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*Research Article*

# Miscarriage on Endometriosis and Adenomyosis in Women by Assisted Reproductive Technology or with Spontaneous Conception: A Systematic Review and Meta-Analysis

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*Background*. In the past several years, there has been an increasing concern on miscarriage caused by endometriosis or adenomyosis. However, the results reported by different studies remain controversial. The present study is aimed at assessing the impact of endometriosis and adenomyosis on miscarriage. *Materials and Methods*. Searches were carried out in PubMed, Embase, and the Cochrane library for studies published from inception until February 29, 2020. The investigators included studies that evaluated miscarriage risk in pregnant women with endometriosis or adenomyosis by assisted reproductive technology (ART), or with spontaneous conception (SC). Miscarriage (<28 weeks) was the primary outcome. The secondary outcomes were antepartum hemorrhage (APH), postpartum hemorrhage (PPH), preterm birth, low birthweight, placenta praevia, placental abruption, ectopic pregnancy, stillbirth, gestational diabetes, preeclampsia, and intrauterine growth restriction (IUGR). Endnote was used for the study collection, and the data analyses were carried out by two authors using Review Manager version 5.2. *Results*. Thirty-nine studies, which is comprised of 697,984 women, were included in the present study. Miscarriage risk increased in women with endometriosis in SC (OR: 1.81, 95% CI: 1.44-2.28, $I^2 = 96\%$) compared with those without endometriosis, while women with endometriosis who underwent ART had a similar miscarriage risk, when compared to those with tubal infertility (OR: 1.03, 95% CI: 0.92-1.14, $I^2 = 0\%$). Compared with those without adenomyosis, women with adenomyosis had an augmented miscarriage risk in ART (OR: 2.81, 95% CI: 1.44-5.47, $I^2 = 64\%$). Compared with those without endometriosis, women with endometriosis had higher odds of APH, PPH, preterm birth, stillbirth, and placenta praevia. No difference was observed in the incidence of ectopic pregnancy, placental abruption, pre-eclampsia, gestational diabetes, low birthweight, and IUGR. *Conclusion*. Women with endometriosis had an augmented miscarriage risk in SC and a similar miscarriage risk during ART. Adenomyosis was associated with miscarriage in pregnant women using ART.

## 1. Introduction

Endometriosis (EMS) and adenomyosis (AD) are both complicated diseases that have influence on pregnancy outcomes. EMS is identified by the endometrium outside the uterus and is correlated to pelvic pain and infertility [1]. It has been reported that the disease affects up to 10%-15% of women during the reproductive age [2]. Adenomyosis, which is defined as ingrowth of the endometrial tissue into the myometrium [3], is associated with heavy menstrual bleeding and dysmenorrhea. It has been estimated that 20.9% of women are diagnosed with AD through transvaginal sonography (TVS) [4].

In the past several years, there has been an increasing concern on miscarriage caused by EMS or AD. Many studies have assessed the miscarriage risk in women with EMS or AD. However, the results reported from different studies remain controversial, since some studies presented positive results, while other studies reported negative results [5, 6]. Therefore, a systematic review and meta-analysis was carried

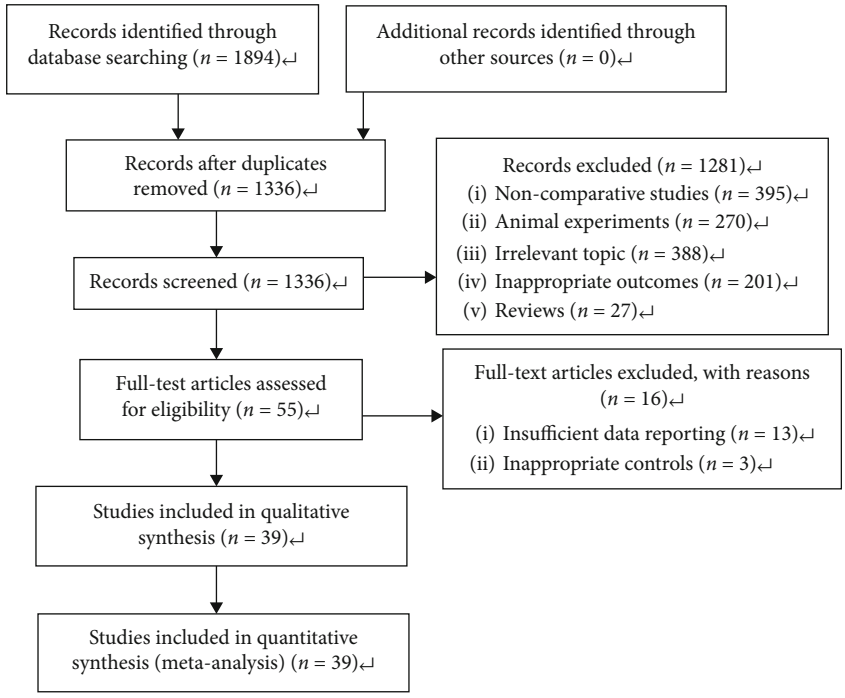


Figure 1: Flow chart of the literature selection.

out to evaluate the impact of EMS or AD on miscarriage in women who are pregnant with spontaneous conception (SC), or by using assisted reproductive technology (ART). The EMS was staged according to the American Fertility Society classification. Where appropriate, EMS I/II was compared with EMS III/IV on miscarriage, and the investigators planned to assess the miscarriage risk according to the types of EMS, including superficial peritoneal endometriosis (SUP), deep infiltrating endometriosis (DIE), and ovarian endometrioma (OMA). Where applicable, the investigators evaluated the effect of EMS or AD on early abortion (at <12 weeks) and late abortion (at ≥12 weeks).

## 2. Materials and Methods

*2.1. Search Strategy.* Electronic databases (PubMed, Embase, and Cochrane library) were searched for published studies from inception to February 29, 2020, in all languages, by two authors, independently. The MeSH terms were as follows: "ademomyosis,""endometriosis," "spontaneous abortion," "miscarriage," "assisted reproductive technique," "ovulation induction," "artificial insemination," "in vitro fertilization," "intracytoplasmic sperm injection," and "embryo transfer." No restriction for geographic location was applied, and the references were collected by Endnote. In addition, the reference lists of eligible articles and relevant reviews were manually examined to identify potentially available studies. The present meta-analysis was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO), and the registration code was CRD42020160594.

*2.2. Inclusion and Exclusion Criteria.* Duplicates were removed prior to the title and abstract screening. The inclusion criteria were as follows: (1) studies that investigated miscarriage risk in pregnant women with SC or using ART; (2) women with EMS or AD who were included in the study group; (3) an appropriate control group; (4) among women with EMS who underwent ART, the control group consisted of only women with tubal infertility; and (5) randomized controlled trials, cohort studies, case control studies, or cross-sectional analysis. The EMS or AD could be preliminarily diagnosed by clinical symptoms, gynecological examination, and instrumental (ultrasound, computed tomography scan, or magnetic resonance imaging) presentation. The golden standard was pathological diagnosis. In addition, the exclusion criteria were as follows: (1) the publication was a conference abstract or a review; (2) the studies were conducted in animals; (3) the outcome did not include miscarriage; and (4) the necessary data was missing. After independently examining the eligibility of studies based on the titles and abstracts, the full texts were reviewed by two authors. A third author was consulted to resolve any discrepancies.

*2.3. Data Extraction and Quality Assessment.* For eligible studies, the data were extracted by two authors independently. A data collection form was designed for the data extraction, which included the first author, publication year, study design, sample size, study location, mode of conception, type of disease, exposure ascertainment, and outcomes. If disagreements appeared, this was discussed with a third reviewer to reach a consensus. If required, the authors of the qualified publications were contacted for detailed results and precise data.

According to the Newcastle-Ottawa Scale (NOS), the investigators evaluated the risk of bias to identify the

Table 1: Characteristics of identified literature.

| Authors (year) | Study design | Sample size | Study location | Mode of conception | Type of disease | Exposure ascertainment | Outcomes |
|---|---|---|---|---|---|---|---|
| Porpora et al. (2020) | Prospective cohort study | 425 | Italy | SC | EMS | Surgical/clinical/instrumental diagnosis | Miscarriage, PPH, IUGR, gestational diabetes, stillbirth, low birthweight preterm birth, placenta praevia, placental abruption, preeclampsia |
| Farland et al. (2019) | Prospective cohort study | 196722 | America | SC | EMS | Laparoscopic diagnosis | Miscarriage, gestational diabetes, ectopic pregnancy, stillbirth, low birthweight, preterm birth |
| Mekaru et al. (2014) | Retrospective cohort study | 108 | Japan | SC | EMS | Laparoscopic evaluation | Miscarriage, low birthweight, preterm birth |
| Pittaway et al. (1988) | Retrospective cohort study | 350 | America | SC | EMS | Laparoscopy or laparotomy | Miscarriage, ectopic pregnancy |
| Hjordt Hansen et al. (2014) | Retrospective cohort study | 123335 | Denmark | SC | EMS | Discharge diagnosis by the international classification of diseases | Miscarriage, ectopic pregnancy |
| Santulli et al. (2016) | Retrospective cohort study | 1851 | France | SC | EMS | Surgical examination of the abdominopelvic cavity | Miscarriage |
| Saraswat et al. (2016) | Retrospective cohort study | 13665 | Scotland | SC | EMS | Laparoscopy or laparotomy | Miscarriage, PPH, APH, low birthweight, stillbirth, ectopic pregnancy, preterm birth, placenta praevia, placental abruption |
| Geber et al. (1995) | Retrospective cohort study | 1506 | London | IVF | EMS | Laparoscopy | Miscarriage, ectopic pregnancy |
| Omland et al. (2005) | Retrospective cohort study | 1026 | Norway | IVF/ICSI | EMS | Laparoscopic diagnosis | Miscarriage, ectopic pregnancy, stillbirth |
| Kuroda et al. (2009) | Case control study | 82 | Japan | IVF/ICSI | EMS | Laparoscopic surgery/ultrasound/MRI | Miscarriage |
| Olivennes et al. (1995) | Retrospective cohort study | 325 | America | IVF | EMS | Laparoscopic evaluation | Miscarriage |
| Polat et al. (2014) | Retrospective cohort study | 616 | Turkey | IVF | EMS | Laparoscopy or laparotomy, transvaginal ultrasonography | Miscarriage |
| Guo et al. (2016) | Retrospective cohort study | 437 | China | IVF | EMS | Laparoscopy or laparotomy | Miscarriage |
| Pop et al. (2014) | Prospective cohort study | 235 | Serbia | IVF | EMS | Surgically confirmed | Miscarriage |
| Sharma et al. (2020) | Prospective cohort study | 652 | India | IVF | EMS | Laparoscopic diagnosis | Miscarriage, PPH, APH, gestational diabetes, preterm birth, IUGR, preeclampsia |
| Matalliotakis et al. (2007) | Case control study | 174 | Greece | IVF-ET | EMS | Laparoscopic diagnosis | Miscarriage |
| Curtis et al. (1993) | Retrospective cohort study | 206 | England | IVF-ET | EMS | Laparoscopic diagnosis | Miscarriage, ectopic pregnancy |
| Arici et al. (1996) | Case control study | 105 | America | IVF-ET | EMS | Laparoscopic diagnosis | Miscarriage |
| Bergendal et al. (1998) | Retrospective cohort study | 146 | Canada | IVF-ET | EMS | Laparoscopic diagnosis | Miscarriage, ectopic pregnancy |
| Pabuccu et al. (2004) | Randomized controlled trials | 171 | Turkey | ICSI | EMS | Laparoscopic diagnosis | Miscarriage |

Table 1: Continued.

| Authors (year) | Study design | Sample size | Study location | Mode of conception | Type of disease | Exposure ascertainment | Outcomes |
|---|---|---|---|---|---|---|---|
| Mathieud et al. (2010) | Retrospective cohort study | 526 | France | IVF | EMS | Sonography, MRI | Miscarriage |
| Kim et al. (2011) | Prospective cohort study | 40 | Korea | IVF-ET | EMS | Laparoscopic diagnosis | Miscarriage |
| Kuivasaari et al. (2005) | Retrospective cohort study | 185 | Finland | IVF/ICSI | EMS | Laparoscopic diagnosis | Miscarriage, ectopic pregnancy |
| Opoien et al. (2012) | Retrospective cohort study | 2245 | Norway | ICSI | EMS | Laparoscopic diagnosis | Miscarriage |
| Singh et al. (2013) | Case control study | 340 | India | IVF | EMS | Laparoscopic diagnosis | Miscarriage |
| Senepati et al. (2016) | Retrospective cohort study | 347185 | Washington | IVF | EMS | Laparoscopic diagnosis | Miscarriage |
| Vaz et al. (2017) | Retrospective cohort study | 181 | Brazil | IVF | EMS | Laparoscopy or MRI | Miscarriage |
| Esinler et al. (2006) | Case control study | 156 | Turkey | IVF/ICSI | EMS | Laparoscopic diagnosis | Miscarriage |
| Bahceci et al. (2005) | Retrospective cohort study | 1244 | Turkey | ICSI | EMS | Laparoscopic diagnosis | Miscarriage |
| Sharma et al. (2019) | Retrospective cohort study | 973 | India | IVF | EMS and AD | EMS confirmed by laparoscopy, AD diagnosed by TVS | Miscarriage, PPH, APH, preterm birth, IUGR, preeclampsia |
| Costello et al. (2011) | Retrospective cohort study | 201 | Australia | IVF/ICSI | AD | Transvaginal ultrasound | Miscarriage |
| Youm et al. (2011) | Case control study | 154 | Korea | IVF-ET | AD | TVS | Miscarriage |
| Thailluri et al. (2012) | Retrospective cohort study | 213 | Australia | IVF-ET | AD | TVS | Miscarriage |
| Benaglia et al. (2014) | Case control study | 98 | Italy | IVF/ICSI | AD | TVS | Miscarriage |
| Hashimoto et al. (2017) | Case control study | 294 | Japan | ART | AD | MRI/TVS | Miscarriage |
| Martinez-Conejero et al. (2011) | Retrospective cohort study | 443 | Spain | ART | AD | TVS | Miscarriage |
| Yan et al. (2014) | Retrospective cohort study | 154 | China | ART | AD | Transvaginal ultrasound | Miscarriage, ectopic pregnancy |
| Salim et al. (2012) | Prospective cohort study | 275 | London | ART | AD | Transvaginal ultrasound | Miscarriage |
| Schwartz et al. (2017) | Cross-sectional study | 940 | Switzerland | SC or ART | EMS | Surgical diagnosis | Miscarriage |

SC: spontaneous conception; ART: assisted reproductive technology; IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; EMS: endometriosis; AD: adenomyosis; TVS: transvaginal sonography; MRI: magnetic resonance imaging; APH: antepartum hemorrhage; PPH: postpartum hemorrhage; IUGR: intrauterine growth restriction.

Table 2: Newcastle-Ottawa risk of bias for included studies.

| Authors (year) | Selection of study group score | Comparability of group score | Ascertainment of exposure or outcome score | Total NOS score | Risk of bias (low, medium, high) |
|---|---|---|---|---|---|
| *Retrospective cohort study* | | | | | |
| Omland et al. (2005) | 3 | 2 | 2 | 7 | Low |
| Martinez-Conejero et al. (2011) | 3 | 2 | 2 | 7 | Low |
| Hjordt Hansen et al. (2014) | 3 | 1 | 3 | 7 | Low |
| Yan et al. (2014) | 3 | 2 | 2 | 7 | Low |
| Santulli et al. (2016) | 3 | 2 | 3 | 8 | Low |
| Saraswat et al. (2016) | 3 | 2 | 3 | 8 | Low |
| Sharma et al. (2019) | 3 | 1 | 3 | 7 | Low |
| Pittaway et al. (1988) | 3 | 1 | 3 | 7 | Low |
| Geber et al. (1995) | 4 | 2 | 2 | 8 | Low |
| Olivennes et al. (1995) | 3 | 2 | 2 | 7 | Low |
| Mekaru et al. (2014) | 3 | 2 | 2 | 7 | Low |
| Polat et al. (2014) | 3 | 2 | 3 | 8 | Low |
| Guo et al. (2016) | 3 | 2 | 2 | 7 | Low |
| Costello et al. (2011) | 3 | 2 | 2 | 7 | Low |
| Mathieud et al. (2010) | 3 | 2 | 2 | 7 | Low |
| Senepati et al. (2016) | 3 | 1 | 2 | 6 | Medium |
| Curtis et al. (1993) | 3 | 2 | 1 | 6 | Medium |
| Bergendal et al. (1998) | 3 | 2 | 2 | 7 | Low |
| Kuivasaari et al. (2005) | 3 | 2 | 2 | 7 | Low |
| Opoien et al. (2012) | 3 | 2 | 2 | 7 | Low |
| Vaz et al. (2017) | 3 | 1 | 2 | 6 | Medium |
| Bahceci et al. (2005) | 3 | 0 | 3 | 6 | Medium |
| Thailluri et al. (2012) | 3 | 2 | 2 | 7 | Low |
| *Prospective cohort study* | | | | | |
| Pop et al. (2014) | 3 | 2 | 2 | 7 | Low |
| Kim et al. (2011) | 3 | 2 | 3 | 8 | Low |
| Salim et al. (2012) | 3 | 2 | 2 | 7 | Low |
| Farland et al. (2019) | 3 | 1 | 3 | 7 | Low |
| Porpora et al. (2020) | 4 | 1 | 2 | 7 | Low |
| Sharma et al. (2020) | 3 | 2 | 2 | 7 | Low |
| *Case control study* | | | | | |
| Arici et al. (1996) | 3 | 1 | 2 | 6 | Medium |
| Singh et al. (2013) | 3 | 2 | 2 | 7 | Low |
| Kuroda et al. (2009) | 3 | 1 | 2 | 6 | Medium |
| Esinler et al. (2006) | 3 | 2 | 2 | 7 | Low |
| Benaglia et al. (2014) | 3 | 2 | 2 | 7 | Low |
| Matalliotakis et al. (2007) | 3 | 2 | 2 | 7 | Low |
| Hashimoto et al. (2017) | 3 | 2 | 2 | 7 | Low |
| Youm et al. (2011) | 4 | 0 | 2 | 6 | Medium |
| *Cross-sectional study* | | | | | |
| Schwartz et al. (2017) | 3 | 2 | 2 | 7 | Low |

Table 3: Risk of bias for randomized controlled trials.

| Bias | Selection | | Performance | Attrition | Reporting | |
|---|---|---|---|---|---|---|
| Studies (year) | Random sequence generation | Allocation concealment | Blinding | Incomplete outcome data | Selective reporting | Other sources of bias |
| Pabuccu et al. (2004) | Low risk | Unclear | Unclear | Low risk | Low risk | Low risk |

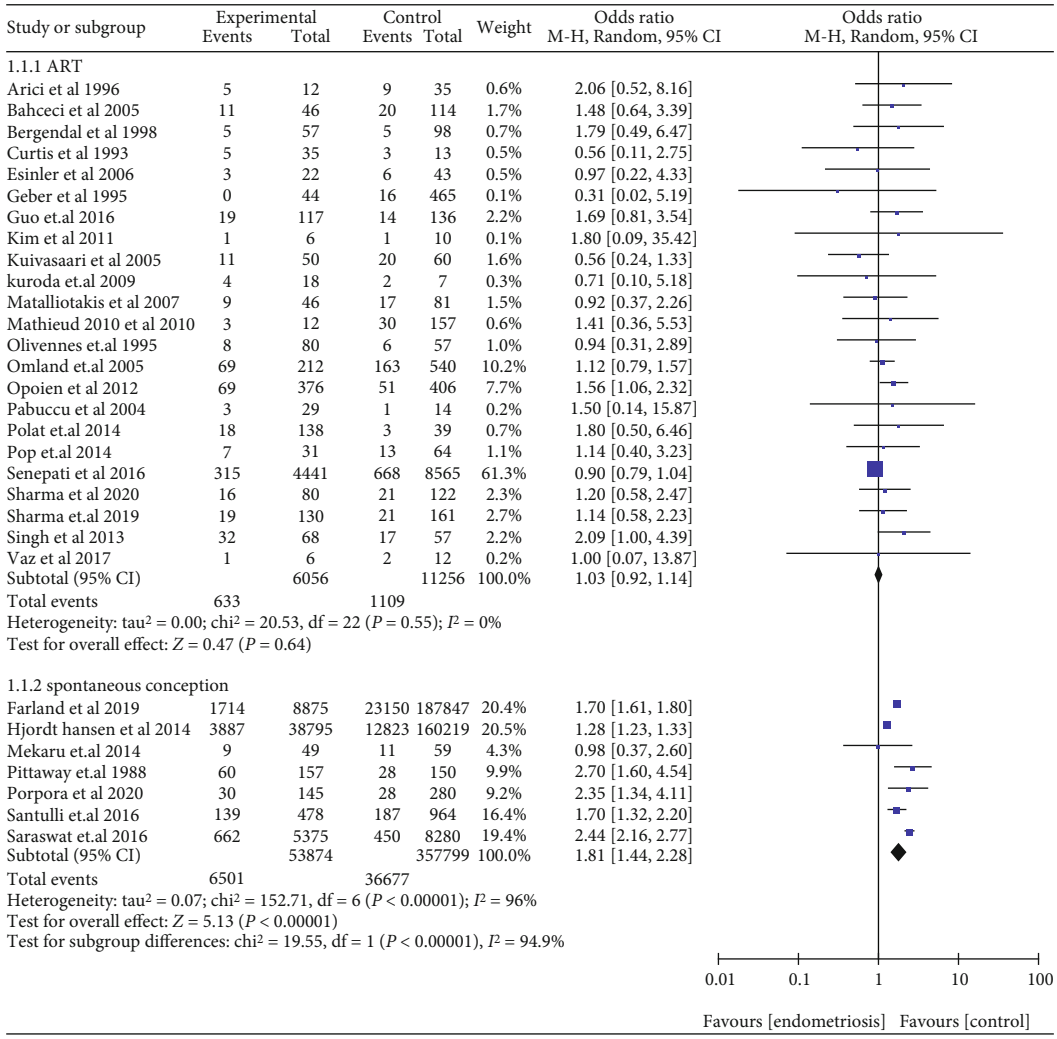


Figure 2: Miscarriage risk in pregnant women with EMS in SC or using ART.

methodology quality of the eligible studies. Nine items were included in the NOS, which were categorized into three groups: consisted of the selection of the study group and control group (4 scores, indicating selection bias), the comparability of two groups (2 scores, indicating confounding bias), and the identification of either outcome or exposure (3 scores, indicating measurement bias). The outcome assessment of seven or more stars implied a low risk of bias. The risk of methodological bias in the randomized controlled trials (RCTs) was evaluated using the Cochrane risk of bias tool, including randomization, allocation concealment, blinding of participants and researchers, blinding of outcomes assessors, incomplete outcome reporting, selective outcome reporting, and other sources of bias.

*2.4. Statistical Analysis.* The data analyses were independently carried out by two authors using Review Manager version 5.2. If differences occurred, a third author was consulted for evaluation. According to the Cochrane handbook [7], the heterogeneity was measured by $I^2$. An $I^2$ value of 0-50% was considered to represent low or moderate heterogeneity, while >50% was taken to indicate substantial heterogeneity. The fixed effects model was applied for the meta-analysis. The random effects model was used when $I^2 > 50\%$. Pregnancy outcomes were depicted using the odds ratio and 95% confidence interval (CI) [8]. $P < 0.05$ was considered statistically significant. Potential publication biases were statistically evaluated using funnel plots and Begg's and Egger's tests [9]. The present study was reported in accordance with the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [10].

The primary outcome was miscarriage, which was defined as spontaneous abortion at <28 weeks. The secondary outcomes were preterm birth (defined as birth < 37 gestational weeks), antepartum hemorrhage (APH), postpartum hemorrhage (PPH), low birthweight (defined as birth weight < 2,500 g), placenta praevia (identified by the placenta implanted in the lower uterine segment), placental abruption (defined as partial or complete detachment of the placenta from the myometrium before delivery), ectopic pregnancy, stillbirth, gestational diabetes, preeclampsia, and intrauterine growth restriction (IUGR).

| Study or subgroup | Adenomyosis Events | Adenomyosis Total | Control Events | Control Total | Weight | Odds ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Benaglia et al 2014 | 4 | 21 | 5 | 14 | 9.5% | 0.42 [0.09, 1.98] |
| Costello et.al 2011 | 2 | 13 | 16 | 59 | 9.1% | 0.49 [0.10, 2.45] |
| Hashimoto et al 2017 | 6 | 49 | 3 | 245 | 10.3% | 11.26 [2.71, 46.72] |
| Martinez et al 2011 | 43 | 131 | 24 | 147 | 17.1% | 2.50 [1.42, 4.43] |
| Salim et.al 2012 | 2 | 4 | 3 | 108 | 6.0% | 35.00 [3.61, 339.20] |
| Sharma et.al 2019 | 6 | 15 | 21 | 161 | 12.5% | 4.44 [1.44, 13.76] |
| Thailluri et al 2012 | 2 | 12 | 5 | 81 | 8.2% | 3.04 [0.52, 17.80] |
| Yan et.al 2014 | 19 | 38 | 17 | 46 | 14.6% | 1.71 [0.71, 4.09] |
| Youm et al 2011 | 13 | 24 | 8 | 42 | 12.6% | 5.02 [1.65, 15.28] |
| Total (95% CI) | | 307 | | 903 | 100.0% | 2.81 [1.44, 5.47] |
| Total events | 97 | | 102 | | | |

Heterogeneity: tau² = 0.59; chi² = 21.95, df = 8 ($P = 0.005$); $I^2 = 64\%$
Test for overall effect: $Z = 3.03$ ($P = 0.002$)

Odds ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours [adenomyosis] Favours [control]

Figure 3: Miscarriage risk in pregnant women with AD in ART.

| Study or subgroup | Adenomyosis Events | Adenomyosis Total | Control Events | Control Total | Weight | Odds ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Benaglia et al 2014 | 4 | 21 | 5 | 14 | 9.6% | 0.42 [0.09, 1.98] |
| Costello et.al 2011 | 2 | 13 | 16 | 59 | 9.1% | 0.49 [0.10, 2.45] |
| Hashimoto et al 2017 | 6 | 49 | 3 | 245 | 10.6% | 11.26 [2.71, 46.72] |
| Martinez et al 2011 | 43 | 131 | 24 | 147 | 19.7% | 2.50 [1.42, 4.43] |
| Sharma et.al 2019 | 6 | 15 | 21 | 161 | 13.3% | 4.44 [1.44, 13.76] |
| Thailluri et al 2012 | 2 | 12 | 5 | 81 | 8.1% | 3.04 [0.52, 17.80] |
| Yan et.al 2014 | 19 | 38 | 17 | 46 | 16.1% | 1.71 [0.71, 4.09] |
| Youm et al 2011 | 13 | 24 | 8 | 42 | 13.5% | 5.02 [1.65, 15.28] |
| Total (95% CI) | | 303 | | 795 | 100.0% | 2.41 [1.29, 4.50] |
| Total events | 95 | | 99 | | | |

Heterogeneity: tau² = 0.43; chi² = 16.73, df = 7 ($P = 0.02$); $I^2 = 58\%$
Test for overall effect: $Z = 2.76$ ($P = 0.006$)

Odds ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours [experimental] Favours [control]

Figure 4: Sensitivity analysis of miscarriage risk in pregnant women with AD.

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| 1.10.1 prospective cohort study | | | | | | |
| Farland et al 2019 | 1714 | 8875 | 23150 | 187847 | 20.4% | 1.70 [1.61, 1.80] |
| Porpora et al 2020 | 30 | 145 | 28 | 280 | 9.2% | 2.35 [1.34, 4.11] |
| Subtotal (95% CI) | | 9020 | | 188127 | 29.5% | 1.76 [1.45, 2.14] |
| Total events | 1744 | | 23178 | | | |
| Heterogeneity: tau² = 0.01; chi² = 1.25, df = 1 ($P = 0.26$); $I^2 = 20\%$ | | | | | | |
| Test for overall effect: $Z = 5.69$ ($P < 0.00001$) | | | | | | |
| 1.10.2 retrospective cohort study | | | | | | |
| Hjordt hansen et al 2014 | 3887 | 38795 | 12823 | 160219 | 20.5% | 1.28 [1.23, 1.33] |
| Mekaru et.al 2014 | 9 | 49 | 11 | 59 | 4.3% | 0.98 [0.37, 2.60] |
| Pittaway et.al 1988 | 60 | 157 | 28 | 150 | 9.9% | 2.70 [1.60, 4.54] |
| Santulli et.al 2016 | 139 | 478 | 187 | 964 | 16.4% | 1.70 [1.32, 2.20] |
| Saraswat et.al 2016 | 662 | 5375 | 450 | 8280 | 19.4% | 2.44 [2.16, 2.77] |
| Subtotal (95% CI) | | 44854 | | 169672 | 70.5% | 1.78 [1.19, 2.66] |
| Total events | 4757 | | 13499 | | | |
| Heterogeneity: tau² = 0.17; chi² = 104.39, df = 4 ($P < 0.00001$); $I^2 = 96\%$ | | | | | | |
| Test for overall effect: $Z = 2.79$ ($P = 0.005$) | | | | | | |
| Total (95% CI) | | 53874 | | 357799 | 100.0% | 1.81 [1.44, 2.28] |
| Total events | 6501 | | 36677 | | | |
| Heterogeneity: tau² = 0.07; chi² = 152.71, df = 6 ($P < 0.00001$); $I^2 = 96\%$ | | | | | | |
| Test for overall effect: $Z = 5.13$ ($P < 0.00001$) | | | | | | |
| Test for subgroup differences: chi² = 0.00, df = 1 ($P = 0.97$), $I^2 = 0\%$ | | | | | | |

Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours [experimental] Favours [control]

Figure 5: Miscarriage risk in women with EMS in retrospective cohort studies and prospective cohort studies in SC.

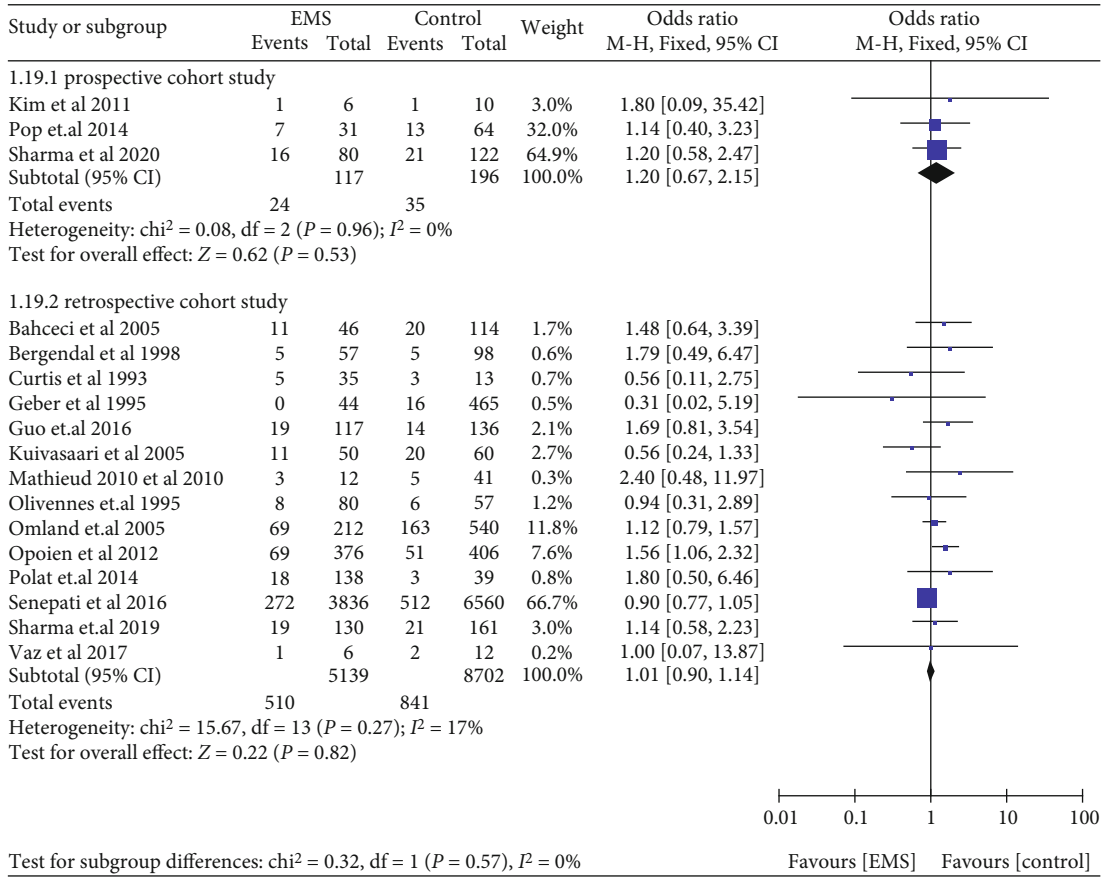


Figure 6: Miscarriage risk in women with EMS in retrospective cohort studies and prospective cohort studies during ART.

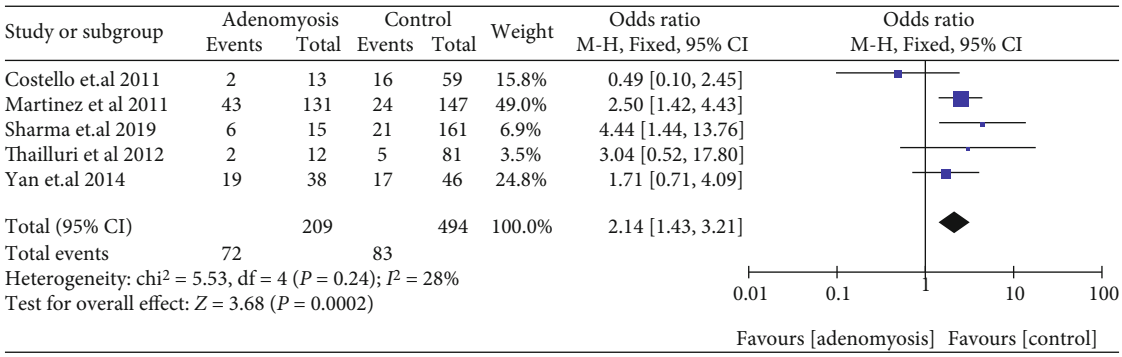


Figure 7: Miscarriage risk in women with AD in retrospective cohort studies during ART.

Where applicable, the subgroup analyses for miscarriage risk in women with EMS were performed based on the method of diagnosis (i.e., laparoscopic diagnosis), type of EMS (i.e., ovarian, peritoneal, or deep infiltrating endometriosis), and staging of EMS (I, II, III, or IV). Sensitivity analyses for miscarriage risk were carried out to evaluate the stability and reliability of the pooled results.

## 3. Results

*3.1. Study Selection.* A total of 1,894 articles were identified using the electronic search strategy. Furthermore, 1,336 articles were evaluated after the duplicates were removed. The eligibility of studies was assessed based on the titles and abstracts, and 1,281 articles were discarded for noncomparative studies ($n = 395$), for animal experiments ($n = 270$), for irrelevant topics ($n = 388$), for inappropriate outcomes ($n = 201$), or for being reviews ($n = 27$). Moreover, 55 articles were eligible for full-text review. Among these, 13 papers were excluded due to inadequate data reporting and 3 studies were excluded because of inappropriate controls. Lastly, 39 publications [11–49], which consisted of 697,984 women, met the present inclusion criteria and were analyzed in the present study (Figure 1).

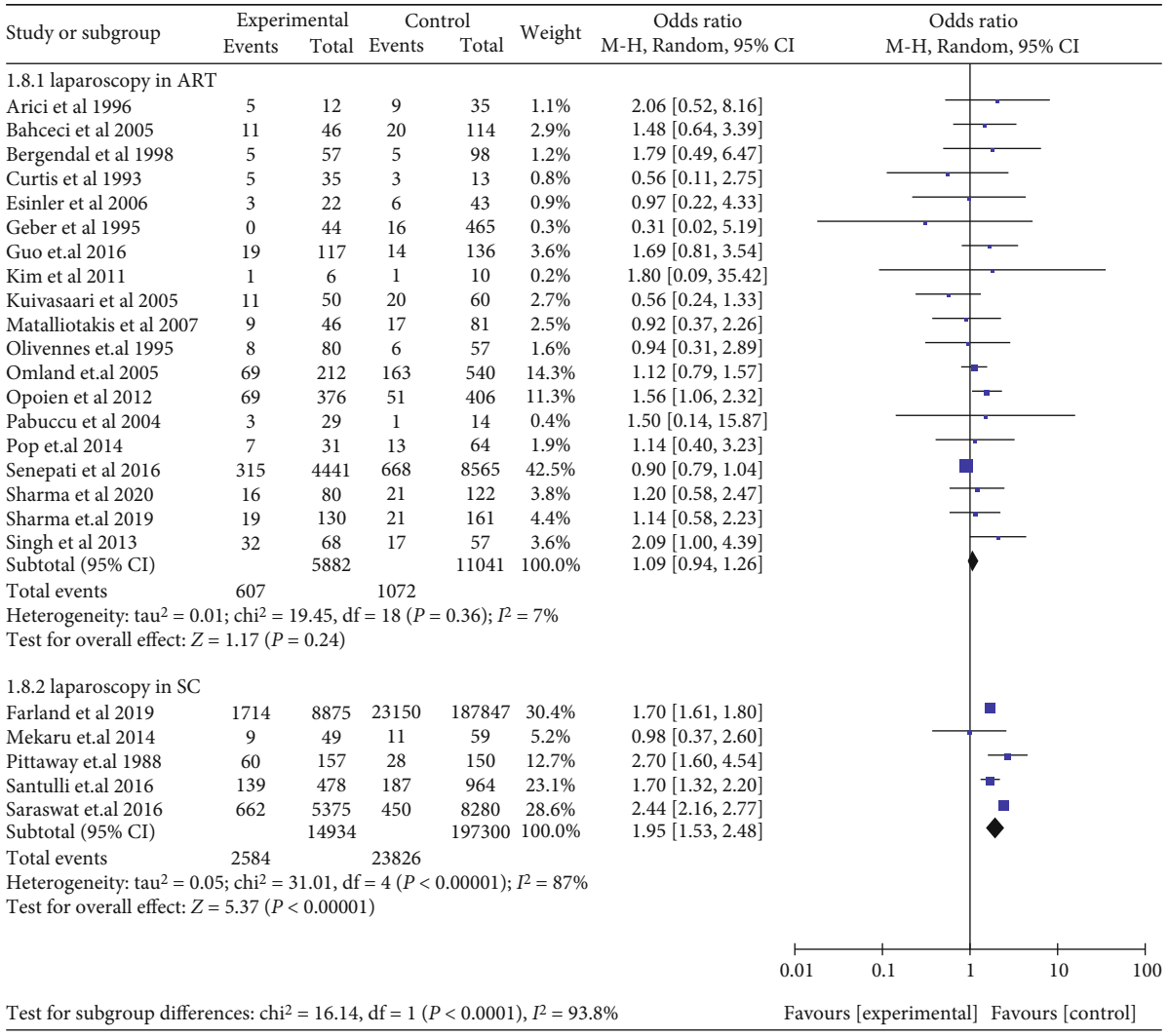


Figure 8: Miscarriage risk in women with EMS diagnosed by laparoscopy.

*3.2. Characteristics of Eligible Studies.* The principal characteristics of the qualified publications are summarized in Table 1. According to the cautious assessment using the NOS, the majority of the studies had scores of 7 or greater (31/38), indicating a low risk of bias. Seven publications had a medium risk of bias, with scores of 6 (Table 2). According to the systematic risk evaluation of methodological bias, the descriptions about allocation concealment and blinding methods were not provided in this RCT (Table 3).

*3.3. Clinical Outcomes.* The risk of miscarriage increased in women with EMS, when compared with those without EMS in SC (OR: 1.81, 95% CI: 1.44-2.28, $I^2 = 96\%$). Among women who underwent ART, women with EMS had a similar miscarriage risk when compared to women with tubal infertility (OR: 1.03, 95% CI: 0.92-1.14, $I^2 = 0\%$) (Figure 2). Compared to women without AD, women who had a prior diagnosis of AD had a higher miscarriage risk in ART (OR: 2.81, 95% CI: 1.44-5.47, $I^2 = 64\%$) (Figure 3). The data of women with AD, who conceived spontaneously, was lacking. In the sensitivity analysis, the results of women with EMS who conceive spontaneously concurred with the pooled results after eliminating anyone study. At the same time, the sensitivity analysis of AD did not alter the conclusion (OR: 2.41, 95% CI: 1.29-4.50, $I^2 = 58\%$) (Figure 4).

The subgroup analyses in women with EMS for retrospective cohort studies (OR: 1.78, 95% CI: 1.19-2.66, $I^2 = 96\%$) and prospective cohort studies (OR: 1.76, 95% CI: 1.45-2.14, $I^2 = 20\%$) were consistent with the overall analysis, observing an increased miscarriage risk in SC (Figure 5). Miscarriage risk was similar between women with EMS and tubal infertility who underwent ART in retrospective cohort studies (OR: 1.01, 95% CI: 0.90-1.14, $I^2 = 17\%$), prospective cohort studies (OR: 1.20, 95% CI: 0.67-2.15, $I^2 = 0\%$), and a RCT (OR: 1.50, 5% CI: 0.14-15.87, 1 study) (Figure 6). Women with AD had higher odds of miscarriage in retrospective cohort studies (OR: 2.14, 95% CI: 1.43-3.21, $I^2 = 28\%$) (Figure 7). In the subgroup analysis, the findings of women with EMS diagnosed by laparoscopy remained in line with the overall results, implying an augmented miscarriage risk in women with or without EMS in SC (OR: 1.95, 95% CI: 1.53-2.48, $I^2 = 87\%$) and a similar miscarriage risk

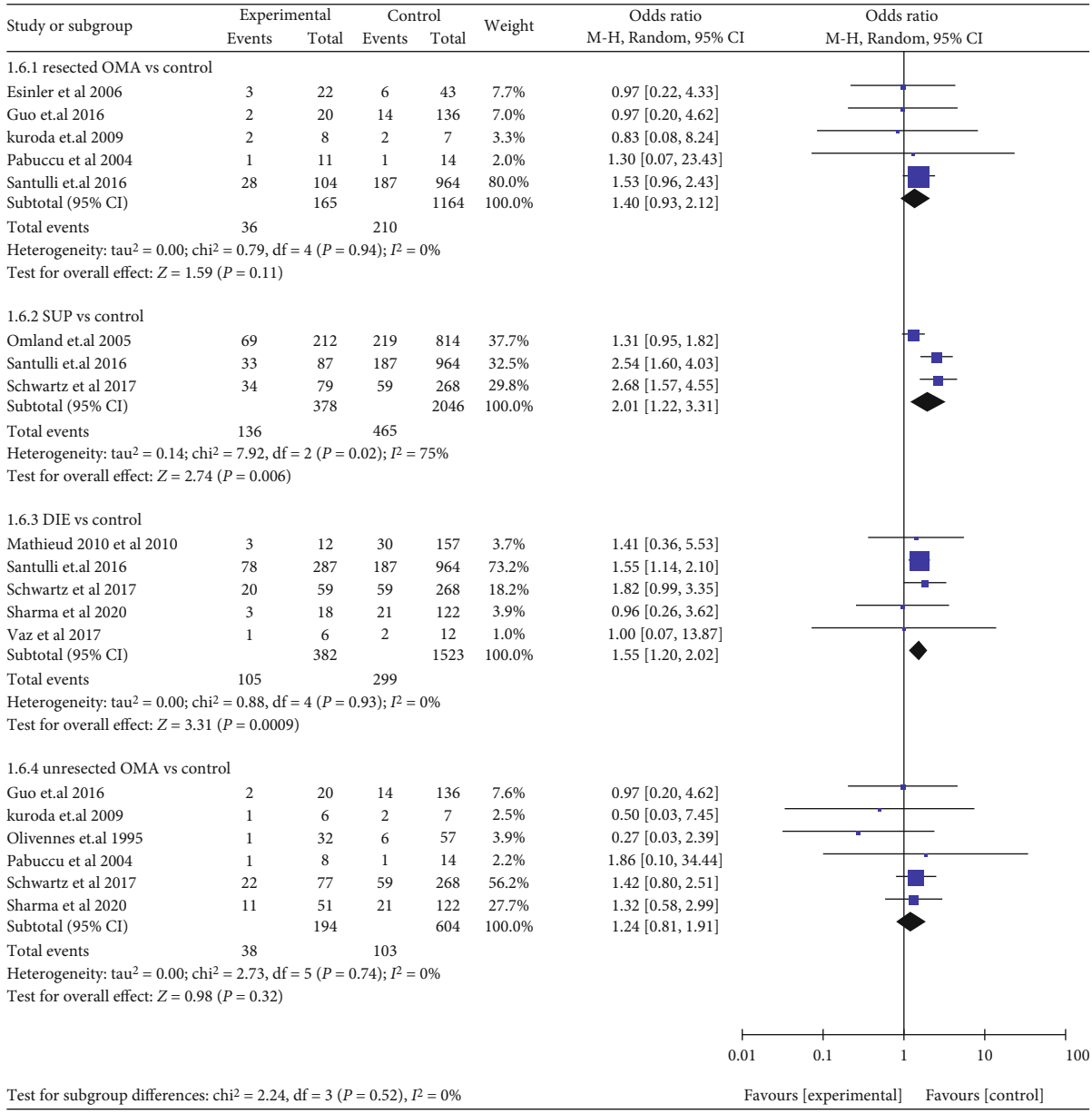


Figure 9: Miscarriage risk in women with resected OMA, unresected OMA, DIE, and SUP.

between women with EMS and tubal infertility during ART (OR: 1.09, 95% CI: 0.94-1.26, $I^2 = 7\%$) (Figure 8).

Compared with women without EMS, women with DIE (OR: 1.55, 95% CI: 1.20-2.02, $I^2 = 0\%$) and women with SUP (OR: 2.01, 95% CI: 1.22-3.31, $I^2 = 75\%$) had a higher miscarriage risk, while resected OMA (OR: 1.40, 95% CI: 0.93-2.12, $I^2 = 0\%$) and unresected OMA (OR: 1.24, 95% CI: 0.81-1.91, $I^2 = 0\%$) both had a similar miscarriage risk (Figure 9). Compared with those with tubal infertility, who underwent ART, women with EMS I/II (OR: 1.27, 95% CI: 0.99-1.62, $I^2 = 0\%$) and women with EMS III/IV (OR: 1.28, 95% CI: 0.95-1.74, $I^2 = 0\%$) had a similar miscarriage risk, respectively. Compared with those without EMS, who conceived spontaneously, women with EMS I/II (OR: 1.68, 95% CI: 1.20-2.35, 1 study) and women with EMS III/IV (OR: 1.72, 95% CI: 1.26-2.34, 1 study) had a higher miscarriage risk, respectively. There was no significant difference observed in miscarriage risk when EMS I/II was compared with EMS III/IV (OR: 1.13, 95% CI: 0.87-1.47, $I^2 = 0\%$) (Figure 10). Compared to those without EMS, women with EMS had a higher risk in early abortion (at <12 weeks) (OR: 1.69, 95% CI: 1.16-2.47, $I^2 = 67\%$), while late abortion risk (at ≥12 weeks) (OR: 2.00, 95% CI: 0.76-5.25, $I^2 = 0\%$) was similar in women with or without EMS. In addition, early abortion risk was higher than late abortion risk in women with EMS (OR: 15.87, 95% CI: 8.12-31.03, $I^2 = 0\%$) (Figure 11). A subgroup analysis for early abortion and late abortion in AD was not feasible, because there were insufficient data stratified by week of miscarriage.

Since there were less than 10 studies presenting the association between AD and miscarriage, the funnel plot was not conducted for publication bias. Furthermore, the funnel plot

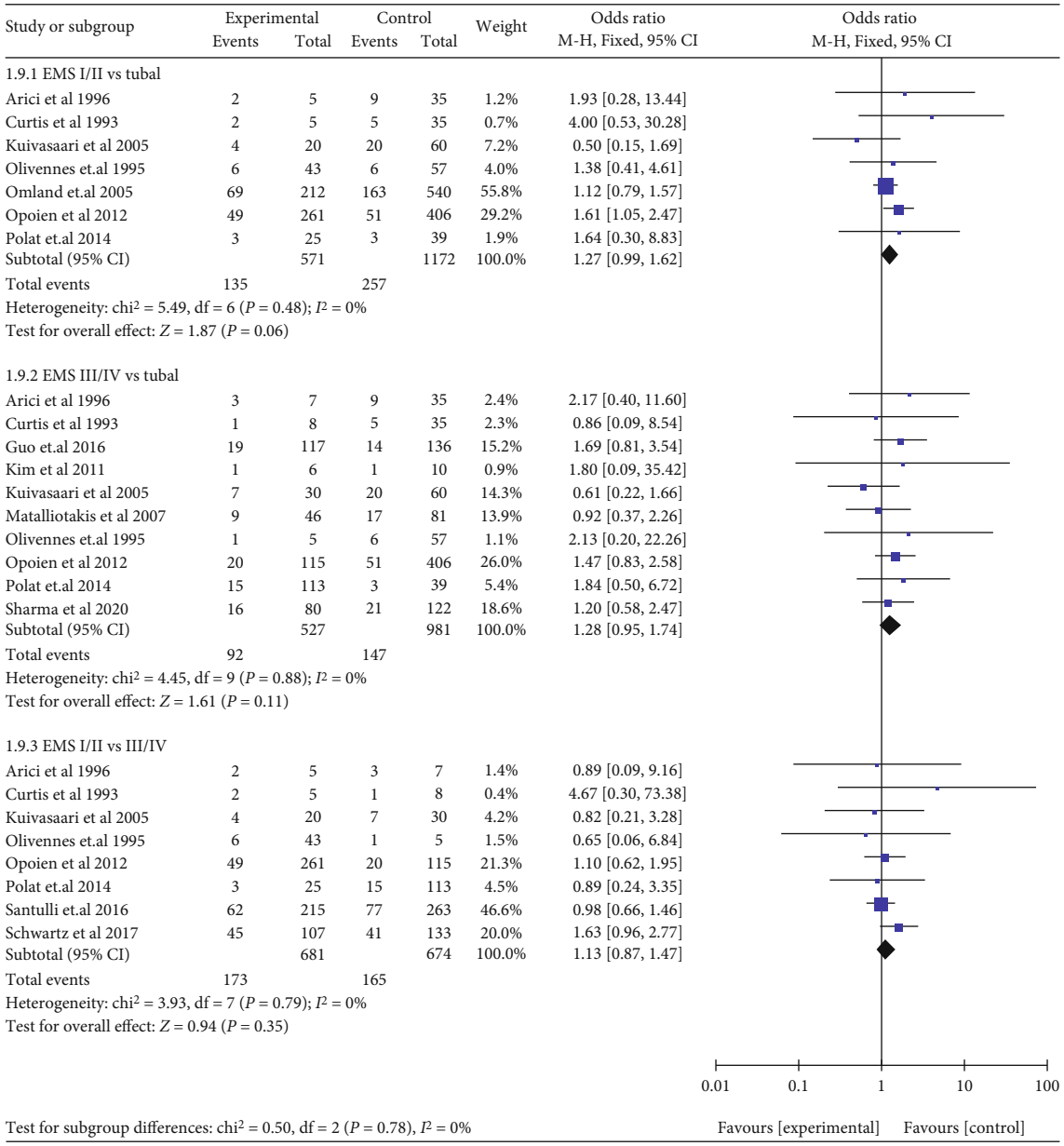


Figure 10: Miscarriage risk in EMS I/II and EMS III/IV.

was made to describe the miscarriage risk in women with EMS (Figure 12), which was generally in symmetry, with the Begg's test ($P = 0.301$) and Egger's test ($P = 0.942$) implying no publication bias.

Women with EMS were not found to be associated with low birthweight (OR: 1.32, 95% CI: 0.98-1.77, $I^2 = 78\%$), placental abruption (OR: 1.90, 95% CI: 0.26-13.76, $I^2 = 51\%$), IUGR (OR: 1.54, 95% CI: 0.71-3.31, $I^2 = 26\%$), and preeclampsia (OR: 1.91, 95% CI: 0.98-3.73, $I^2 = 0\%$) (Figure 13). Compared to those without EMS, women with EMS had higher odds of APH (OR: 1.49, 95% CI: 1.26-1.76, $I^2 = 0\%$), PPH (OR: 1.76, 95% CI: 1.59-1.95, $I^2 = 0\%$), and preterm birth (OR: 1.54, 95% CI: 1.26-1.87, $I^2 = 55\%$) (Figure 14). Women with EMS were more likely to have placenta praevia (OR: 2.09, 95% CI: 1.48-2.96, $I^2 = 0\%$) and stillbirth (OR: 1.41, 95% CI: 1.19-1.68, $I^2 = 0\%$) compared to women without EMS, while no difference was observed in gestational diabetes (OR: 1.24, 95% CI: 0.71-2.14, $I^2 = 32\%$) and ectopic pregnancy (OR: 0.77, 95% CI: 0.38-1.58, $I^2 = 97\%$) (Figure 15).

## 4. Discussion

The present study revealed that EMS is correlated to increased miscarriage risk in pregnant women with SC, while women with EMS had a similar miscarriage risk when compared to those with tubal infertility, who underwent ART. At the same time, an increased miscarriage risk was observed in women with EMS during ART/SC, when compared to those without EMS [50]. No difference was observed in women with or without EMS, who underwent IVF/ICSI [6]. As it is known, EMS was defined as the endometrium outside the uterus, which has major effects

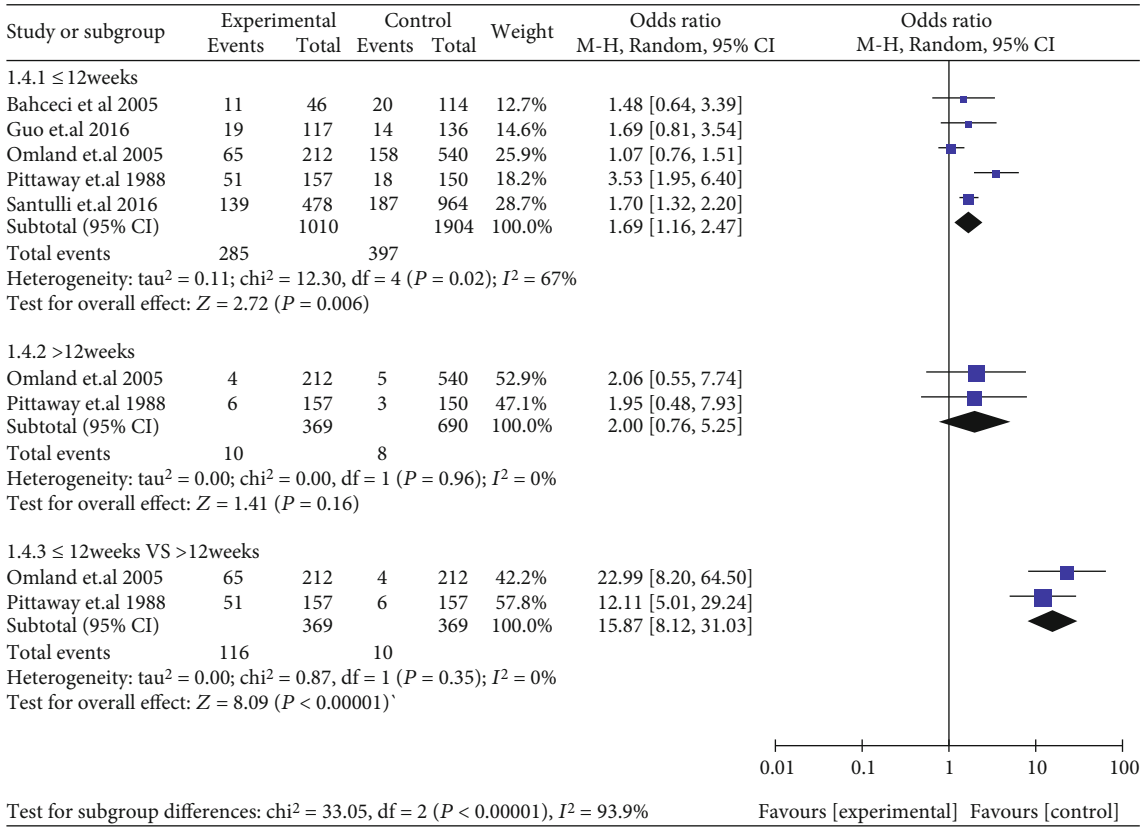


Figure 11: Early abortion and late abortion in women with EMS.

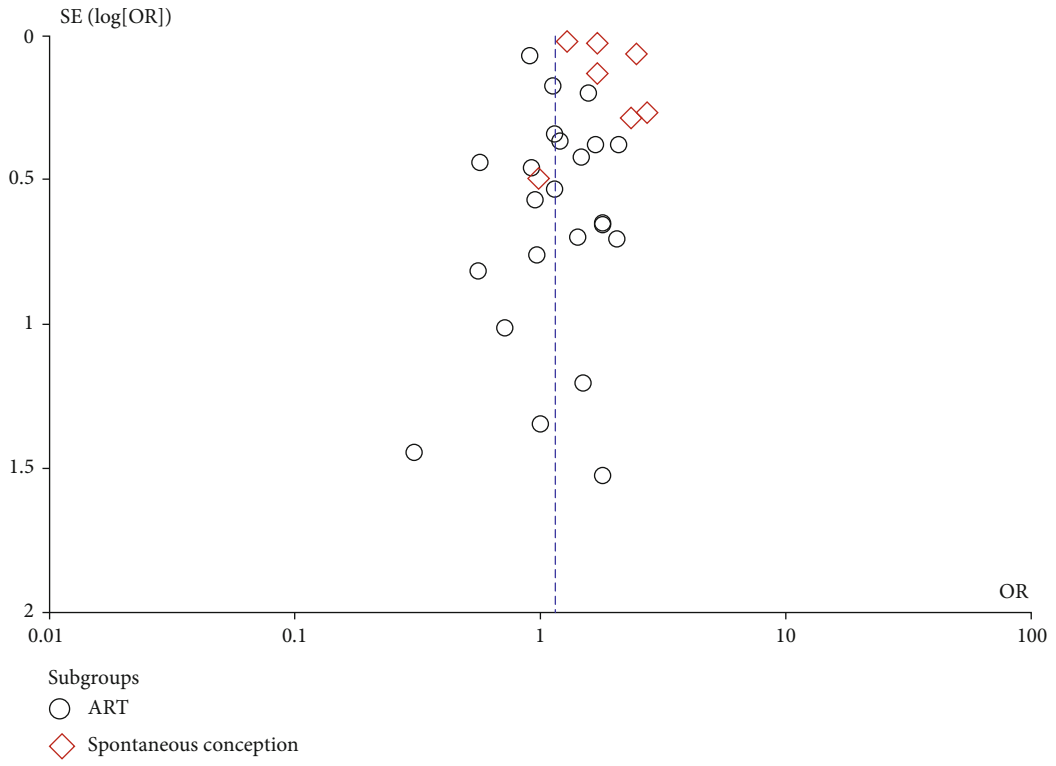


Figure 12: Funnel plot of miscarriage risk in women with EMS.

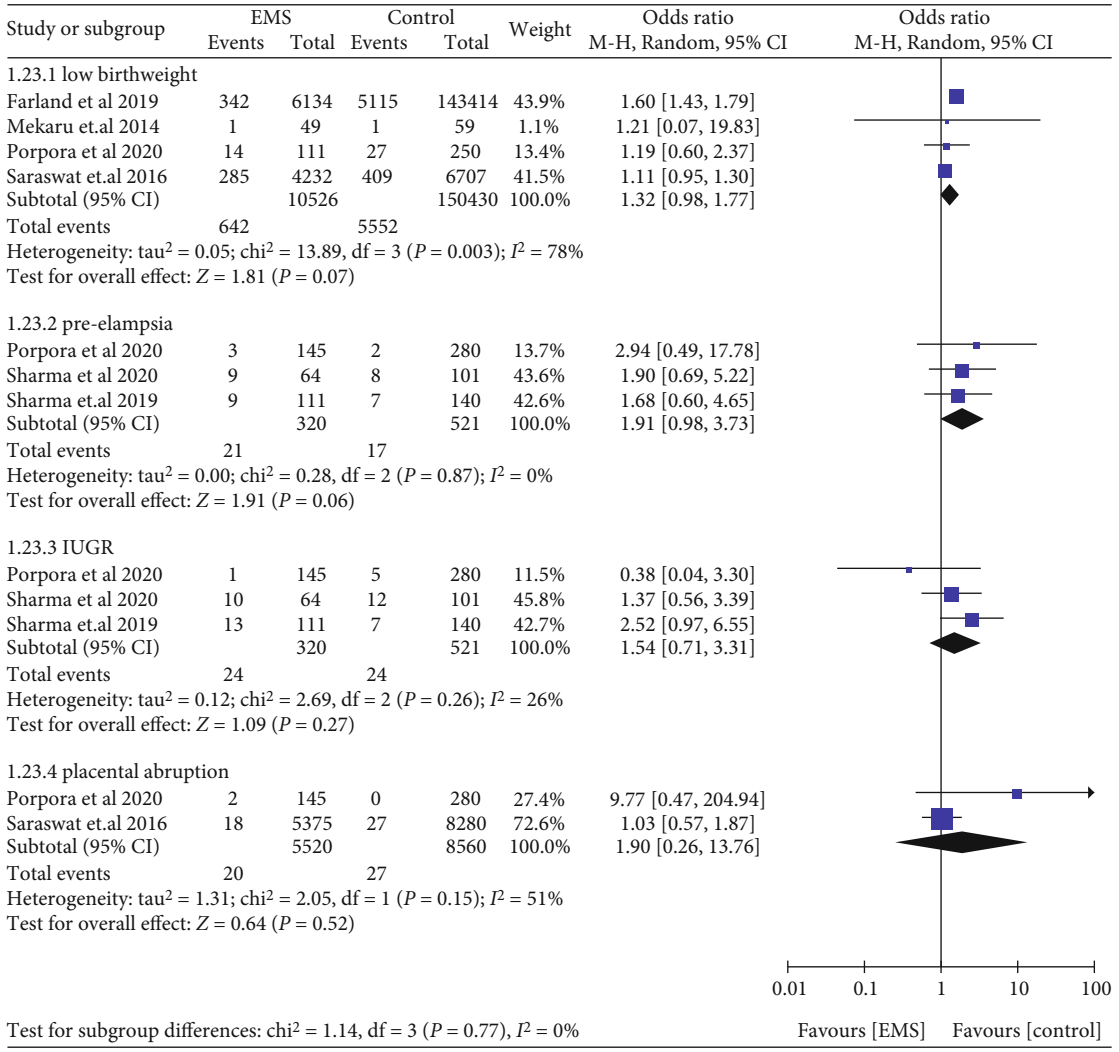


Figure 13: Low birthweight, preeclampsia, IUGR, and placental abruption in women with EMS.

on the pelvic environment. The potential explanation might be that EMS generates major effects on the process of fertilization. Therefore, EMS has less impact on women using ART, whose site of fertilization is not in the pelvis. Among women who underwent ART, AD was found to be associated with miscarriage, which is consistent with some literatures [5, 51]. Adenomyosis is identified by ingrowth of the endometrial tissue into the myometrium, which may have a major impact on intrauterine embryos in women using ART.

The sensitivity analyses of miscarriage risk in EMS or AD were both consistent with the whole conclusion, which proves the stability and reliability of the pooled results. In the subgroup analysis, AD was found to be associated with miscarriage in the retrospective cohort study. The findings in the retrospective cohort study, prospective cohort study, and RCT for women with EMS concurred with the overall results, implying the augmented miscarriage risk in women with SC and a similar miscarriage risk in women who underwent ART. Similarly, among women whose EMS was diagnosed by laparoscopy, it was found that there was a similar miscarriage risk in women during ART and an increased miscarriage risk in women who conceived spontaneously.

As it is known, the major indications of ART were various factors of infertility. The risk of spontaneous abortion might be affected by different factors of infertility and not ascribed to EMS or AD alone. In the present included studies, some publications included purely endometriosis-associated infertility or purely adenomyosis-associated infertility in the study group. Among the other studies, adjustments were made for patients with other factors of infertility between the two groups. Therefore, the robustness of the present finding was proven, indicating that women who suffer from EMS in SC or AD during ART should be included among those who may need closer prenatal monitoring and follow-up to prevent miscarriage.

The present study demonstrated that compared with women with tubal infertility during ART, women with EMS I/II or EMS III/IV had a similar miscarriage risk, respectively. However, one included study revealed that women with EMS I/II or EMS III/IV had a higher miscarriage risk in SC, when compared with those without EMS, separately. It was reported that there was no obvious difference observed in miscarriage risk when 238 women with EMS III/IV were compared with 439 women with stage I/II EMS during

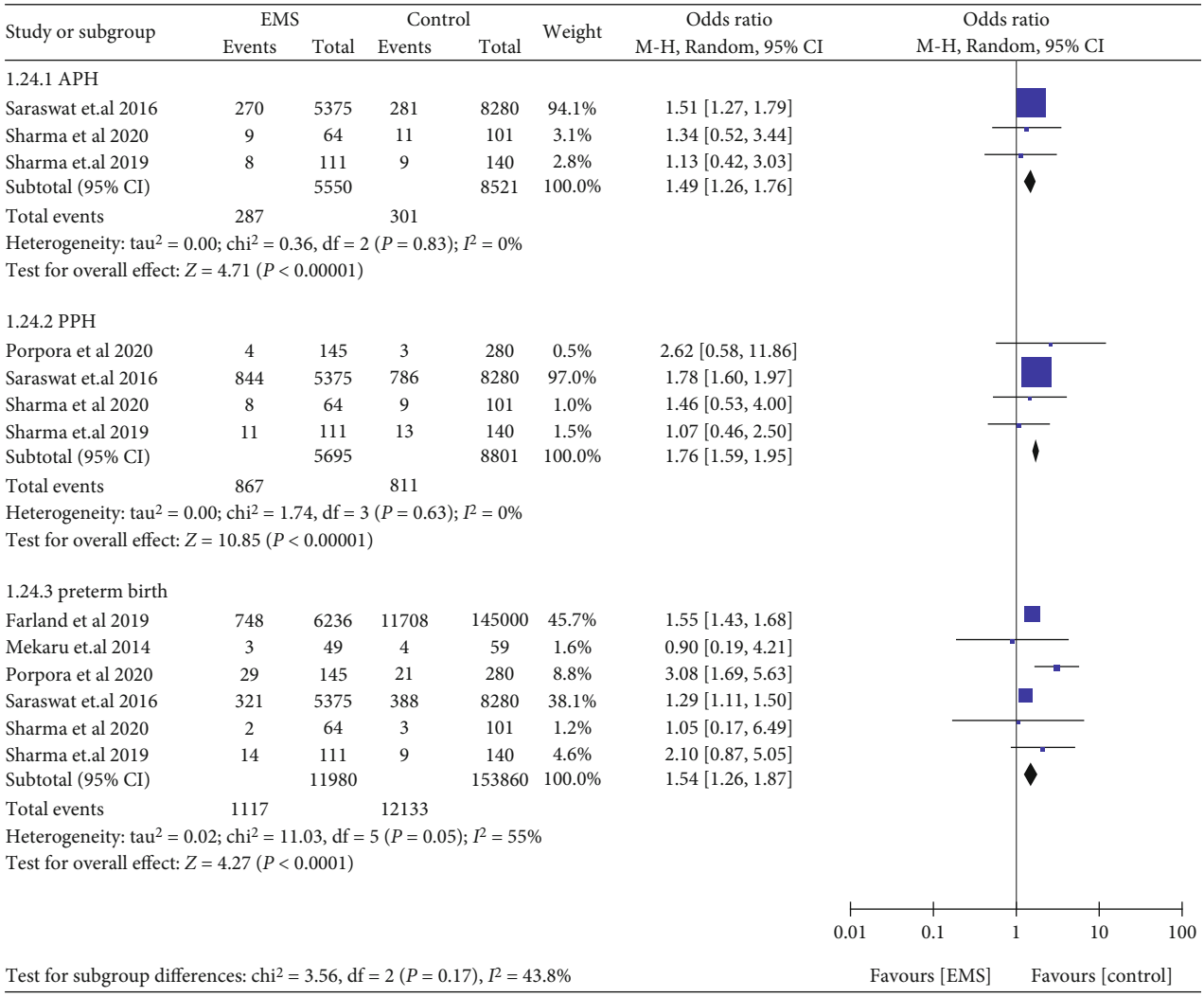


Figure 14: APH, PPH, and preterm birth in women with EMS.

ART [52]. At the same time, a similar miscarriage risk was observed between 674 women with stage III/IV EMS and 681 women with EMS I/II. In addition, the early and late stages of EMS were observed to share similar epidemiological characteristics, suggesting an epidemiological (and pathogenetic) continuum between different stages of EMS [53]. The present results imply that with the increase in staging of EMS, miscarriage risk appeared not to show significant differences. In the present included papers, unresected and resected OMA were both not found to be associated with miscarriage. At the same time, the surgical and expectant management of OMA in infertile women prior to ART did not show significant differences in miscarriage risk, suggesting that OMA might not be the main causative factor of spontaneous abortion [54]. Therefore, there might be a lack of sufficient evidence to remove OMA before pregnancy. It is recommended to adopt a conservative treatment plan in the long-term management of OMA. Furthermore, it was revealed that DIE was associated with miscarriage and that women with SUP had a higher miscarriage risk. However, the surgical excision of the DIE did not significantly decrease the incidence of miscarriage [55, 56]. In addition, in the following laparoscopic surgery for SUP, the diminished ovarian reserve resulted in the adverse prognosis for pregnancy [57]. Considering the lack of number of studies and sample size, the observation should be cautiously interpreted. Larger high-quality studies are expected to verify these present results in the future.

A systematic review considered that in the second half of pregnancy, the EMS appeared not to have negative effects on pregnancy outcomes [58]. In the present study, compared with those without EMS, women with EMS had a higher early abortion risk, while late abortion risk was similar in women with or without EMS. In addition, women with EMS had a higher early abortion risk (at <12weeks) than late abortion risk (at ≥12 weeks). It was revealed that women with EMS appeared to be associated with first-trimester spontaneous abortion [59]. The limited data available for analysis should be highlighted. Future studies are required to determine whether women with EMS are more likely to have early pregnancy loss.

The pathophysiology of EMS and AD remains poorly understood. However, growing studies have suggested that oxidative stress, inflammation factors/cytokines, angiogenesis,

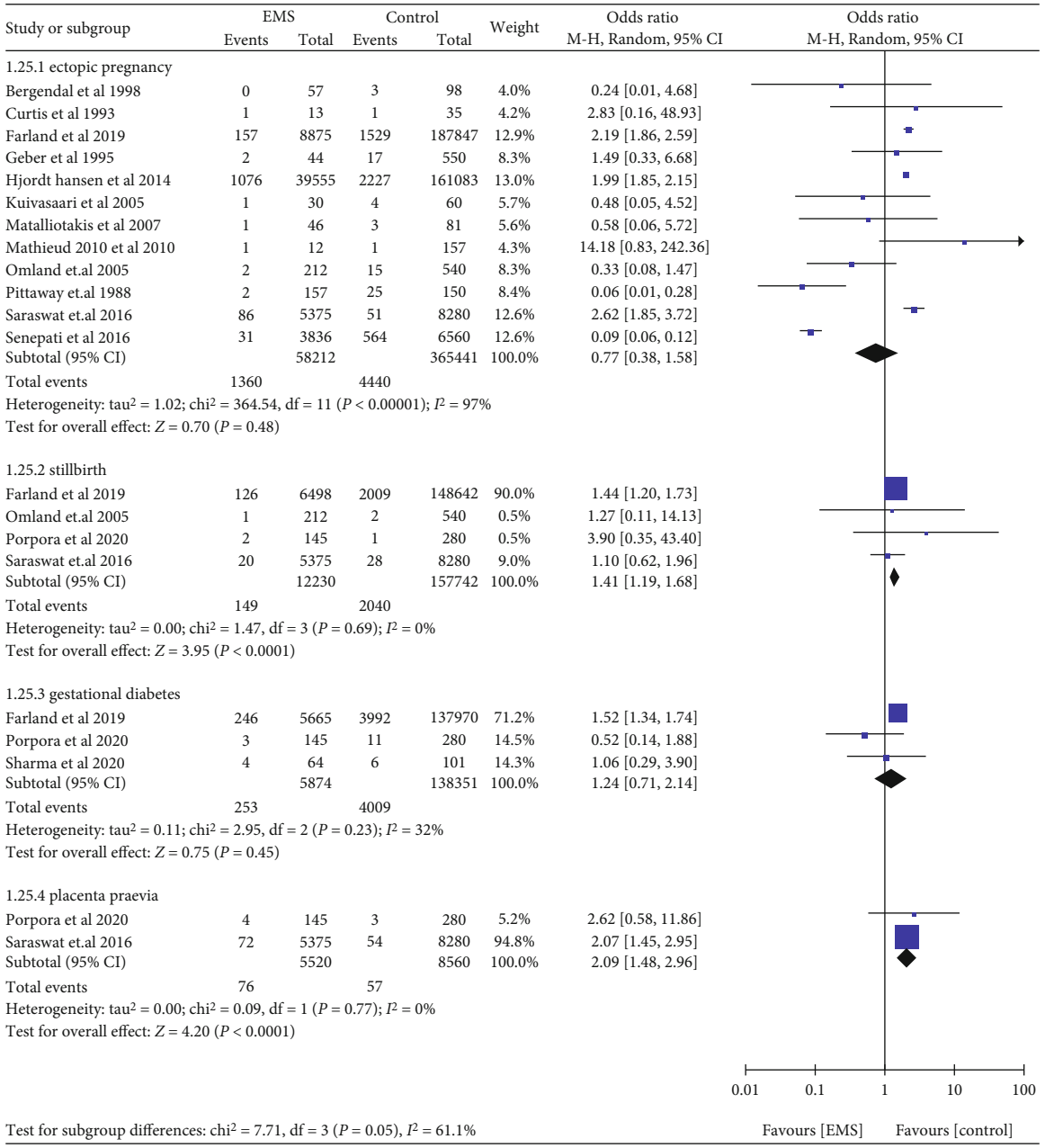


Figure 15: Ectopic pregnancy, stillbirth, gestational diabetes, and placenta praevia in women with EMS.

and hormonal interactions play major roles in EMS [60–63]. Meanwhile, sex hormone receptors, junctional zone disruption, and inflammatory factors are considered the causal factors for AD [64, 65]. It has been reported that an increased expression level of nitric oxide species (eNOS) and reactive oxygen species (ROS) in oxidative stress can influence the oocyte and embryo quality, which leads to declined embryo implantation rate in EMS patients [61]. It was reported that attenuated progesterone action might be the basis for the implantation failure in EMS [66]. Vascularization was considered a major pathogenesis in EMS. Proper endometrial vascular development was considered crucial for successful embryo implantation. However, abnormal angiogenesis and uterine natural killer cell (uNK cell) number/function might result in reproductive failure [64]. Disturbances in vascular development might be a causal factor in spontaneous abortion. In addition, it was reported that an increased number of CD56+ uNK cells were detected in the peri-implantation endometrium from women with recurrent miscarriage [67]. It was interesting that the EMS and AD frequently coexisted [68, 69]. The presence of oxidative stress and anomalies in free-radical metabolism might alter the uterine receptivity in EMS and AD. The abnormal endometrial milieu and endometrial dysfunction in EMS and AD contributed to the adverse pregnancy outcome through hormonal, metabolic, and inflammatory mechanisms [70]. Among these theories, inflammatory mechanisms were considered more relevant in EMS and AD. Overall, further researches are required to

confirm the biochemical links between EMS and AD and miscarriage to develop preventive measures.

The present study had several strengths. A large amount of studies had allowed for the subgroup analyses to prove the robustness of the results, and subgroup analyses were carried out to evaluate the miscarriage risk by week of pregnancy loss, which has not yet been reported in prior literatures [71]. In addition to reporting the miscarriage risk in women with EMS, the investigators also reported some important reproductive outcomes that were not presented in previous reviews [50], such as ectopic pregnancy. The limitations of the present study were affected by the quality of each of the included studies and the heterogeneity of the overall eligible publications. Since the diagnostic methods were not restricted, the diagnoses of EMS or AD were not uniform between studies. The included studies differed in the selection of control groups with the use of fertility women and subfertility women as the controls. One potential limitation was that unpublished studies were not searched, which might limit the comprehensiveness of retrieved literatures. In addition, since the articles that reported positive results were more likely to be published, the present study had a potential risk of reporting bias.

## 5. Conclusions

Women with EMS have an augmented miscarriage risk, when compared to those without EMS in SC, and women with EMS have a similar miscarriage risk, when compared to those with tubal infertility during ART. Meanwhile, it is found that women with EMS have higher odds of early abortion (<12 weeks). Miscarriage risk increases in women with AD using ART. With the increase in staging of EMS, miscarriage risk appears not to show significant differences. Women with SUP and DIE have an increased miscarriage risk, respectively, while unresected and resected OMA are both not observed to be associated with miscarriage. These present findings suggest that pregnant women with EMS in SC or AD during ART may require closer prenatal monitoring and follow-ups to prevent miscarriage, especially in the first trimester (<12 weeks). Furthermore, a consensus on its accurate recording is required in future studies, including the types and stages of EMS and week of miscarriage.

## Data Availability

The data used to support the findings of this study are included within the article.

## Conflicts of Interest

All authors declare no conflict of interest.

## Acknowledgments

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## References

[1] P. Parasar, P. Ozcan, and K. L. Terry, "Endometriosis: epidemiology, diagnosis and clinical management," *Current Obstetrics and Gynecology Reports*, vol. 6, no. 1, pp. 34–41, 2017.

[2] M. L. Macer and H. S. Taylor, "Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility," *Obstetrics and Gynecology Clinics of North America*, vol. 39, no. 4, pp. 535–549, 2012.

[3] G. Benagiano, I. Brosens, and M. Habiba, "Structural and molecular features of the endomyometrium in endometriosis and adenomyosis," *Human Reproduction Update*, vol. 20, no. 3, pp. 386–402, 2014.

[4] J. Naftalin, W. Hoo, K. Pateman, D. Mavrelos, T. Holland, and D. Jurkovic, "How common is adenomyosis? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic," *Human Reproduction (Oxford, England)*, vol. 27, no. 12, pp. 3432–3439, 2012.

[5] J. Horton, M. Sterrenburg, S. Lane, A. Maheshwari, T. C. Li, and Y. Cheong, "Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis," *Human Reproduction Update*, vol. 25, no. 5, pp. 592–632, 2019.

[6] M. Hamdan, S. Z. Omar, G. Dunselman, and Y. Cheong, "Influence of endometriosis on assisted reproductive technology outcomes: a systematic review and meta-analysis," *Obstetrics and Gynecology*, vol. 125, no. 1, pp. 79–88, 2015.

[7] Higgins JPT GSe, *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Updated March 2011]*, The Cochrane Collaboration, 2011, http://handbook.cochrane.org.

[8] R. DerSimonian and N. Laird, "Meta-analysis in clinical trials," *Controlled Clinical Trials*, vol. 7, no. 3, pp. 177–188, 1986.

[9] M. Egger, G. D. Smith, M. Schneider, and C. Minder, "Bias in meta-analysis detected by a simple, graphical test," *BMJ*, vol. 315, no. 7109, pp. 629–634, 1997.

[10] D. Moher, A. Liberati, J. Tetzlaff, and D. G. Altman, "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," *International Journal of Surgery*, vol. 8, no. 5, pp. 336–341, 2010.

[11] D. E. Pittaway, C. Vernon, and J. A. Fayez, "Spontaneous abortions in women with endometriosis," *Fertility and Sterility*, vol. 50, no. 5, pp. 711–715, 1988.

[12] P. Curtis, A. Jackson, A. Bernard, and R. W. Shaw, "Pretreatment with gonadotrophin releasing hormone (GnRH) analogue prior to in vitro fertilisation for patients with endometriosis," *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, vol. 52, no. 3, pp. 211–216, 1993.

[13] S. Geber, T. Paraschos, G. Atkinson, R. Margara, and R. M. L. Winston, "Results of IVF in patients with endometriosis: the severity of the disease does not affect outcome, or the incidence

of miscarriage," *Human Reproduction (Oxford, England)*, vol. 10, no. 6, pp. 1507–1511, 1995.

[14] F. Olivennes, D. Feldberg, H. C. Liu, J. Cohen, F. Moy, and Z. Rosenwaks, "Endometriosis: a stage by stage analysis–the role of in vitro fertilization," *Fertility and Sterility*, vol. 64, no. 2, pp. 392–398, 1995.

[15] A. Arici, E. Oral, O. Bukulmez, A. Duleba, D. L. Olive, and E. E. Jones, "The effect of endometriosis on implantation: results from the Yale University in vitro fertilization and embryo transfer program," *Fertility and Sterility*, vol. 65, no. 3, pp. 603–607, 1996.

[16] R. Pabuccu, G. Onalan, U. Goktolga, T. Kucuk, E. Orhon, and T. Ceyhan, "Aspiration of ovarian endometriomas before intracytoplasmic sperm injection," *Fertility and Sterility*, vol. 82, no. 3, pp. 705–711, 2004.

[17] M. Bahceci and U. Ulug, "Does underlying infertility aetiology impact on first trimester miscarriage rate following ICSI? A preliminary report from 1244 singleton gestations," *Human Reproduction (Oxford, England)*, vol. 20, no. 3, pp. 717–721, 2005.

[18] P. Kuivasaari, M. Hippeläinen, M. Anttila, and S. Heinonen, "Effect of endometriosis on IVF/ICSI outcome: stage III/IV endometriosis worsens cumulative pregnancy and live-born rates," *Human Reproduction (Oxford, England)*, vol. 20, no. 11, pp. 3130–3135, 2005.

[19] A. K. Omland, T. Åbyholm, P. Fedorcsák et al., "Pregnancy outcome after IVF and ICSI in unexplained, endometriosis-associated and tubal factor infertility," *Human Reproduction (Oxford, England)*, vol. 20, no. 3, pp. 722–727, 2005.

[20] I. Esinler, G. Bozdag, F. Aybar, U. Bayar, and H. Yarali, "Outcome of in vitro fertilization/intracytoplasmic sperm injection after laparoscopic cystectomy for endometriomas," *Fertility and Sterility*, vol. 85, no. 6, pp. 1730–1735, 2006.

[21] I. M. Matalliotakis, H. Cakmak, N. Mahutte, Y. Fragouli, A. Arici, and D. Sakkas, "Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility," *Fertility and Sterility*, vol. 88, no. 6, pp. 1568–1572, 2007.

[22] K. Kuroda, M. Kitade, I. Kikuchi et al., "The impact of endometriosis, endometrioma and ovarian cystectomy on assisted reproductive technology," *Reproductive Medicine and Biology*, vol. 8, no. 3, pp. 113–118, 2009.

[23] E. Mathieu d'Argent, C. Coutant, M. Ballester et al., "Results of first in vitro fertilization cycle in women with colorectal endometriosis compared with those with tubal or male factor infertility," *Fertility and Sterility*, vol. 94, no. 6, pp. 2441–2443, 2010.

[24] M. F. Costello, K. Lindsay, and G. McNally, "The effect of adenomyosis on in vitro fertilisation and intra-cytoplasmic sperm injection treatment outcome," *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, vol. 158, no. 2, pp. 229–234, 2011.

[25] C. H. Kim, J. W. Ahn, S. H. Kim, H. D. Chae, and B. M. Kang, "Effects on in vitro fertilization-embryo transfer outcomes of vascular endothelial growth factor receptor-1, -2 and -3 in eutopic endometrial tissue of women with endometriosis," *The Journal of Obstetrics and Gynaecology Research*, vol. 37, no. 11, pp. 1631–1637, 2011.

[26] J. A. Martínez-Conejero, M. Morgan, M. Montesinos et al., "Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation," *Fertility and Sterility*, vol. 96, no. 4, pp. 943–950.e1, 2011.

[27] H. K. Opøien, P. Fedorcsak, A. K. Omland et al., "In vitro fertilization is a successful treatment in endometriosis-associated infertility," *Fertility and Sterility*, vol. 97, no. 4, pp. 912–918, 2012.

[28] R. Salim, S. Riris, W. Saab, B. Abramov, I. Khadum, and P. Serhal, "Adenomyosis reduces pregnancy rates in infertile women undergoing IVF," *Reproductive Biomedicine Online*, vol. 25, no. 3, pp. 273–277, 2012.

[29] L. Benaglia, L. Cardellicchio, M. Leonardi et al., "Asymptomatic adenomyosis and embryo implantation in IVF cycles," *Reproductive Biomedicine Online*, vol. 29, no. 5, pp. 606–611, 2014.

[30] M. V. Hjordt Hansen, T. Dalsgaard, D. Hartwell, C. W. Skovlund, and Ø. Lidegaard, "Reproductive prognosis in endometriosis. A national cohort study," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 93, no. 5, pp. 483–489, 2014.

[31] K. Mekaru, H. Masamoto, H. Sugiyama et al., "Endometriosis and pregnancy outcome: are pregnancies complicated by endometriosis a high-risk group?," *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, vol. 172, pp. 36–39, 2014.

[32] M. Polat, F. K. Boynukalın, İ. Yaralı, İ. Esinler, and H. Yaralı, "Endometriosis is not associated with inferior pregnancy rates in in vitro fertilization: an analysis of 616 patients," *Gynecologic and Obstetric Investigation*, vol. 78, no. 1, pp. 59–64, 2014.

[33] S. Pop-Trajkovic, V. Kopitovic, J. Popovic, V. Antic, D. Radovic, and R. Zivadinovic, "In vitro fertilization outcome in women with endometriosis & previous ovarian surgery," *The Indian Journal of Medical Research*, vol. 140, no. 3, pp. 387–391, 2014.

[34] L. Yan, L. Ding, R. Tang, and Z. J. Chen, "Effect of adenomyosis on in vitro fertilization/intracytoplasmic sperm injection outcomes in infertile women: a retrospective cohort study," *Gynecologic and Obstetric Investigation*, vol. 77, no. 1, pp. 14–18, 2014.

[35] H. Guo, Y. Wang, Q. Chen, W. Chai, Q. Lv, and Y. Kuang, "Effect of natural cycle endometrial preparation for frozen-thawed embryo transfer in patients with advanced endometriosis," *Medical Science Monitor*, vol. 22, pp. 4596–4603, 2016.

[36] P. Santulli, L. Marcellin, S. Menard et al., "Increased rate of spontaneous miscarriages in endometriosis-affected women," *Human Reproduction (Oxford, England)*, vol. 31, no. 5, pp. 1014–1023, 2016.

[37] S. Senapati, M. D. Sammel, C. Morse, and K. T. Barnhart, "Impact of endometriosis on in vitro fertilization outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database," *Fertility and Sterility*, vol. 106, no. 1, pp. 164–71.e1, 2016.

[38] A. K. Singh, R. Chattopadhyay, B. Chakravarty, and K. Chaudhury, "Altered circulating levels of matrix metalloproteinases 2 and 9 and their inhibitors and effect of progesterone supplementation in women with endometriosis undergoing in vitro fertilization," *Fertility and Sterility*, vol. 100, no. 1, pp. 127–34.e1, 2013.

[39] G. Queiroz Vaz, A. V. Evangelista, M. C. Almeida Cardoso, P. Gallo, M. C. Erthal, and M. A. Pinho Oliveira, "Frozen embryo transfer cycles in women with deep endometriosis," *Gynecological Endocrinology*, vol. 33, no. 7, pp. 540–543, 2017.

[40] L. Saraswat, D. T. Ayansina, K. G. Cooper et al., "Pregnancy outcomes in women with endometriosis: a national record linkage study," *BJOG: An International Journal of Obstetrics & Gynaecology*, vol. 124, no. 3, pp. 444–452, 2016.

[41] A. Hashimoto, T. Iriyama, S. Sayama et al., "Adenomyosis and adverse perinatal outcomes: increased risk of second trimester miscarriage, preeclampsia, and placental malposition," *The Journal of Maternal-Fetal & Neonatal Medicine*, vol. 31, no. 3, pp. 364–369, 2018.

[42] L. V. Farland, J. Prescott, N. Sasamoto et al., "Endometriosis and risk of adverse pregnancy outcomes," *Obstetrics and Gynecology*, vol. 134, no. 3, pp. 527–536, 2019.

[43] S. Sharma, S. Bathwal, N. Agarwal, R. Chattopadhyay, I. Saha, and B. Chakravarty, "Does presence of adenomyosis affect reproductive outcome in IVF cycles? A retrospective analysis of 973 patients," *Reproductive Biomedicine Online*, vol. 38, no. 1, pp. 13–21, 2019.

[44] M. G. Porpora, F. Tomao, A. Ticino et al., "Endometriosis and pregnancy: a single institution experience," *International Journal of Environmental Research and Public Health*, vol. 17, no. 2, p. 401, 2020.

[45] S. Sharma, S. RoyChoudhury, S. Bathwal et al., "Pregnancy and live birth rates are comparable in young infertile women presenting with severe endometriosis and tubal infertility," *Reproductive Sciences*, vol. 27, no. 6, pp. 1340–1349, 2020.

[46] A. Bergendal, S. Naffah, C. Nagy, A. Bergqvist, P. Sjöblom, and T. Hillensjö, "Outcome of IVF in patients with endometriosis in comparison with tubal-factor infertility," *Journal of Assisted Reproduction and Genetics*, vol. 15, no. 9, pp. 530–534, 1998.

[47] A. S. Kohl Schwartz, M. M. Wölfler, V. Mitter et al., "Endometriosis, especially mild disease: a risk factor for miscarriages," *Fertility and Sterility*, vol. 108, no. 5, pp. 806–814.e2, 2017.

[48] H. S. Youm, Y. S. Choi, and H. D. Han, "In vitro fertilization and embryo transfer outcomes in relation to myometrial thickness," *Journal of Assisted Reproduction and Genetics*, vol. 28, no. 11, pp. 1135–1140, 2011.

[49] V. Thalluri and K. P. Tremellen, "Ultrasound diagnosed adenomyosis has a negative impact on successful implantation following GnRH antagonist IVF treatment," *Human Reproduction (Oxford, England)*, vol. 27, no. 12, pp. 3487–3492, 2012.

[50] F. Zullo, E. Spagnolo, G. Saccone et al., "Endometriosis and obstetrics complications: a systematic review and meta-analysis," *Fertility and Sterility*, vol. 108, no. 4, pp. 667–72.e5, 2017.

[51] G. Younes and T. Tulandi, "Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis," *Fertility and Sterility*, vol. 108, no. 3, pp. 483–90.e3, 2017.

[52] M. A. Barbosa, D. M. Teixeira, P. A. Navarro, R. A. Ferriani, C. O. Nastri, and W. P. Martins, "Impact of endometriosis and its staging on assisted reproduction outcome: systematic review and meta-analysis," *Ultrasound in Obstetrics & Gynecology*, vol. 44, no. 3, pp. 261–278, 2014.

[53] F. Parazzini, M. Ferraroni, L. Fedele, L. Bocciolone, S. Rubessa, and A. Riccardi, "Pelvic endometriosis: reproductive and menstrual risk factors at different stages in Lombardy, northern Italy," *Journal of Epidemiology and Community Health*, vol. 49, no. 1, pp. 61–64, 1995.

[54] C. Q. Wu, A. Albert, S. Alfaraj et al., "Live birth rate after surgical and expectant management of endometriomas after in vitro fertilization: a systematic review, meta-analysis, and critical appraisal of current guidelines and previous meta-analyses," *Journal of Minimally Invasive Gynecology*, vol. 26, no. 2, pp. 299–311.e3, 2019.

[55] U. Leone Roberti Maggiore, C. Scala, E. Tafi et al., "Spontaneous fertility after expectant or surgical management of rectovaginal endometriosis in women with or without ovarian endometrioma: a retrospective analysis," *Fertility and Sterility*, vol. 107, no. 4, pp. 969–976.e5, 2017.

[56] L. Mounsambote, J. Cohen, S. Bendifallah et al., "Deep infiltrative endometriosis without digestive involvement, what is the impact of surgery on in vitro fertilization outcomes? A retrospective study," *Gynécologie Obstétrique Fertilité & Sénologie*, vol. 45, no. 1, pp. 15–21, 2017.

[57] J. Boujenah, I. Cedrin-Durnerin, C. Herbemont, C. Sifer, and C. Poncelet, "Non-ART pregnancy predictive factors in infertile patients with peritoneal superficial endometriosis," *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, vol. 211, pp. 182–187, 2017.

[58] S. Palomba, R. Homburg, S. Santagni, G. B. la Sala, and R. Orvieto, "Risk of adverse pregnancy and perinatal outcomes after high technology infertility treatment: a comprehensive systematic review," *Reproductive Biology and Endocrinology*, vol. 14, no. 1, p. 76, 2016.

[59] M. Groll, "Endometriosis and spontaneous abortion," *Fertility and Sterility*, vol. 41, no. 6, pp. 933–935, 1984.

[60] A. Maheshwari, S. Gurunath, F. Fatima, and S. Bhattacharya, "Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes," *Human Reproduction Update*, vol. 18, no. 4, pp. 374–392, 2012.

[61] S. Asghari, A. Valizadeh, L. Aghebati-Maleki, M. Nouri, and M. Yousefi, "Endometriosis: perspective, lights, and shadows of etiology," *Biomedicine & Pharmacotherapy*, vol. 106, pp. 163–174, 2018.

[62] A. D. Greene, S. A. Lang, J. A. Kendziorski, J. M. Sroga-Rios, T. J. Herzog, and K. A. Burns, "Endometriosis: where are we and where are we going?," *Reproduction*, vol. 152, no. 3, pp. R63–R78, 2016.

[63] C. Tomassetti, C. Meuleman, A. Pexsters et al., "Endometriosis, recurrent miscarriage and implantation failure: is there an immunological link?," *Reproductive Biomedicine Online*, vol. 13, no. 1, pp. 58–64, 2006.

[64] X. Chen, G. C. W. Man, Y. Liu et al., "Physiological and pathological angiogenesis in endometrium at the time of embryo implantation," *American Journal of Reproductive Immunology*, vol. 78, no. 2, article e12693, 2017.

[65] S. Vannuccini and F. Petraglia, "Recent advances in understanding and managing adenomyosis," *F1000Research*, vol. 8, 2019.

[66] S. Campo, V. Campo, and G. Benagiano, "Infertility and adenomyosis," *Obstetrics and Gynecology International*, vol. 2012, Article ID 786132, 8 pages, 2012.

[67] M. W. Laschke and M. D. Menger, "Basic mechanisms of vascularization in endometriosis and their clinical implications," *Human Reproduction Update*, vol. 24, no. 2, pp. 207–224, 2018.

[68] M. Gonzales, L. A. de Matos, M. O. da Costa Gonçalves et al., "Patients with adenomyosis are more likely to have deep endometriosis," *Gynecological Surgery*, vol. 9, no. 3, pp. 259–264, 2012.

[69] W. Naphatthalung and S. Cheewadhanaraks, "Prevalence of endometriosis among patients with adenomyosis and/or myoma uteri scheduled for a hysterectomy," *Journal of the*

*Medical Association of Thailand*, vol. 95, no. 9, pp. 1136–1140, 2012.

[70] S. Vannuccini, V. L. Clifton, I. S. Fraser et al., "Infertility and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy outcome," *Human Reproduction Update*, vol. 22, no. 1, pp. 104–115, 2016.

[71] S. Lalani, A. J. Choudhry, B. Firth et al., "Endometriosis and adverse maternal, fetal and neonatal outcomes, a systematic review and meta-analysis," *Human Reproduction (Oxford, England)*, vol. 33, no. 10, pp. 1854–1865, 2018.