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Adverse pregnancy outcomes for women with endometriosis: a systematic review and meta-analysis

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ABSTRACT

Objectives: This study aimed at assessing the adverse outcomes of pregnancy in women with endometriosis.

Material and methods: The Cochrane, Embase and PubMed databases were searched for identifying the required studies published before June 2019. Meta-analyses of relative risk (RR) were performed under the random-effects model to estimate the risk of selected adverse outcomes of pregnancy in females with endometriosis.

Results: Twenty-eight studies (53,141 women with and 2,355,923 women without endometriosis data) were selected for meta-analysis. Endometriosis bearing females had a significantly higher risk placenta previa (RR 3.92 [95% CI 2.48–6.20]), miscarriage (RR 1.31 [95% CI 1.06–1.61), gestational hypertension (RR 1.30 [95% CI 1.02–1.65]), cesarean section (RR 1.48 [95% CI 1.33–1.65]) and preeclampsia (RR 1.18 [95% CI 1.09–1.28]). The incidence of placental abruption was not statistically significant between the groups (RR 3.62 [95% CI [0.99–13.28]).

Conclusions: Women suffering from endometriosis are at higher risks of miscarriage, preterm birth, gestational hypertension, placenta previa, cesarean section, and preeclampsia.

Key words: endometriosis; meta-analysis; pregnancy outcome

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INTRODUCTION

Endometriosis, a chronic benign proliferative condition, is the result of the ectopic growth of living endometrial tissue with stroma and glands outside the uterus [1]. Major symptoms of endometriosis are dysmenorrhea, infertility, sexual discomfort, and abnormal menstruation [2]. Approximately 20–25% of women with endometriosis remain asymptomatic [3]. It has been reported that the incidence of endometriosis is 10% to 40% in women with pelvic pain or a history of infertility [4, 5]. In Germany, the standardized incidence and prevalence rates of endometriosis are reported to be 3.5 and 8.1 per 1000 women, respectively [6]. However, the incidence in women between the age of 35 and 44 years was 12.8 per 1000 women [6]. Diagnosis of endometriosis is often delayed (average delay is 6.7 years). Earlier referral and diagnosis can help in controlling pain and pathology and in preserving fertility. High cost of diagnosis, treatment and overlapping symptoms e.g., cyclic or acyclic pain are among notable delaying factors [7].

Endometriosis pathophysiology is still misunderstood. Menstrual blood regurgitation, Mullerian duct abnormalities and coelomic epithelial metaplasia are among notable theories. Historically, retrograde menstruation (menstrual blood with living cells backflow towards the peritoneum via the fallopian tubes) and the implantation of endometrial tissue in the peritoneum were identified as the etiological features of endometriosis [8]. Later research showed that inflammatory processes such as the over secretion of inflammatory cytokines and chemokine and other mediators such as prostaglandins and metalloproteinases play a vital role in the pathodynamics and pathogenesis of endometriosis [9]. Such pathogenetic processes are supported by the presence of free radicals and reactive oxygen entities which promote the processes leading to symptomatic

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intensity and infertility [10]. The most common symptoms of endometriosis include irregular menstruation, dysmenorrhea, chronic pelvic pain, infertility, and dyspareunia. These often affect psychological and social well-being of patients which makes endometriosis a debilitating condition that compromises the sexuality and social relationships, as well as mental health [11, 12].

Objectives

Numerous research publications have indicated a link between endometriosis and consequent complications in pregnancy. Our goal was to identify studies which reported the adverse outcomes of pregnancy in women with endometriosis and perform a meta-analysis of statistical indices to attain up to date evidence on the link between endometriosis and pregnancy complications.

MATERIAL AND METHODS

Search strategy

PubMed, Embase and Cochrane databases were consulted for research articles related to the influence of endometriosis on adverse pregnancy outcomes published in the English language. We also screened the reference lists of related articles and if the literature search was finished by June 2019. Two independent investigators performed the literature search. An additional investigator was involved if any disagreements arose.

Primary search terms were 'endometriosis–pregnancy––adverse outcomes'. This phrase was used in combination (conjunctions: "AND" or "OR") with several other keywords in secondary searches including preterm birth, placenta previa, miscarriage, gestational hypertension, caesarean section, preeclampsia, placental abruption, adenomyosis, fertility, obstetric, assisted reproduction technology, ART, *in vitro* fertilization, IVF, and spontaneous.

All publications were independently assessed by two reviewers to establish if they met the inclusion and exclusion criteria. A third reviewer decided any discrepancies.

Inclusion and exclusion criteria

In following the principles of PICOS (Participants, Interventions, Comparisons, Outcomes and Study design), the inclusion criteria were patients, women suffering from endometriosis in the exposed group, while the control group included healthy women; Intervention, with and without ART pregnancies; Comparison, Adverse pregnancy outcomes between endometriosis and control groups; Outcomes of interest, Adverse pregnancy outcomes; Studies, Cohort studies. Exclusions were the studies without a control group, lacking numerical data, reporting only post-parturition outcomes, or describing a case only.

Extraction of data and quality assessment

The data were obtained from selected publications as basic information which include the country, author name, year of publication, interventions of the exposed and control groups, age, sample size, and pregnancy method. Also included were the clinical outcomes including preterm birth, miscarriage, placenta previa, cesarean section, gestational hypertension, preeclampsia, and placental abruption. The quality of the performed studies was investigated by using the Jadad checklist. Two independent reviewers performed the data extraction and assessed the quality of the studies. Disagreements were solved through dialogue between these two reviewers or by involving a third reviewer.

Statistical analysis

The statistical heterogeneity of the data of the clinical trials was assessed using the Chi-squared and I^2 tests. The publication bias was examined using Egger's test funnel plot, as well as the Begg's and Mazumdar's rank test. Meta-analyses of relative risk (RR) for preterm birth, miscarriage, placenta previa, caesarean section, gestational hypertension, preeclampsia, and placental abruption were performed under the random-effects model using the dichotomous data reported by the individual studies. According to the pregnancy method, we used subgroups as: a) ART (both exposed and control groups were treated by ART), b) spontaneous or ART (SART; both groups had either spontaneous or ART pregnancies), c) natural pregnancy (NP; both groups had natural pregnancies), unclear (UC; the articles did not provide information to differentiate pregnancy type). All the analyses were carried out with Stata software (version 10; Stata Corporation, TX, USA).

RESULTS

Study characteristics

A total of 1,679 publications were found during the literature search. Excluded were 1,572 articles after title or abstract screening. A review of 107 research articles led to exclusion of 79 articles based on failure to fulfil inclusion criteria. Finally, 28 cohort studies were selected for meta-analysis including 53,141 women in the exposed group and 2,355,923 women in the control group [13–39]. The process of screening and selection of the study is presented in Figure 1. The main features of the study are given in Table 1.

The funnel plot for log RR in the risk of preterm birth was markedly symmetrical, signifying a lack of bias (Fig. S1). No significant funnel plot asymmetry was identified by Begg's and Mazumdar's rank test ($Z = 0.20$, $p = 0.844$) or the Egger's test ($p = 0.438$).

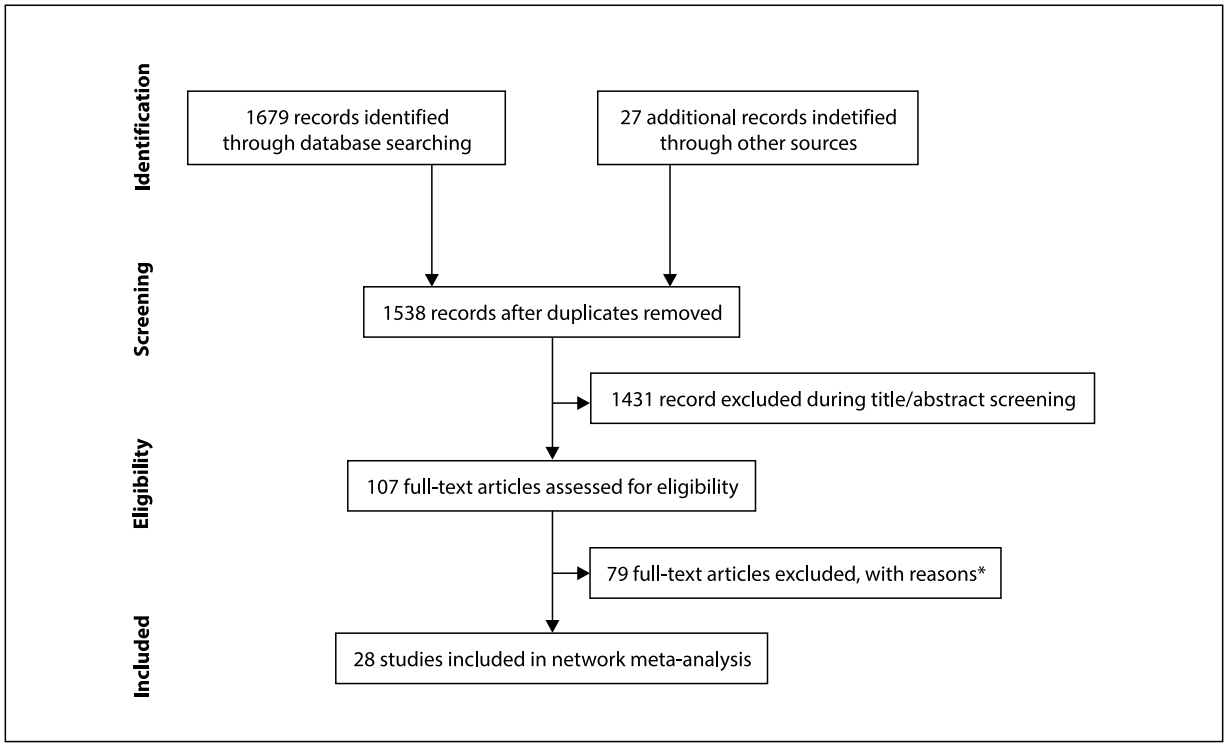

Figure 1. Flow diagram of the literature search and selection process

Preterm birth

Twenty studies with 23,072 women in the exposed and 2,226,870 in the control groups reported the risk of preterm birth. Endometriosis-affected women showed significantly higher incidence of preterm birth (RR 1.59 [95% CI 1.35–1.87]; Fig. 2). In subgroup analyses, the prevalence of preterm birth was significantly higher in spontaneous or ART (RR 1.78 [95% CI 1.29–2.45]), NP (RR 1.62 [95% CI 1.30–2.02]), and UC (RR 1.40 [95% CI 1.03–1.90]) subgroups.

Miscarriage

Nine studies with 33935 women in the exposed and 127,224 in the control groups reported the risk of miscarriage. Endometriosis considerably enhanced the risk of miscarriage (RR 1.31 [95% CI 1.06–1.61]; Fig. 3). The miscarriage risk was significantly higher in ART (RR 1.12 [95% CI 1.01–1.25]) and UC (RR 1.93 [95% CI 1.47–2.25]) subgroups.

Placenta previa

Twelve studies with 6,258 women in the exposed and 96,214 in the control groups reported the risk of placenta previa. Compared to the control group, endometriosis group had a considerably larger risk of placenta previa (RR 3.92 [95% CI 2.48–6.20]; Fig. 4). The placenta previa risk was significantly higher in ART (RR 3.12 [95% CI 1.06–9.21]), SART (RR 4.87 [95% CI 2.46–9.63]), and NP (RR 4.33 [95% CI = 1.25–15.02]) subgroups.

Caesarean section

Sixteen studies with 21,901 women in the exposed and 216, 8884 in the control groups reported the risk of caesarean section. Endometriosis increased the risk of caesarean section significantly (RR 1.48 [95% CI 1.33–1.65]; Fig. S2). The risk of caesarean section was significantly higher in ART (RR 1.45 [95% CI 1.15–1.82]), SART (RR 1.46 [95% CI 1.22––1.75]), NP (RR 1.86 [95% CI 1.13–3.06]), and UC (RR = 1.33, [95% CI = 1.07–1.65]) subgroups.

Gestational hypertension

Eleven studies with 7,119 women in the exposed and 636,681 in the controlled groups reported the prevalence of gestational hypertension. Endometriosis was linked to a significantly enhanced risk of gestational hypertension (RR 1.30 [95% CI 1.02–1.65]; Fig. S3). A significantly higher gestational hypertension risk was observed in ART (RR = 1.78, 95% CI = 1.43–2.23) subgroup.

Preeclampsia

Eleven studies with 16,901 women in the exposed and 1,579,453 in the controlled groups reported the risk of preeclampsia. Endometriosis remarkably enhanced the risk of preeclampsia (RR 1.18 [95% CI 1.09–1.28]; Fig. S4). The preeclampsia risk was significant higher in ART (RR 1.16 [95% CI 1.06–1.27]), and SART (RR 1.25 [95% CI 1.03–1.53]) subgroups.

Table 1. The basic characteristics description of included studies

Ref	Study	No. of patients		Age		Pregnancy method	
		EN	C	EN	C	EN	C
13	Aris 2014	784	30284	–	–	SPONT/ART	SPONT/ART
14	Benaglia 2012	61	130	35.6	36.1	IVF	IVF
15	Benaglia 2016	239	239	35.5	35.5	IVF	IVF
16	Bourdon 2018	201	402	33.7	33.7	ART	ART
17	Chen 2018	469	51733	32.25	30.45	SPONT/ART	SPONT/ART
18	Conti 2015	219	1331	–	–	–	–
19	Exacoustos 2016	41	300	–	–	SPONT/ART	SPONT/ART
20	FitzSimmons 1987	52	134	30.3	30.1	IVF	IVF
21	Glavind 2017	1719	81074	–	–	SPONT/ART	SPONT/ART
22	Gonzalez-Comadran 2017	3583	18833	34.83	34.61	IVF	IVF
23	Harada 2016	330	8856	–	–	SPONT/ART	SPONT/ART
24	Hjordt Hansen 2014	24667	98668	–	–	ART	ART
25	Jacques 2016	113	113	32.4	31.4	ART	ART
26	Kortelahti 2003	137	137	–	–	IVF	IVF
27	Kuivasaari-Pirinen 2012	49	26870	–	–	IVF/ICSI	IVF/ICSI
28	Li 2017	75	300	32.8	30.1	SPONT/ART	SPONT/ART
29	Lin 2015	249	249	32.8	30.6	Nulliparous / NP	Nulliparous /NP
30	Mannini 2017	262	524	36.89	36.88	SPONT/ART	SPONT/ART
31	Matorras 1988	174	174	29.49	29.58	IVF	IVF
32	Mekaru 2014	40	48	–	–	IVF/ET	IVF/ET
33	Nirgianakis 2018	62	186	33.7	33.8	SPONT/ART	SPONT/ART
34	Pittaway 1988	100	250	–	–	–	–
35	Safdarian 2018	32	32	31.37	31.28	IVF	IVF
36	Saraswat 2016	4232	6707	30.5	27.2	–	–
37	Stephansson 2009	13090	1429585	–	–	ART	ART
38	Stern 2015	996	297987	35.2	29.7	ART/ NP	ART
39	Yang 2019	1006	2012	33.04	32.83	IVF	IVF

ART — assisted reproductive technology; C — control; ET — embryo transfer; ICSI — Intracytoplasmic sperm injection; IVF — *in vitro* fertilization; NE — endometriosis group; NP — natural pregnancy; SPONT — spontaneous; T — treatment

Placental abruption

Ten studies with 5,615 women in the exposed and 86,907 in the controlled groups reported the risk of placental abruption. No significant difference was observed in the risk of placental abruption between women with and without endometriosis (RR 3.62 [95% CI 0.99–13.28]; Fig. S5). However, the incidence of placental abruption was significantly higher in SART (RR 10.94 [95% CI 1.17–102.38]) subgroup.

DISCUSSION

The meta-analysis performed for 28 studies has successfully identified the presence of endometriosis in women increases the risk of placenta previa, preterm birth, miscarriage, gestational hypertension, caesarean section, and preeclampsia. In ART subgroup, the incidence of preterm birth, miscarriage, caesarean section, placenta previa, caesarean section, gestational hypertension, and preeclampsia was higher in endometriosis affected women, whereas in NP subgroup, the incidence of placenta previa, preterm birth, and caesarean section was significant higher in women with endometriosis. Higher statistical heterogeneity in the meta-analyses is an important concern which creates a need for further studies and the availability of more homogeneous data for refining the evidence gathered herein.

In a recently published meta-analysis, in comparison with endometriosis women, women with endometriosis exhibited enhanced odds of gestational hypertension, pre-eclampsia and/or pre-eclampsia, gestational cholestasis and diabetes, antepartum hemorrhage, placenta previa, vantepartum hospital admissions, malpresenta-

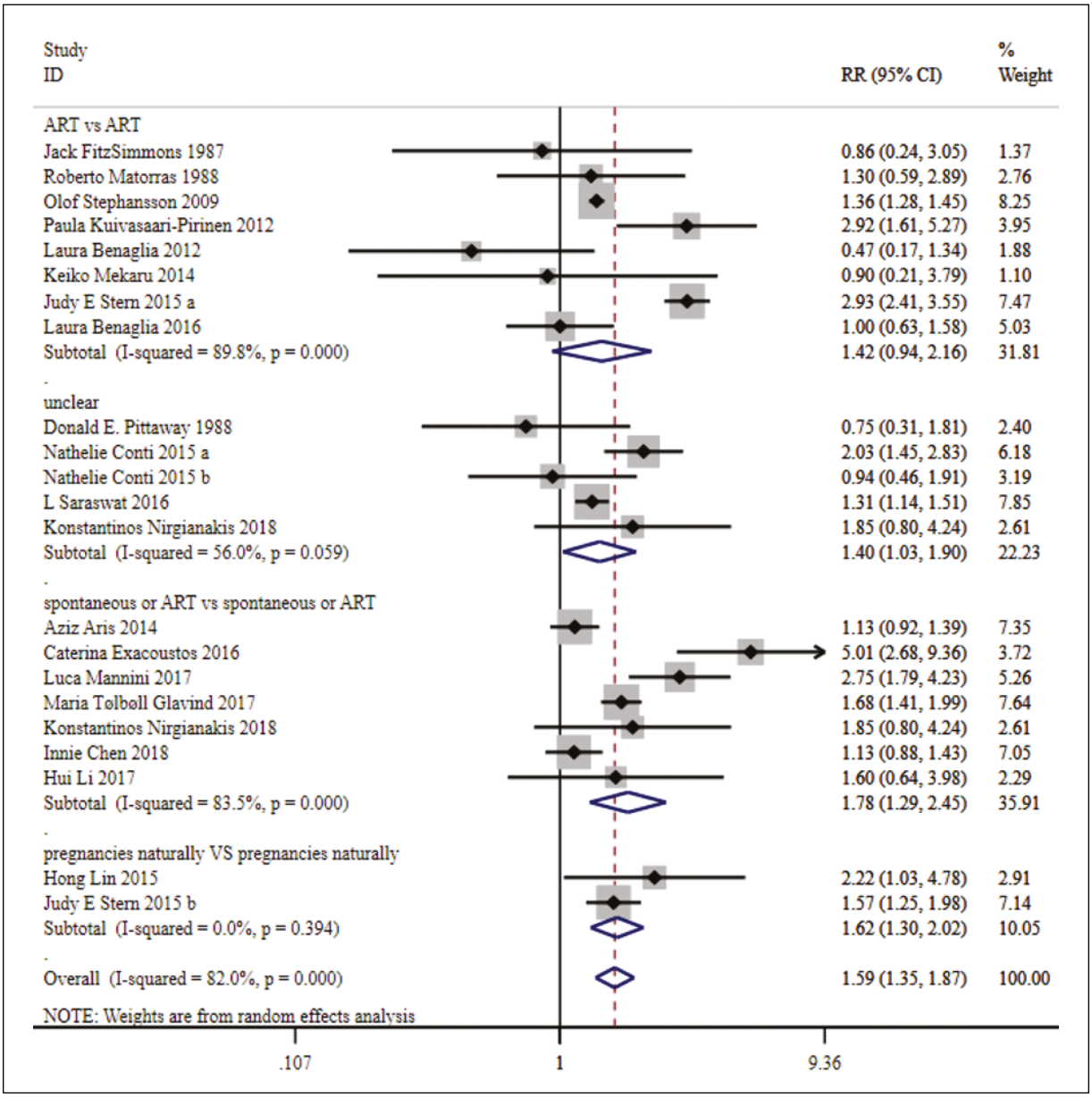

Figure 2. Forest plot for the risk of preterm birth

tion, labor dystocia, caesarean section. Fetal preterm premature rupture of membranes, preterm birth, small for gestational age < 10th%, NICU admission, stillbirth and neonatal death [40].

In a similar report, compared with heathy controls, women with endometriosis had a significantly greater chance of miscarriage (odds ratio (OR) 1.75 [95% CI 1.29––2.37], preterm birth (OR 1.63 [95% CI 1.32–2.01]), caesarean delivery (OR 1.57 [95% CI [1.39–1.78]), small size for gestational stage (OR 1.27 [95% CI 1.03–1.57]) and placenta previa (OR 3.03 [95% CI 1.50–6.13]). The incidence of preeclampsia and gestational hypertension had no significant difference between the women of control and endometriosis group [41]. These findings are consistent with our results in general. However, the conclusions regarding gestational hypertension and preeclampsia are inconsistent. The risks of gestational hypertension and preeclampsia in the eligible studies were also inconsistent suggesting that future studies with larger sized and better design of studies are required to authenticate these findings. Recently, in a population-based longitudinal study in Taiwan with 6300 women, a prior diagnosis of endometriosis was found to be an independent risk factor for the incidence of gestational hypertension or preeclampsia [42]. On the other hand, a recent meta-analysis has reported that endometriosis does not pose a significant risk

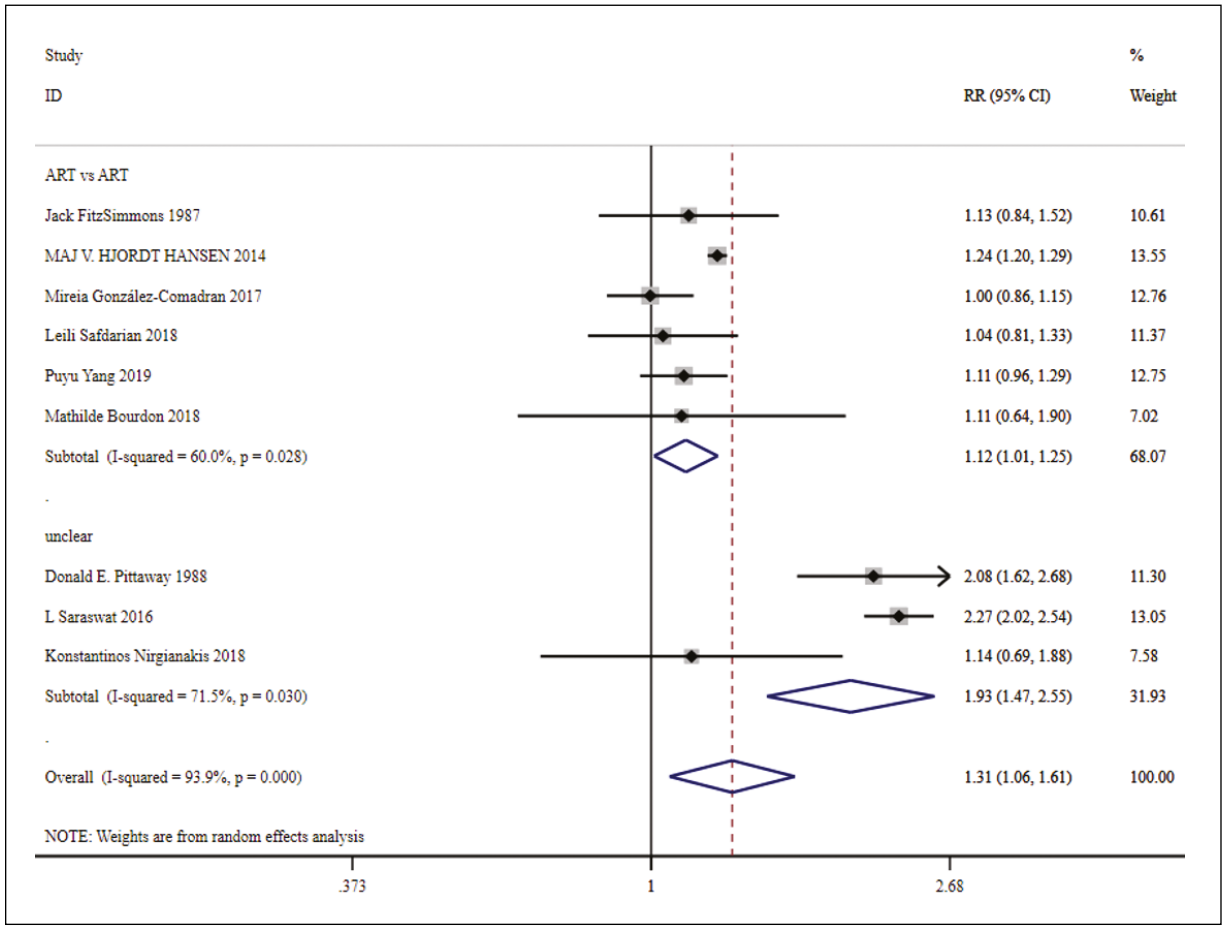

Figure 3. Forest plot for the risk of miscarriage

of preeclampsia or its more severe forms in either natural or ART pregnancies [43].

We have also found the incidence of placental abruption to be insignificantly different between women of control and endometriosis group. A meta-analysis of five case-controlled studies has also found no differences in the incidence of placental abruption (OR 0.44 (95% CI 0.10–1.87) between women with and without endometriosis [44].

Endometrium is a healthy tissue that resides in the uterine cavity. When endometrium is found growing outside the uterus, a diagnosis of endometriosis is given. Patients with endometriosis typically have difficulty forming luteinium and have abnormalities in ovulation due to dysfunction of the ovaries. Transport of fertilized eggs in patients with moderate to severe disease is easily disturbed by adhesion between the ovaries and fallopian tubes, resulting in infertility. However, the treatment of endometriosis may also have an effect later in the reproductive cycle.

Although ovarian endometriomas and peritoneal superficial lesions represent the majority of implanted endometriosis within the pelvis, the most challenging conditions are extra pelvic endometriosis and deep infiltrating endometriosis. Occasionally signs and symptoms are reduced by using medical therapy [45]. However, in various patients, a complete eradication with nerve-sparing and vascular sparing approach [46, 47] is desired to restore anatomy and function of normal pelvic.

Among the strengths of the present study, to the quantification of the endometriosis effect on pregnancy outcomes in as a pooled effect size of large sample, use of specified inclusion and exclusion criteria, use of precise statistical measures for seeking risk indices, and the inclusion of studies with considerably larger population sizes are notable points. There were however some limitations that should be noted. These include: 1) only cohort studies were used for the analyses; 2) many studies had some limitations to fulfil the inclusion and exclusion criteria; 3) use of a variety of reproduction techniques in included studies might had contributed to the statistical heterogeneity observed in the meta-analyses; 4) the severity of endometriosis was variable; 5) studies with unclear pregnancy type could have influenced the overall risk ratio values.

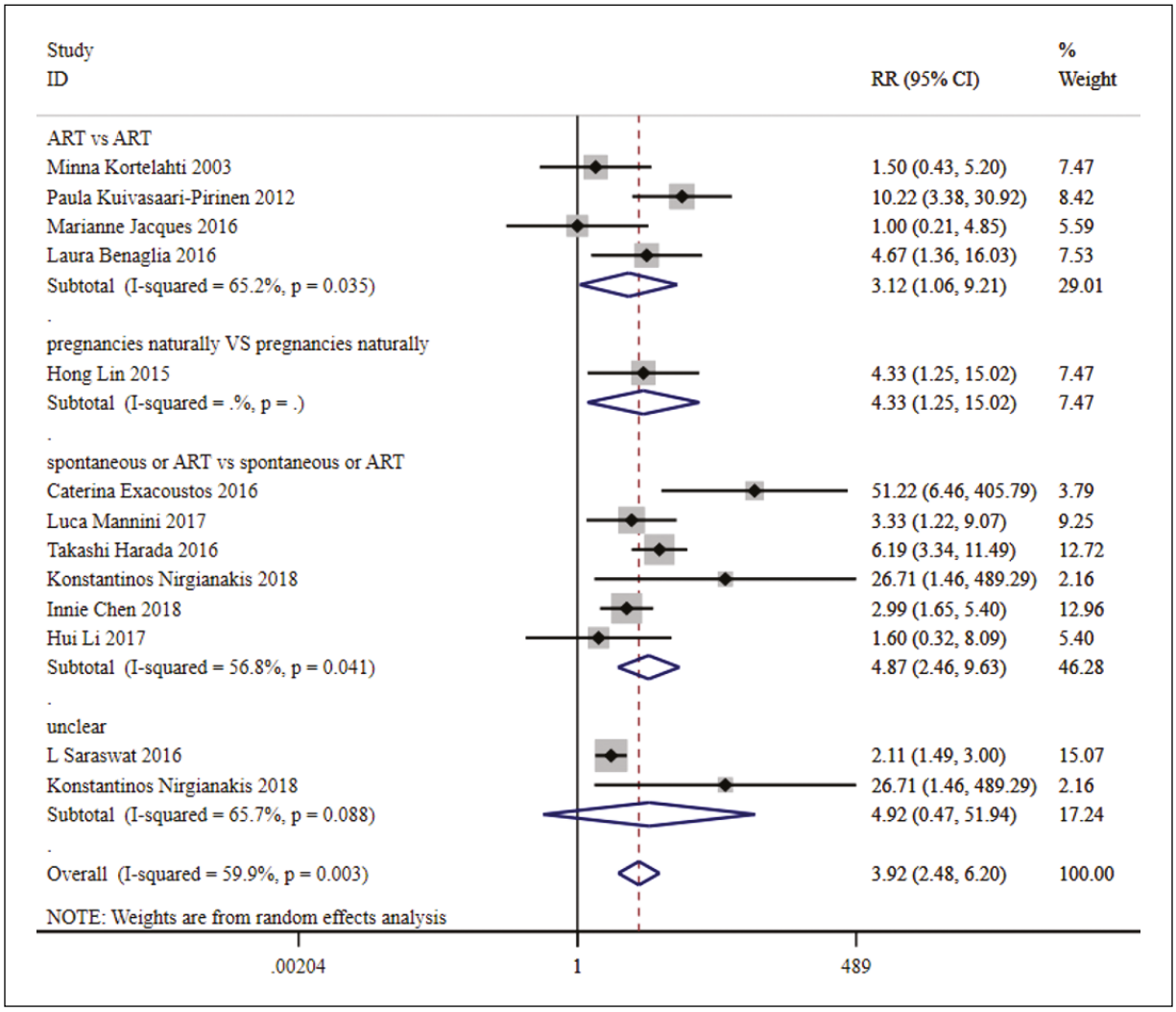

Figure 4. Forest plot for the risk of placenta previa

CONCLUSIONS

Based on the available evidence, this meta-analysis reveals that compared to women without endometriosis, endometriosis women have significantly increased risk of miscarriage, preterm birth, gestational hypertension, placenta previa, cesarean section, and preeclampsia. In the future, research studies should explore the relationship of varying clinical stages of endometriosis on pregnancy outcomes.

Article information and declarations

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Conflicts of interest

None.

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