

Endometriosis and obstetrics complications: a systematic review and meta-analysis

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Objective: To evaluate the effect of endometriosis on pregnancy outcomes.

Design: Systematic review and meta-analysis.

Setting: Not applicable.

Patient(s): Women with or without endometriosis.

Intervention(s): Electronic databases searched from their inception until February 2017 with no limit for language and with all cohort studies reporting the incidence of obstetric complications in women with a diagnosis of endometriosis compared with a control group (women without a diagnosis of endometriosis) included.

Mean Outcome Measure(s): Primary outcome of incidence of preterm birth at <37 weeks with meta-analysis performed using the random effects model of DerSimonian and Laird to produce an odds ratio (OR) with 95% confidence interval (CI).

Result(s): Twenty-four studies were analyzed comprising 1,924,114 women. In most of them, the diagnosis of endometriosis was made histologically after surgery. Women with endometriosis had a statistically significantly higher risk of preterm birth (OR 1.63; 95% CI, 1.32–2.01), miscarriage (OR 1.75; 95% CI, 1.29–2.37), placenta previa (OR 3.03; 95% CI, 1.50–6.13), small for gestational age (OR 1.27; 95% CI, 1.03–1.57), and cesarean delivery (OR 1.57; 95% CI, 1.39–1.78) compared with the healthy controls. No differences were found in the incidence of gestational hypertension and preeclampsia.

Conclusion(s): Women with endometriosis have a statistically significantly higher risk of preterm birth, miscarriage, placenta previa, small for gestational age infants, and cesarean delivery. (Fertil Steril® 2017; ■:■–■. ©2017 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, gynecology, miscarriage, outcomes, preterm birth, ultrasound

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Endometriosis, an estrogen-dependent chronic gynecologic disease, affects about 10% of women in the general population and about 40% of women with a history of subfertility or pelvic pain (1). It is defined

by the presence of endometrium-like tissue outside the uterus, including on the ovaries and in the fallopian tube and the posterior cul-de-sac (2). The main symptoms are pelvic pain and infertility. Pain during sex is also common. The less

common symptoms include urinary or bowel symptoms (3).

Traditionally, pregnancy was considered to have a positive effect on endometriosis and its symptoms, including the pain (1). However, the pathophysiology of endometriosis is not well understood, and its impact on pregnancy is relatively unexplored (4, 5). Several observational nonrandomized studies evaluating the effect of endometriosis on pregnancy outcomes have been published, so far with conflicting results. Our systematic review and meta-analysis evaluated the effect of endometriosis on pregnancy outcomes.

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F.Z. has nothing to disclose. E.S. has nothing to disclose. G.S. has nothing to disclose. M.A. has nothing to disclose. S.X. has nothing to disclose. M.C. has nothing to disclose. V.B. has nothing to disclose.

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MATERIALS AND METHODS

Search Strategy

Electronic databases (Medline, Scopus, ClinicalTrials.gov, EMBASE, Sciencedirect) were searched from their inception until February 2017 with no limit for language. The search terms used were the following: “preterm,” “placental disorders,” “endometriosis,” “infertility,” “pre-eclampsia,” “pregnancy hypertension,” “pregnancy,” “population based studies,” “complications,” and “obstetric outcome.” No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify any studies not captured by the electronic searches. The electronic search and the eligibility of the studies were independently assessed by two of the authors (F.Z., E.S.). The differences were discussed with a third reviewer (V.B.).

Study Selection

We included all cohort studies reporting the incidence of obstetric complications in women with a diagnosis of endometriosis compared with a control group of women without a diagnosis of endometriosis. Studies without a control group were excluded. Case-control studies, reporting the incidence of endometriosis in women with obstetric complications, were also excluded. The diagnosis of endometriosis included surgical, clinical, or instrumental (ultrasound, magnetic resonance imaging, or computed tomography scan) diagnosis.

Two authors (F.Z., E.S.) independently assessed the inclusion criteria and study selection. Disagreements were resolved by discussion with a third reviewer (V.B.).

Data abstraction was completed by two independent investigators (F.Z., V.B.). Each investigator independently abstracted data from each study separately. Data from each eligible study were extracted without modification of the original data onto custom-made data collection forms. Differences were resolved by consensus. Information on confounders adjusted and adjusted risk estimates were collected when available.

Primary and Secondary Outcomes

Primary and secondary outcomes were planned a priori. The primary outcome was the incidence of preterm birth (PTB) at less than 37 weeks. Secondary outcomes were PTB at <34 weeks, incidence of miscarriage (defined as spontaneous abortion at <22 weeks), gestational hypertension, preeclampsia, placenta previa and accreta, small for gestational age (SGA, defined as birth weight <10th percentile for the gestational age), and cesarean delivery. If outcomes were reported in the original studies for more than one pregnancy, only the first pregnancy after the diagnosis of endometriosis was considered for the meta-analysis.

We planned a sensitivity analysis for the primary outcome (i.e., incidence of PTB at <37 weeks) according to the study design. We also planned to assess the incidence of PTB in subgroup analyses of only assisted reproductive

technology (ART) and non-ART women, and according to the type of endometriosis.

Risk of Bias

The risk of bias of the included studies was assessed via the Methodological Index for Non-Randomized Studies (MINORS). Seven domains related to risk of bias were assessed in each study: [1] aim (i.e., clearly stated aim), [2] rate (i.e., inclusion of consecutive patients and response rate), [3] data (i.e., prospective collection of data or data collected using a high-quality population-based data set), [4] bias (i.e., unbiased assessment of study end points), [5] time (i.e., follow-up time appropriate), [6] loss (i.e., loss to follow-up), and [7] size (i.e., calculation of the study size) (6). The review authors' judgments were categorized as “low risk,” “high risk,” or “unclear risk of bias.” Discrepancies were resolved by discussion.

Two authors (FZ, GS) independently assessed the risk of bias. Disagreements were resolved by discussion with a third reviewer (VB).

Statistical Analysis

The data analysis was completed independently by two authors (FZ, GS) using Review Manager version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Denmark). The completed analyses were then compared, and any differences were resolved by discussion with a third reviewer (V.B.).

Data from each eligible study were extracted without modification onto custom-made data collection forms. A 2×2 table was assessed for the odds ratio (OR); for continuous outcomes the mean \pm standard deviation was extracted and imported into Review Manager version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark).

The meta-analysis was performed using the random effects model of DerSimonian and Laird, to produce summary treatment effects in terms of OR with 95% confidence interval (CI) (7). Heterogeneity was measured using I-squared (Higgins I^2) (8, 9). Potential publication biases were assessed statistically by using Begg's and Egger's tests (8). $P < .05$ was considered statistically significant.

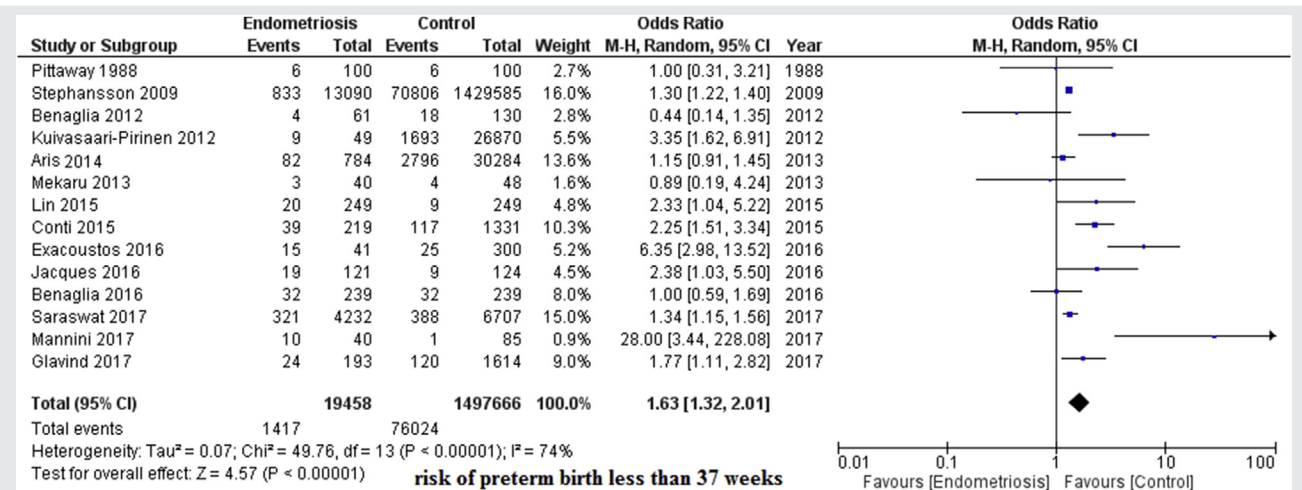
The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement (10). The review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no. CRD42017057259).

RESULTS

Study Selection and Study Characteristics

We assessed 34 studies for eligibility (4, 11–43). Ten studies were excluded (30–34, 36–38, 44). Three were excluded because they did not have a control group (30, 33, 36). Four were excluded because they were case-control studies (31, 32, 35, 37). One was excluded because they included in the intervention group all types of infertility rather than only women with endometriosis (34). One was excluded because it was a review (38). Another one was excluded due to the

FIGURE 1



Forest plot for the risk of preterm birth at less than 37 weeks. M-H = Mantel-Haenszel test; CI = confidence interval.

Zullo. Pregnancy complications with endometriosis. *Fertil Steril* 2017.

lack of outcome of interest (43). Therefore, 24 studies, which included 1,924,114 women, were analyzed (4, 11–29, 39–42) (Supplemental Fig. 1, available online). Out of the 1,924,114 women included, 52,111 (2.7%) had a prior diagnosis of endometriosis before pregnancy, and 1,872,003 (97.3%) were included in the control group (Supplemental Table 1, available online).

Most of the included studies clearly stated the aim of the research and were judged as low risk of bias in their aim. Given that the majority of them were retrospective studies, they had a high risk of bias in their data. Appropriate follow-up observations were found in most of the studies. The sample sizes ranged from 88 (a high risk of bias in size) to 1,442,675 (a low risk of bias in size) (Supplemental Fig. 2, available online). The publication bias, assessed using Begg's and Egger's tests, was not statistically significant ($P = .81$ and $.83$, respectively).

Most of the included studies came from Europe (19 of 24, 79%). Three (12.5%) came from the United States. Two (8%) studies were prospective cohort studies, 13 (54%) were retrospective cohort, and 9 (38%) were high-quality population-based studies (see Supplemental Table 1).

In all the studies, the diagnosis of endometriosis was made before pregnancy. In 21 studies the diagnosis of endometriosis was made histologically after surgery; in three studies it was determined based on the relevant ICD codes. In 14 studies, all women included in the analysis underwent assisted reproductive techniques (ART): in the intervention group for endometriosis, and in the control group for reasons other than endometriosis (including tubal factor, male factor, or unexplained infertility). Nine studies included also women who did not undergo ART. Finally, Lin et al. (26) included only women who did not undergo ART in both the endometriosis and control groups.

Twenty-one studies included any type of endometriosis; one study included only women with ovarian endometrioma, one included only women with deep infiltrating endometriosis, and another study included superficial, ovarian, and deep infiltrating endometriosis (Supplemental Table 2, available online).

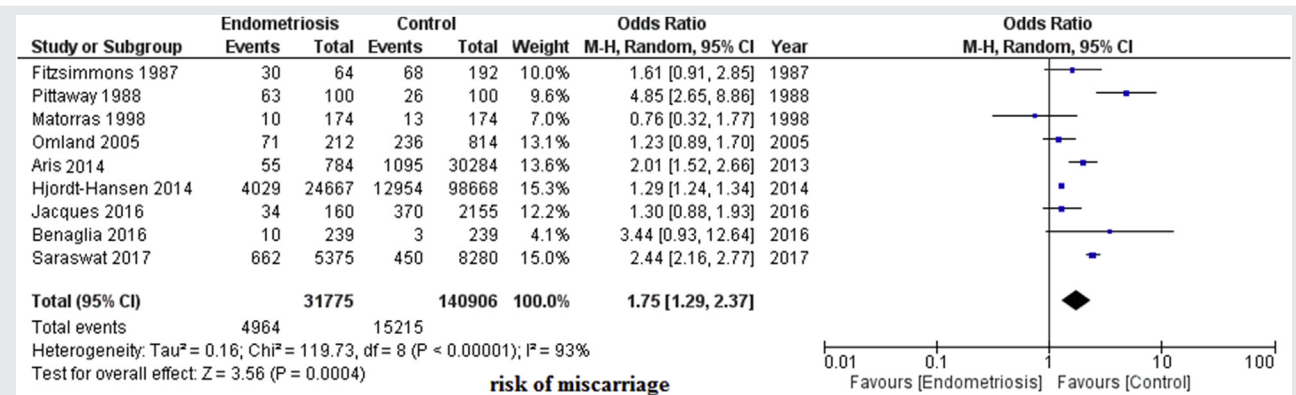
Synthesis of Results

Compared with the control group, women who had a prior diagnosis of endometriosis had a statistically significantly higher risk of PTB at <37 weeks (OR 1.63; 95% CI, 1.32–2.01) (Fig. 1), of PTB at <34 weeks (OR 1.58; 95% CI, 1.09–2.67), and of miscarriage (OR 1.75; 95% CI, 1.29–2.37) (Fig. 2). No differences were found in the incidence of gestational hypertension (OR 0.90; 95% CI, 0.59–1.37) (Supplemental Fig. 3, available online) or preeclampsia (OR 1.04; 95% CI, 0.83–1.29) (Supplemental Fig. 4, available online). Women with endometriosis had also a statistically significantly higher risk of placenta previa (OR 3.03; 95% CI, 1.50–6.13) (Supplemental Fig. 5, available online), SGA (OR 1.27; 95% CI, 1.03–1.57) (Fig. 3), and cesarean delivery (OR 1.57; 95% CI, 1.39–1.78) (Fig. 4). Data on placenta accreta were not available.

The sensitivity analysis for only retrospective cohort studies (OR 2.05; 95% CI, 1.24–3.38; 10 studies, 30,635 participants) and for only population-based studies (OR 1.30; 95% CI, 1.23–1.39; 4 studies, 1,486,489 participants) both concurred with the overall analysis finding an increase in PTB at <37 weeks.

The subgroup analysis of only the women who underwent ART concurred with the overall analysis in the increase in PTB (OR 1.26; 95% CI, 1.13–1.76; 6 studies, 28,121 participants). A subgroup analysis for the non-ART women was not feasible because the data were not reported separately for this group.

FIGURE 2



Forest plot for the risk of miscarriage. M-H = Mantel-Haenszel test; CI = confidence interval.

Zullo. *Pregnancy complications with endometriosis. Fertil Steril* 2017.

A subgroup analysis for the type of endometriosis also was not feasible because the vast majority of studies reported all types of endometriosis together with no stratification of data by type; the three studies that did report on the type of endometriosis reported different types (see [Supplemental Table 2](#)).

DISCUSSION

Main Findings

This meta-analysis, from 24 studies, including 1,924,114 women, evaluated the effect of endometriosis on future pregnancy outcome. We found that endometriosis was an independent risk factor for PTB, miscarriage, placenta previa, SGA, and cesarean delivery. Sensitivity and subgroup analyses for the primary outcome for type of study and for ART women only both concurred with the overall analysis.

Comparison with Existing Literature

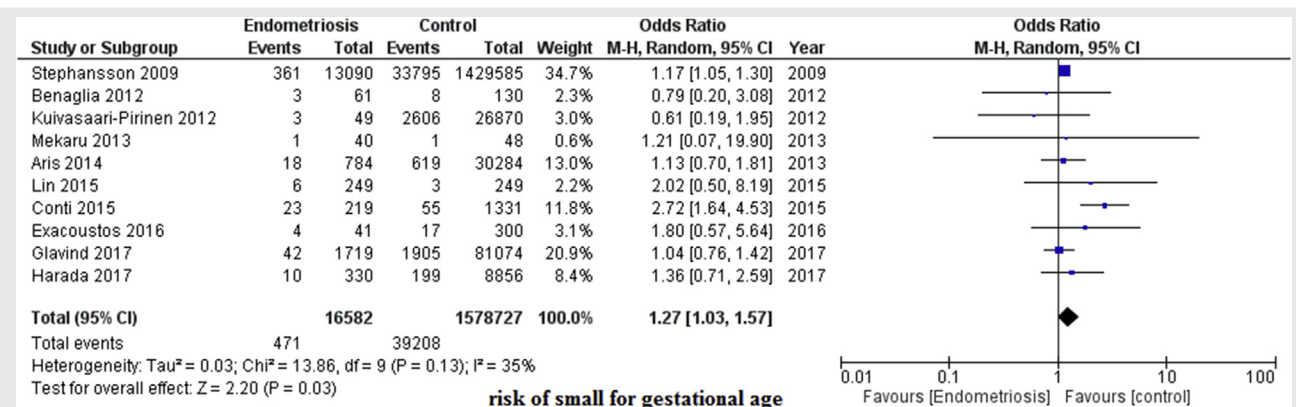
A prior review by Leone Roberti Maggiore et al. (5) aimed to study the effect of pregnancy on endometriosis and hypothesized mechanisms to explain the underlying relationships. They found that complications of endometriosis during pregnancy were rare, but the effect of endometriosis on pregnancy outcomes was not well evaluated.

Strengths and Limitations

Our study has several strengths. To our knowledge, no prior meta-analysis on this issue is as large, up to date, or comprehensive. The number of the included women is large. We planned sensitivity and subgroup analyses to reduce the heterogeneity between the studies.

The limitations of our study are inherent to the limitations of the included studies. Diagnosis and management of pregnancy complications (e.g., preeclampsia) could differ across

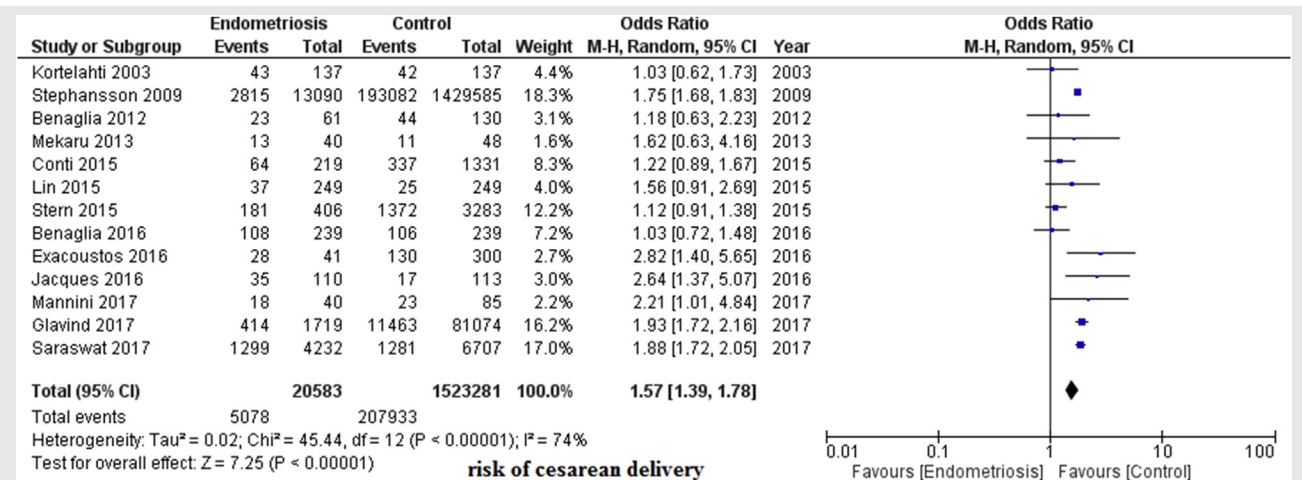
FIGURE 3



Forest plot for the risk of small for gestational age. M-H = Mantel-Haenszel test; CI = confidence interval.

Zullo. *Pregnancy complications with endometriosis. Fertil Steril* 2017.

FIGURE 4



Forest plot for the risk of cesarean delivery. M-H = Mantel-Haenszel test; CI = confidence interval.

Zullo. *Pregnancy complications with endometriosis. Fertil Steril* 2017.

the studies. Most outcomes had very high statistical heterogeneity. Given the limited data, subgroup analyses of only the non-ART women and according to the type of endometriosis were not feasible. In several studies, adjustment was made for potential confounders, but in other studies no such adjustment was indicated. Lack of information on stage and outcomes, treatment and outcomes, and ART and outcomes were the major shortcomings of the meta-analysis. Only one study reported data on PTB at <32 weeks, so a meta-analysis for this outcome was not feasible.

Implications

Endometriosis, a disease associated with pelvic pain, subfertility, and impaired quality of life, affects many women around the globe. The pathophysiology of endometriosis remains poorly understood. To date, no studies have been performed on biopsies of the placental bed in women with endometriosis to investigate any potential changes in the development of the uteroplacental circulation. However, several clinical studies have reported an association between endometriosis and subsequent pregnancy complications.

Our meta-analysis showed that women with diagnosed endometriosis (mostly via surgery) had poorer pregnancy outcomes, with a statistically significantly increased risk of PTB, miscarriage, placenta previa, SGA, and cesarean delivery. Hypertensive disorders, including gestational hypertension and preeclampsia, seem not to be influenced by endometriosis.

In human pregnancies the implantation of the blastocyst into a receptive endometrium, successful placentation, and remodeling of the uterine vasculature require the integration of a number of critical stages. Dysfunction may occur in several stages of the process, and pregnancy complications are thought to depend on the dysregulation of such events (44). In women affected by endometriosis, several adverse events may occur in the peri-implantation period as well as throughout the pregnancy, including endometrial resistance

to selective actions of progesterone, inflammatory processes at the endometrial and systemic levels, inadequate uterine contractility, and endometrial excessive activation of free radical metabolism (45–49). All these alterations of the local endometrial environment have been described in women with endometriosis as well as in women at risk of preterm labor, fetal growth restriction, and placental disorders (31, 50).

Conclusions

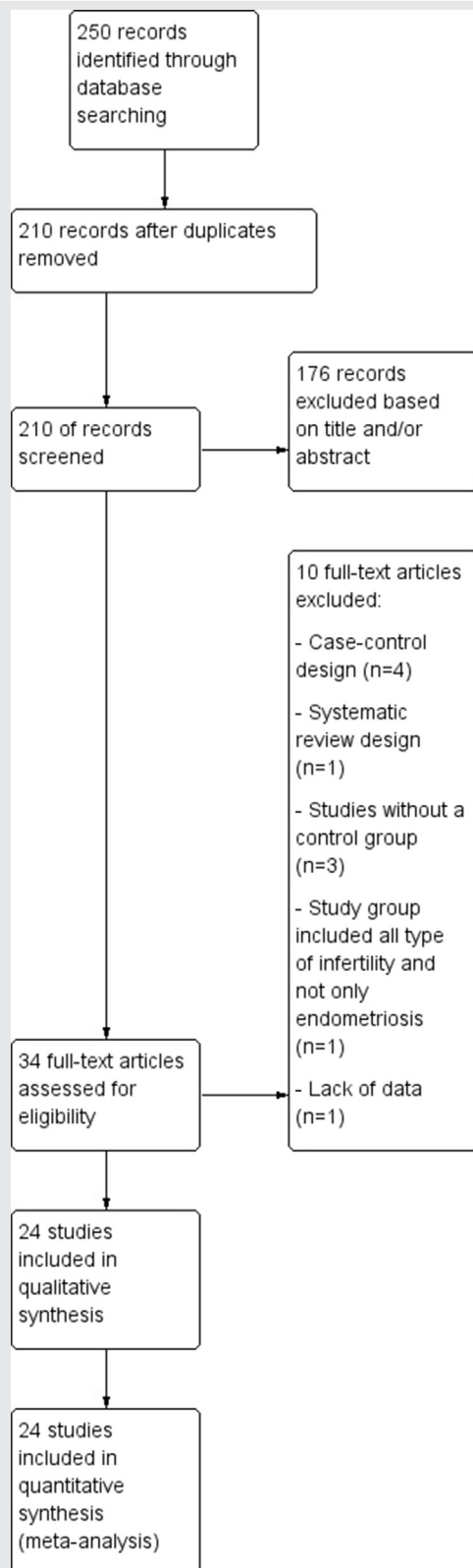
Women with endometriosis have a statistically significantly higher risk of PTB, miscarriage, placenta previa, SGA, and cesarean delivery. This information might be helpful for women and their providers when managing these pregnancies. Further studies are required to assess whether any modification is needed to conventional pregnancy monitoring for patients with endometriosis.

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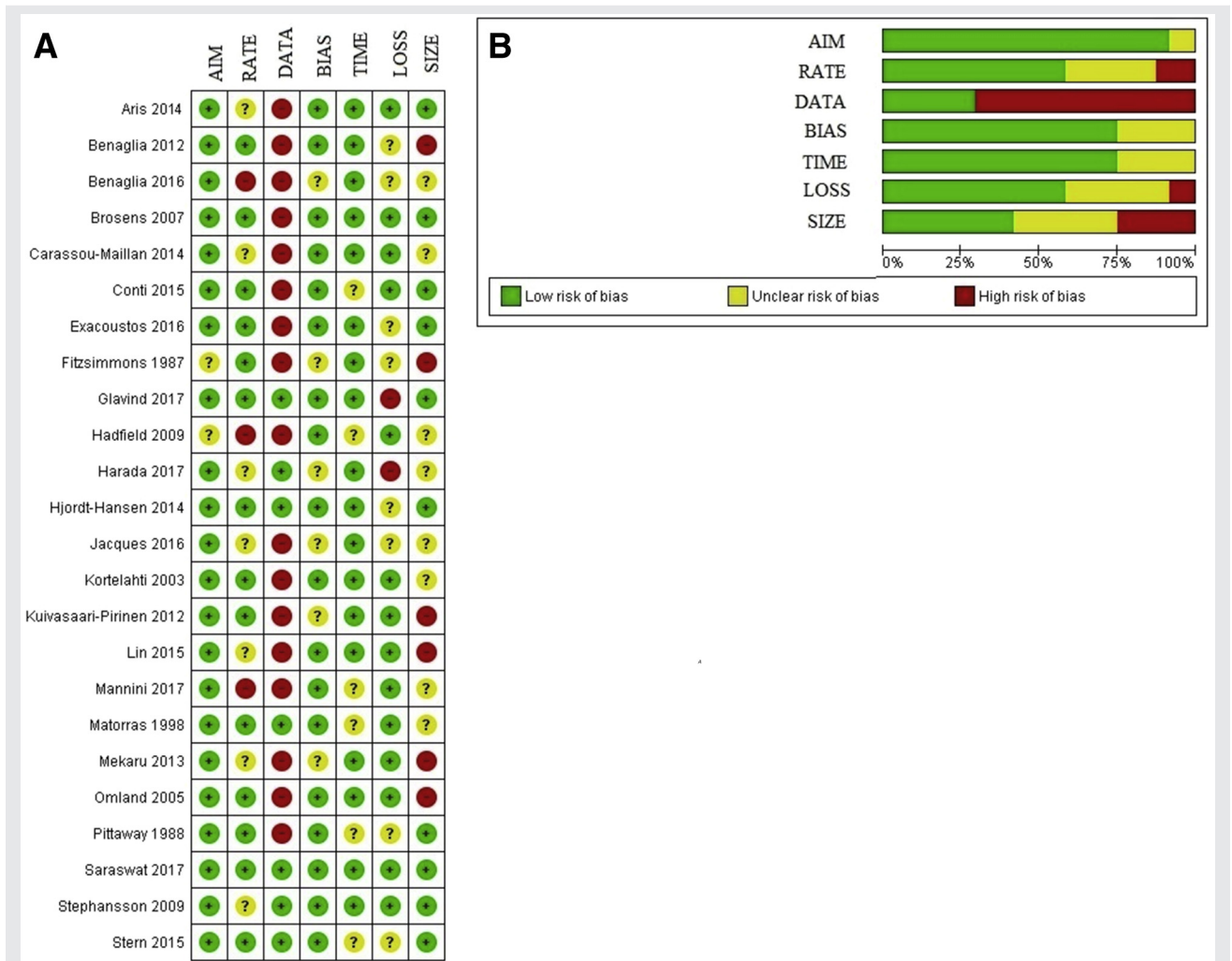
SUPPLEMENTAL FIGURE 1



Flow diagram of studies identified in the systematic review. (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

Zullo. Pregnancy complications with endometriosis. *Fertil Steril* 2017.

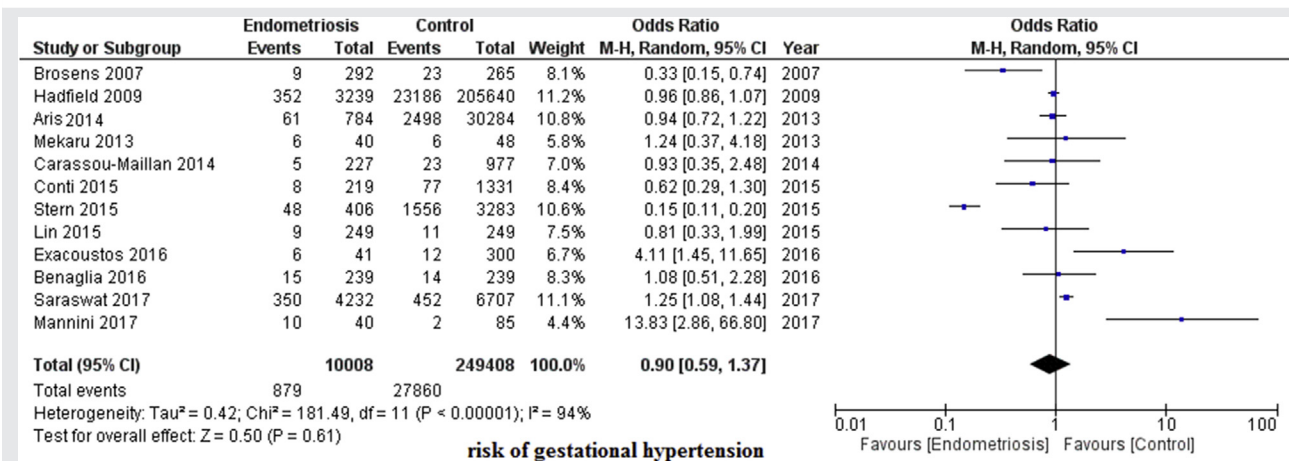
SUPPLEMENTAL FIGURE 2



Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Zullo. *Pregnancy complications with endometriosis. Fertil Steril* 2017.

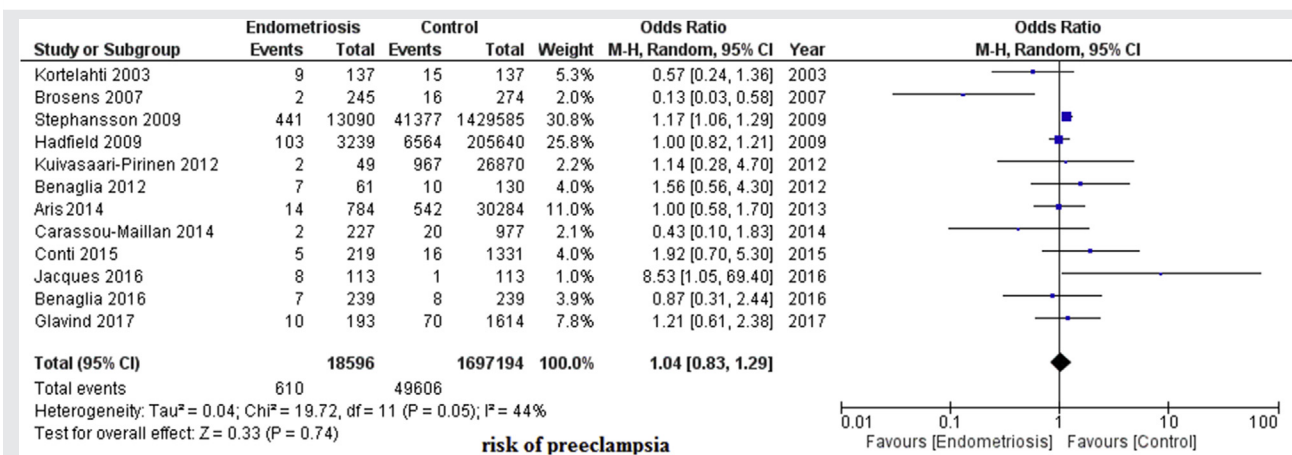
SUPPLEMENTAL FIGURE 3



Forest plot for the risk of gestational hypertension. M-H = Mantel-Haenszel test; CI = confidence interval.

Zullo. Pregnancy complications with endometriosis. *Fertil Steril* 2017.

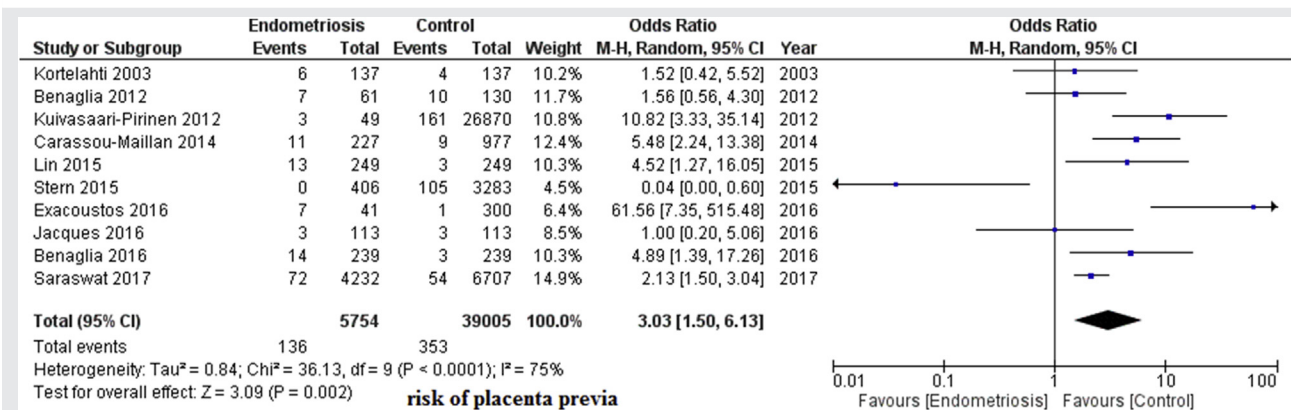
SUPPLEMENTAL FIGURE 4



Forest plot for the risk of preeclampsia. M-H = Mantel-Haenszel test; CI = confidence interval.

Zullo. *Pregnancy complications with endometriosis. Fertil Steril* 2017.

SUPPLEMENTAL FIGURE 5



Forest plot for the risk of placenta previa. M-H = Mantel-Haenszel test; CI = confidence interval.

Zullo. Pregnancy complications with endometriosis. *Fertil Steril* 2017.