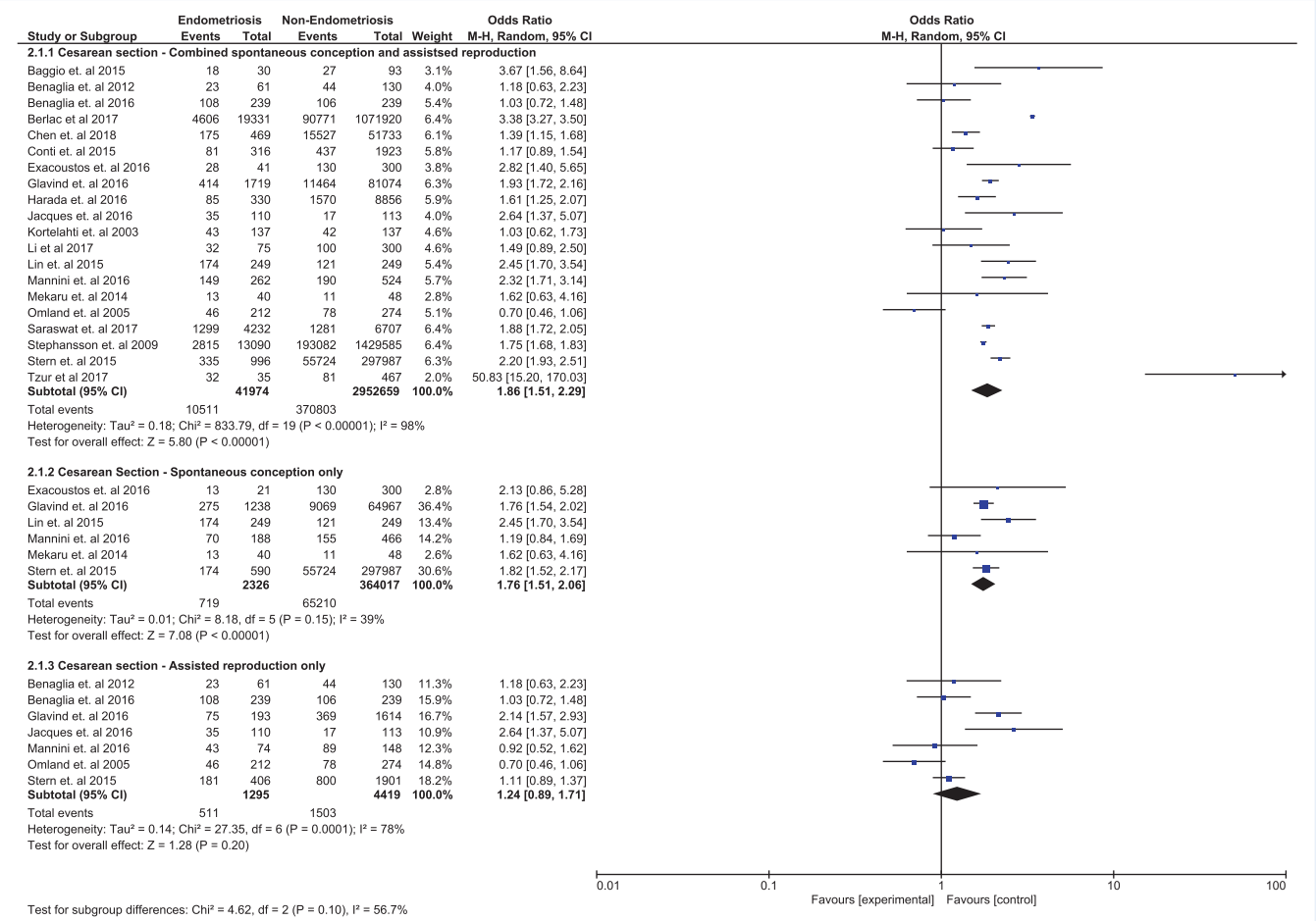

Figure 3 Forest plot for association between endometriosis and cesarean section by mode of conception.

While one potential explanation could be confounding with assisted reproduction, we found that this relationship was observed in both women with spontaneous conception and assisted reproduction (Stephansson *et al.*, 2009; Exacoustos *et al.*, 2016; Glavind *et al.*, 2017; Mannini *et al.*, 2017). Our findings are also consistent with the observation that endometriosis was associated with other adverse neonatal outcomes that have not been as extensively reported in the literature, including preterm premature rupture of membranes, small for gestational age, low birth weight and admission to neonatal intensive care.

Stillbirth and neonatal death

Stillbirth and neonatal death are uncommon but morbid adverse pregnancy outcome affecting <1% of all pregnancies (Say *et al.*, 2006). Due to the low frequency of this event, the detection of statistically significant differences for this outcome requires large sample sizes that are difficult to achieve through individual studies. One consistent finding between studies was that all studies reporting these outcomes had odds ratios greater than one, despite variable confidence intervals. When pooled, we found that women with endometriosis had 1.29-fold (95% CI: 1.10–1.52) increased odds of stillbirth and 1.78-fold (95% CI: 1.46–2.16) increased odds of neonatal death compared with women without endometriosis.

Postulated mechanisms

Several postulated mechanisms for these observations have been presented in the literature. Mechanisms involving altered vascular endothelial growth factor and angiogenesis (Palei *et al.*, 2013; Laschke and Menger, 2018), deferred implantation due to altered contractility and increased progesterone resistance (Maggiore *et al.*, 2016), altered eutopic endometrium due to increased secretion of interleukins and chronic inflammation (Brosens *et al.*, 2007), and increased history of uterine trauma from increased pregnancy loss among women with endometriosis (Chen *et al.*, 2018) help explain the findings of altered placentation and pre-eclampsia. In addition to suboptimal placentation, the increased expression of Cox-2, secretion of prostaglandins and chronic inflammation at the eutopic endometrium (Harada *et al.*, 2016; Maggiore *et al.*, 2016), early cervical ripening and increased uterine tone and contractilility (Brosens *et al.*, 2007) in women with endometriosis can lead to a variety of adverse fetal and neonatal effects.

Differences in subgroup analysis

For the pregnancy outcomes of cesarean section and low birth weight, we found an association with endometriosis among women with spontaneous conception but not women with assisted reproduction. While

Table II Association between endometriosis and adverse maternal outcomes.

Outcome indicator	Study population	No. of studies	Patients with endometriosis	Patients without endometriosis	I^2	OR [95% CI]
Pre-eclampsia	Combined spontaneous and assisted	13	39 653	2 857 045	63%	1.18 [1.01, 1.39]
	Spontaneous only	2	3636	265 672	51%	1.21 [0.94, 1.56]
	Assisted reproduction only	7	1741	7348	59%	0.89 [0.48, 1.67]
Gestational hypertension and/or pre-eclampsia	Combined spontaneous and assisted	24	48 660	3 225 765	77%	1.21 [1.05, 1.39]
	Spontaneous only	5	3298	499 289	33%	1.12 [0.90, 1.39]
	Assisted reproduction only	5	1792	7479	52%	0.79 [0.56, 1.11]
Gestational diabetes	Combined spontaneous and assisted	12	3275	367 537	31%	1.26 [1.03, 1.55]
	Spontaneous only	2	209	766	0%	1.30 [0.85, 1.98]
	Assisted reproduction only	5	881	2444	34%	1.08 [0.73, 1.60]
Gestational cholestasis	Combined spontaneous and assisted	1	262	524	–	4.87 [1.85, 12.83]
Placenta praevia	Combined spontaneous and assisted	18	27 395	1 178 425	77%	3.31 [2.37, 4.63]
	Spontaneous only	3	458	1015	49%	6.83 [2.10, 22.24]
	Assisted reproduction only	8	1937	6911	70%	3.33 [1.52, 7.30]
Antepartum hemorrhage	Combined spontaneous and assisted	5	38 055	2 513 814	83%	1.69 [1.38, 2.07]
	Assisted reproduction only	1	1265	5465	–	1.21 [0.96, 1.52]
Subchorionic hematoma	Combined spontaneous and assisted	1	40	48	–	2.47 [0.22, 28.33]
Placental abruption	Combined spontaneous and assisted	12	25 248	1 167 908	53%	1.46 [0.98, 2.19]
	Spontaneous only	2	270	549	71%	2.53 [0.08, 79.34]
	Assisted reproduction only	3	349	412	0%	0.35 [0.09, 1.32]
Antepartum hospital admissions	Combined spontaneous and assisted	1	996	297 987	–	3.18 [2.60, 3.87]
Induction of labor	Combined spontaneous and assisted	2	578	2447	94%	1.23 [0.44, 3.44]
Malpresentation	Combined spontaneous and assisted	1	996	297 987	–	1.71 [1.34, 2.18]
Labor dystocia	Combined spontaneous and assisted	1	996	297 987	–	1.45 [1.04, 2.01]
Operative vaginal delivery	Combined spontaneous and assisted	5	5722	307 054	69%	1.05 [0.70, 1.57]
Cesarean section	Combined spontaneous and assisted	20	41 974	2 952 659	98%	1.86 [1.51, 2.29]
	Spontaneous only	6	2326	364 017	39%	1.76 [1.51, 2.06]
	Assisted reproduction only	7	1295	4419	78%	1.24 [0.89, 1.71]
Postpartum hemorrhage	Combined spontaneous and assisted	10	27 817	1 220 226	95%	1.19 [0.89, 1.59]
	Spontaneous only	2	1426	65 433	0%	0.85 [0.70, 1.04]
	Assisted reproduction only	3	380	1875	0%	1.21 [0.86, 1.71]

–Pooled analysis was not performed for single studies.

this may seem counter-intuitive, one potential explanation may be that assisted reproduction may be an independent risk factor for such adverse pregnancy outcomes for both women with and without endometriosis, so fewer adverse pregnancy complications can be attributed to endometriosis alone. However, it is also possible that the lack of statistically significant associations in the subgroup of women with assisted reproduction may be due in part to beta-error.

Strengths

There are several methodologic strengths to our review. First, it was registered *a priori* in the International Prospective Register of Systematic Reviews (PROSPERO), thereby reducing risk of reporting bias. Second, the search strategy includes the results of an extensive and updated search of the literature with over 3000 records, and resulted in the identification of several additional papers compared with a previous review whose electronic search included 250 records (Zullo *et al.*, 2017). Third, it included several important pregnancy outcomes that have not yet been reported as pooled outcomes in prior reviews (Maggiore *et al.*, 2016; Zullo *et al.*, 2017), especially for serious fetal and neonatal outcomes, such as stillbirth and neonatal death, and also. In addition to describing the pregnancy outcomes associated with endometriosis, we have also included outcomes that were found not to be associated, as well as outcomes for which there was insufficient evidence. Fourth, in addition to

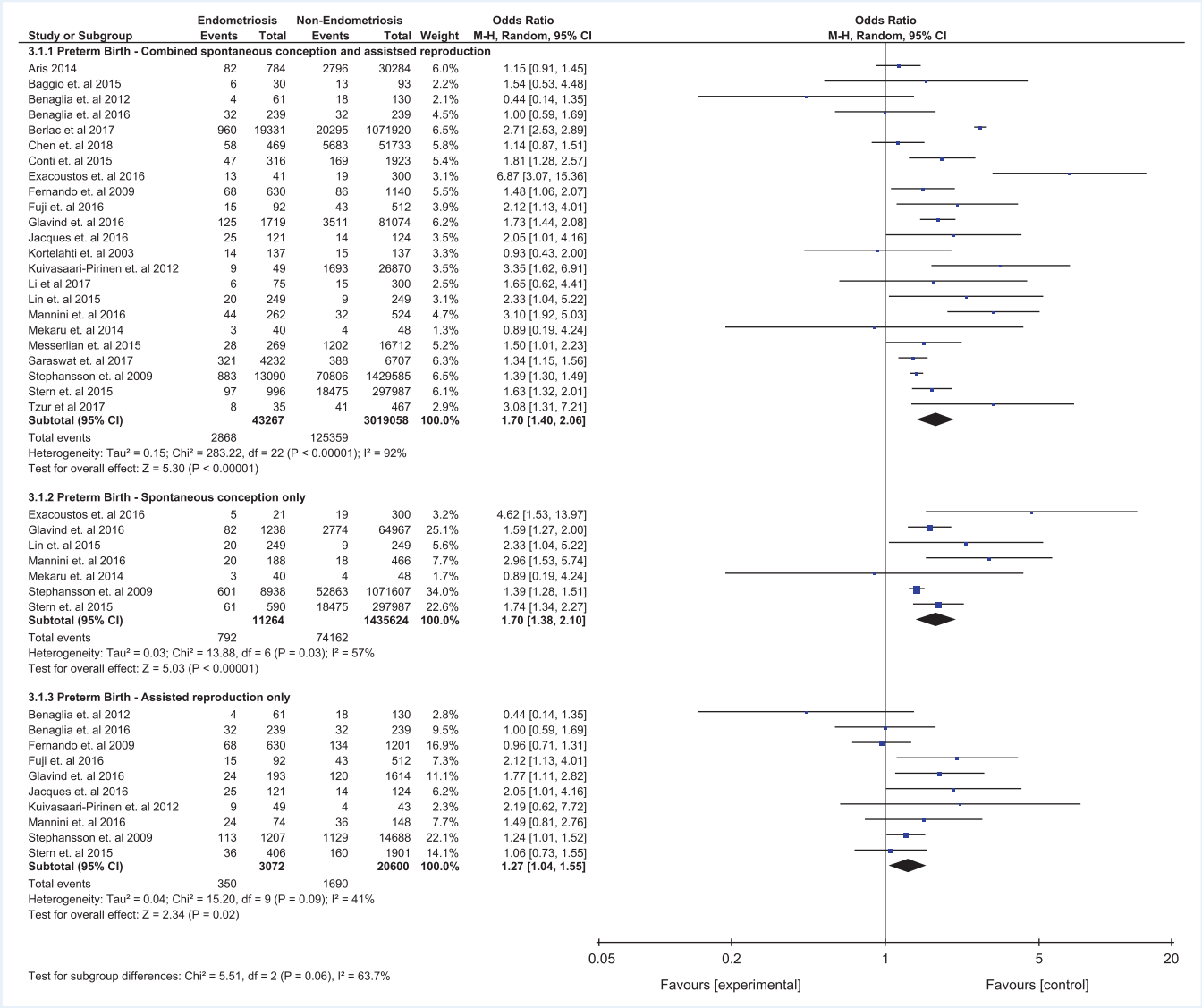

Figure 4 Forest plot for association between endometriosis and preterm birth by mode of conception.

providing a descriptive review on the topic (Maggiore *et al.*, 2016), we have also performed meta-analysis to provide a more precise estimate of the effect of endometriosis on various pregnancy outcomes. Fifth, where possible, subgroup analyses for spontaneous and assisted conception were performed to remove the effect of confounding by assisted reproduction and to enable comparison of the effect sizes between the two groups. While this type of subgroup analysis for women with assisted reproduction has been performed for preterm birth (Zullo *et al.*, 2017), we were able to perform this type of stratified analyses for many other outcomes other than preterm birth. Finally, when necessary, authors of original studies were contacted to provide additional information to assist with the interpretation, synthesis and analysis of their study results.

Limitations

As with any systematic review on observational studies, the review is limited by the quality and heterogeneity of the studies included. One finding was that the diagnosis for endometriosis was not uniform between the studies. While smaller studies using surgical data were able to confirm a surgical diagnosis of endometriosis, large population-based studies used International Classification of Diseases (ICD) codes to identify endometriotic patients. Despite the potential lack of specificity with the use of ICD codes compared with surgical records, the effect of potential misclassification would be bias towards the null hypothesis. Also, selection of control groups was not uniform across studies, with some studies using fertile patients, subfertile patients or patients affected by male factor infertility as non-endometriotic controls. Despite these limitations, most studies adjusted for or restricted according to age, parity or number of gestations in pregnancy. These factors contributed towards the heterogeneity between the studies, which is generally expected for a systematic review on observational studies. Finally, although this review fulfills its purpose of providing a synthesis of the current literature on this important topic, the exact mechanism of how the presence of endometriosis leads to adverse pregnancy outcomes has yet to be elucidated.

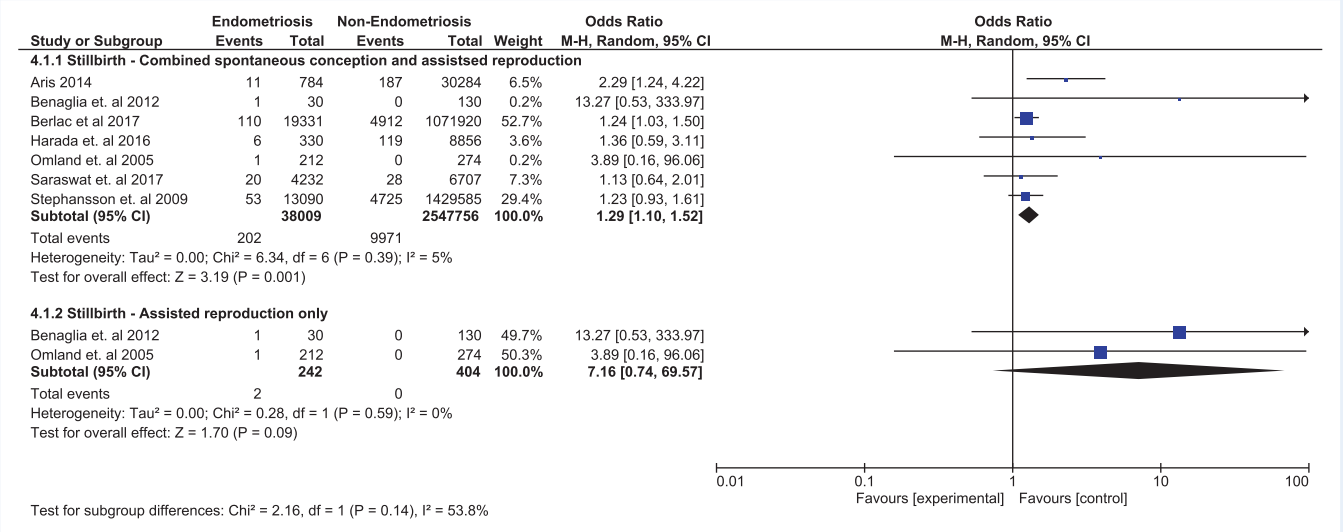

Figure 5 Forest plot for association between endometriosis and stillbirth by mode of conception.

Table III Association between endometriosis and adverse fetal and neonatal outcomes.

Outcome indicator	Study population	No. of studies	Patients with endometriosis	Patients without endometriosis	I^2	OR [95% CI]
Preterm birth	Combined spontaneous and assisted	23	43 267	3 019 058	92%	1.70 [1.40, 2.06]
	Spontaneous only	7	11 264	1 435 624	57%	1.70 [1.38, 2.10]
	Assisted reproduction only	10	3072	20 600	41%	1.27 [1.04, 1.55]
Premature preterm rupture of membranes (PPROM)	Combined spontaneous and assisted	7	1751	63 580	64%	2.33 [1.39, 3.90]
Small for gestational age <10th percentile	Combined spontaneous and assisted	19	38 514	2 952 409	64%	1.28 [1.11, 1.49]
	Spontaneous only	6	2326	3 64 017	0%	1.13 [0.92, 1.40]
	Assisted reproduction only	9	1857	5901	12%	1.04 [0.83, 1.30]
Low birth weight <2500 g	Combined spontaneous and assisted	12	7597	414 803	7%	1.13 [1.00, 1.27]
	Spontaneous only	3	879	298 284	0%	1.52 [1.13, 2.05]
	Assisted reproduction only	6	1096	2732	41%	0.87 [0.59, 1.27]
APGAR <7 at 1 min	Combined spontaneous and assisted	2	172	604	0%	0.75 [0.34, 1.68]
APGAR <7 at 5 min	Combined spontaneous and assisted	4	287	952	0%	0.65 [0.20, 2.11]
Low venous pH (<7.15)	Combined spontaneous and assisted	1	137	137	–	2.01 [0.18, 22.48]
NICU admission	Combined spontaneous and assisted	7	1371	81 074	23%	1.39 [1.08, 1.78]
	Spontaneous only	1	40	48	–	0.81 [0.28, 2.36]
	Assisted reproduction only	3	409	406	24%	1.58 [0.91, 2.75]
Stillbirth	Combined spontaneous and assisted	7	38 009	2 547 756	5%	1.29 [1.10, 1.52]
	Assisted reproduction only	2	242	404	0%	7.16 [0.74, 69.57]
Neonatal death	Combined spontaneous and assisted	3	23 700	1 078 764	0%	1.78 [1.46, 2.16]

–Pooled analysis was not performed for single studies.

Conclusion

Women with endometriosis are at elevated risk for serious and important adverse maternal, fetal and neonatal outcomes. Though effect sizes for specific outcomes may differ between the two subgroups, both women with spontaneous conception and assisted reproduction are at elevated risk for adverse pregnancy outcomes. The association of endometriosis with morbid fetal and neonatal outcomes, such as stillbirth and neonatal death, is concerning and warrants further study.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgements

The authors would like to specially thank Ms. Erica Wright, who developed the search protocol used for this systematic review.

Authors' roles

I.C.: Conception and design, acquisition of data, analysis plan, interpretation of data, drafting/revising and final approval of article. S.L.: Conception and design, acquisition of data, analysis, interpretation of data, drafting/revising and final approval of article. A.J.C.: Analysis, interpretation of data, drafting/revising and final approval of article. B. F.: Acquisition of data, drafting/revision and final approval. V.B.: acquisition of data, interpretation of data, drafting/revision and final approval. M.W.: Conception and design, revision and final approval of the article. S.W.W.: Conception and design, analysis plan, interpretation of data, revising and final approval of article. S.S.: Conception and design, revision and final approval of the article. A.A.: Acquisition of data, interpretation of data, drafting and final approval. M.H.: Acquisition of data, interpretation of data, drafting and final approval.

Funding

Dr Shifana Lalani is supported by a Physicians' Services Incorporated Foundation Research Grant, and Dr Innie Chen is supported by a University of Ottawa Clinical Research Chair in Reproductive Population Health and Health Services.

Conflict of interest

Dr Singh declares conflicts of interests with Bayer, Abvie, Allergan and Cooper Surgical. All other authors have no conflicts of interests to declare.

References

Acién P, Velasco I. Endometriosis: a disease that remains enigmatic. *ISRN Obstet Gynecol* 2013;**2013**:1–12.

Aris A. A 12-year cohort study on adverse pregnancy outcomes in Eastern Townships of Canada: impact of endometriosis. *Gynecol Endocrinol* 2014;**30**:34–37.

Baggio S, Pomini P, Zecchin A, Garzon S, Bonin C, Santi L, Festi A, Franchi MP. Delivery and pregnancy outcome in women with bowel resection for deep endometriosis: a retrospective cohort study. *Gynecol Surg* 2015;**12**:279–285.

Benaglia L, Bermejo A, Somigliana E, Scarduelli C, Ragni G, Fedele L, Garcia-Velasco JA. Pregnancy outcome in women with endometriomas achieving pregnancy through IVF. *Hum Reprod* 2012;**27**:1663–1667.

Benaglia L, Candotti G, Papaleo E, Pagliardini L, Leonardi M, Reschini M, Quaranta L, Munaretto M, Viganò P, Candiani M *et al*. Pregnancy outcome in women with endometriosis achieving pregnancy with IVF. *Hum Reprod* 2016;**31**:2730–2736.

Berlac JF, Hartwell D, Skovlund CW, Langhoff-Roos J, Lidegaard Ø. Endometriosis increases the risk of obstetrical and neonatal complications. *Acta Obstet Gynecol Scand* 2017;**96**:751–760.

Brosens IA, Sutter P De, Hamerlynck T, Imeraj L, Yao Z, Cloke B, Brosens JJ, Dhont M. Endometriosis is associated with a decreased risk of pre-eclampsia. *Hum Reprod* 2007;**22**:1725–1729.

Chen I, Lalani S, Xie R, Shen M, Singh SS, Wen S-W. Association between surgically diagnosed endometriosis and adverse pregnancy outcomes. *Fertil Steril* 2018;**109**:142–147. Elsevier Inc.

Conti N, Cevenini G, Vannuccini S, Orlandini C, Valensise H, Gervasi MT, Ghezzi F, Di Tommaso M, Severi FM, Petraglia F. Women with endometriosis at first pregnancy have an increased risk of adverse obstetric outcome. *J Matern Fetal Neonatal Med* 2014;**7058**:1–16.

Exacoustos C, Lauriola I, Lazzeri L, De Felice G, Zupi E. Complications during pregnancy and delivery in women with untreated rectovaginal deep infiltrating endometriosis. *Fertil Steril* 2016;**106**:1129–1135.e1. Elsevier Inc.

Fernando S, Breheny S, Jaques AM, Halliday JL, Baker G, Healy D. Preterm birth, ovarian endometriomata, and assisted reproduction technologies. *Fertil Steril* 2009;**91**:325–330. American Society for Reproductive Medicine.

Fujii T, Wada-Hiraike O, Nagamatsu T, Harada M, Hirata T, Koga K, Fujii T, Osuga Y. Assisted reproductive technology pregnancy complications are significantly associated with endometriosis severity before conception: a retrospective cohort study. *Reprod Biol Endocrinol* 2016;**14**:73–77. Reproductive Biology and Endocrinology.

Glavind MT, Forman A, Arendt LH, Nielsen K, Henriksen TB. Endometriosis and pregnancy complications: a Danish cohort study. *Fertil Steril* 2017;**107**:160–166.

Guo H, Wang Y, Chen Q, Chai W, Lv Q, Kuang Y. Effect of natural cycle endometrial preparation for frozen-thawed embryo transfer in patients with advanced endometriosis. *Med Sci Monit* 2016;**22**:4596–4603.

Hadfield RM, Lain SJ, Raynes-Greenow CH, Morris JM, Roberts CL. Is there an association between endometriosis and the risk of pre-eclampsia? A population based study. *Hum Reprod* 2009;**24**:2348–2352.

Harada TT, Taniguchi F, Onishi K, Kurozawa Y, Hayashi K, Harada TT, Kawamoto T, Saito H, Kishi R, Yaegashi N *et al*. Obstetrical complications in women with endometriosis: a cohort study in Japan. *PLoS One* 2016;**11**:1–13.

Harb HM, Gallos ID, Chu J, Harb M, Coomarasamy A. The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. *BJOG An Int J Obstet Gynaecol* 2013;**120**:1308–1320.

Healy DL, Breheny S, Halliday J, Jaques A, Rushford D, Garrett C, Talbot JM, Baker HWG. Prevalence and risk factors for obstetric haemorrhage in 6730 singleton births after assisted reproductive technology in Victoria Australia. *Hum Reprod* 2010;**25**:265–274.

Jacques M, Freour T, Barriere P, Ploteau S. Adverse pregnancy and neonatal outcomes after assisted reproductive treatment in patients with pelvic endometriosis: a case–control study. *Reprod Biomed Online* 2016;**32**:626–634. Elsevier Ltd.

Koch J, RowanK, RombautsL, YazdaniA, ChapmanM, JohnsonN. Endometriosis and infertility—a consensus statement from ACCEPT (Australasian CREI Consensus Expert Panel on Trial evidence). *Aust New Zeal J Obstet Gynaecol* 2012;**52**:513522.

Kortelahti M, Anttila MA, Hippeläinen MI, Heinonen ST. Obstetric outcome in women with endometriosis—a matched case-control study. *Gynecol Obstet Invest* 2003;**56**:207–212.

Kuivasaari-Pirinen P, Raatikainen K, Hippeläinen M, Heinonen S. Adverse outcomes of IVF/ICSI pregnancies vary depending on aetiology of infertility. *ISRN Obstet Gynecol* 2012;**2012**:1–5.

Laschke MW, Menger MD. Basic mechanisms of vascularization in endometriosis and their clinical implications. *Hum Reprod Update* 2018;**24**: 207–224.

Leyland N, Casper R, Laberge P, Singh SS, Allen L, Arendas K, Allaire C, Awadalla A, Best C, Contestabile E *et al*. Endometriosis: diagnosis and management. *J Obstet Gynaecol Canada* 2010;**32**:S1–S3. Elsevier Masson SAS.

Li H, Zhu HL, Chang XH, Li Y, Wang Y, Guan J, Cui H. Effects of previous laparoscopic surgical diagnosis of endometriosis on pregnancy outcomes. *Chin Med J (Engl)* 2017;**130**:428–433.

Lin H, Leng J-H, Liu J-T, Lang J-H. Obstetric outcomes in Chinese women with endometriosis: a retrospective cohort study. *Chin Med J (Engl)* 2015;**128**:455–458.

Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am* 2012;**39**:535–549.

Maggiore ULR, Ferrero S, Mangili G, Bergamini A, Inversetti A, Giorgione V, Viganò P, Candiani M. A systematic review on endometriosis during pregnancy: diagnosis, misdiagnosis, complications and outcomes. *Hum Reprod Update* 2016;**22**:70–103.

Mannini L, Sorbi F, Noci I, Ghizzoni V, Perelli F, Tommaso M Di, Mattei A, FambriniM. New adverse obstetrics outcomes associated with endometriosis: a retrospective cohort study. *Arch Gynecol Obstet* 2017;**295**:1411151.

Mekaru K, Masamoto H, Sugiyama H, Asato K, Heshiki C, Kinjyo T, Aoki Y. Endometriosis and pregnancy outcome: are pregnancies complicated by endometriosis a high-risk group? *Eur J Obstet Gynecol Reprod Biol* 2014;**172**:36–39. Elsevier Ireland Ltd.

Messerlian C, Platt RW, Ata B, Tan SL, Basso O. Do the causes of infertility play a direct role in the aetiology of preterm birth? *Paediatr Perinat Epidemiol* 2015;**29**:101–112.

Missmer SA, Cramer DW. The epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 2003;**30**:1–19. vii. United States.

Morassutto C, Monasta L, Ricci G, Barbone F, Ronfani L. Incidence and estimated prevalence of endometriosis and adenomyosis in Northeast Italy: a data linkage study. *PLoS One* 2016;**11**:1–11.

Omland AK, Åbyholm T, Fedorcsák P, Ertzeid G, Oldereid NB, Bjercke S, Tanbo T. Pregnancy outcome after IVF and ICSI in unexplained, endometriosis-associated and tubal factor infertility. *Hum Reprod* 2005; **20**:722–727.

Palei AC, Spradley FT, Warrington JP, George EM, Granger JP. Pathophysiology of hypertension in pre-eclampsia: a lesson in integrative physiology. *Acta Physiol* 2013;**208**:224–233.

Pan ML, Chen LR, Tsao HM, Chen KH. Risk of gestational hypertension-preeclampsia in women with preceding endometriosis: a nationwide population-based study. *PLoS One* 2017;**12**:1–14.

Pérez-López FR, Martínez-Domínguez SJ, Viñas A, Pérez-Tambo R, Lafita A, Lajusticia H, Chedraui P. Endometriosis and gestational diabetes mellitus risk: a systematic review and meta-analysis. *Gynecol Endocrinol* 2017; **0**:1–7. Informa UK Ltd.

Rombauts L, Motteram C, Berkowitz E, Fernando S. Risk of placenta praevia is linked to endometrial thickness in a retrospective cohort study of 4537 singleton assisted reproduction technology births. *Hum Reprod* 2014;**29**:2787–2793.

Saraswat L, Ayansina DT, Cooper KG, Bhattacharya S, Miligkos D, Horne AW, Bhattacharya S. Pregnancy outcomes in women with endometriosis: a national record linkage study. *BJOG An Int J Obstet Gynaecol* 2017; **124**:444–452.

Say L, Donner A, Gülmezoglu AM, Taljaard M, Piaggio G. The prevalence of stillbirths: a systematic review. *Reprod Health* 2006;**3**:1–11.

Stephansson O, Kieler H, Granath F, Falconer H. Endometriosis, assisted reproduction technology, and risk of adverse pregnancy outcome. *Hum Reprod* 2009;**24**:2341–2347.

Stern JE, Brown MB, Wantman E, Kalra SK, Luke B. Live birth rates and birth outcomes by diagnosis using linked cycles from the SART CORS database. *J Assist Reprod Genet* 2013;**30**:1445–1450.

Stern JE, Luke B, Tobias M, Gopal D, Hornstein MD, Diop H. Adverse pregnancy and birth outcomes associated with underlying diagnosis with and without assisted reproductive technology treatment. *Fertil Steril* 2015;**103**:1438–1445. Elsevier Inc.

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology—a proposal for reporting. *J Am Med Assoc* 2000;**283**:2008–2012.

Takemura Y, Osuga Y, Fujimoto A, Oi N, Tsutsumi R, Koizumi M, Yano T, Taketani Y. Increased risk of placenta previa is associated with endometriosis and tubal factor infertility in assisted reproductive technology pregnancy. *Gynecol Endocrinol* 2013;**29**:113–115.

Tzur T, Weintraub AY, Arias Gutman O, Baumfeld Y, Soriano D, Mastrolia SA, Sheiner E. Pregnancy outcomes in women with endometriosis. *Minerva Ginecol* 2018;**70**:144–149.

Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses*. 2014. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Zullo F, Spagnolo E, Saccone G, Acunzo M, Xodo S, Ceccaroni M, Berghella V. Endometriosis and obstetrics complications: a systematic review and meta-analysis. *Fertil Steril* 2017;**108**:667–672.e5. Elsevier Inc.