Received: 1 July 2018 | Revised: 5 November 2018 | Accepted: 1 March 2019

DOI: 10.1002/ijgo.12799

REVIEW ARTICLE

Obstetrics

WILEY International Journal of Gynecology Obstetrics FIGO

Systematic review and meta-analysis of adverse pregnancy outcomes after uterine adenomyosis

Maryam Razavi[1] | Arezoo Maleki-Hajiagha[2] | Mahdi Sepidarkish[3] | Safoura Rouholamin[4] | Amir Almasi-Hashiani[5] | Mahroo Rezaeinejad[6,*]

[1]Pregnancy Health Research Center, Department of Obstetrics and Gynecology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

[2]Research Development Center, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran

[3]Department of Biostatistics and Epidemiology, Babol University of Medical Sciences, Babol, Iran

[4]Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical sciences, Isfahan, Iran

[5]Department of Epidemiology, School of Health, Arak University of Medical Sciences, Arak, Iran

[6]Department of Obstetrics and Gynecology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

*Correspondence
Mahroo Rezaeinejad, Imam Khomeini Hospital Complex, Tehran, Iran.
Email: Mahroo.Rezaeinejad1397@gmail.com

Abstract

Background: Studies on the impact of adenomyosis and its pregnancy complications have yielded conflicting results.

Objective: To determine the likelihood of adverse pregnancy outcomes among women with adenomyosis relative to women without adenomyosis.

Search strategy: PubMed, Embase, Scopus, and Web of Science were searched for studies published up to June 15, 2018.

Selection criteria: Observational studies with medically confirmed pregnancy outcomes as endpoints.

Data collection and analysis: Two researchers independently screened and selected relevant studies. Dichotomous data for all adverse pregnancy outcomes were expressed as an odds ratio (OR) with 95% confidence interval (CI), and combined in a meta-analysis by using a random-effects model.

Main results: Six studies (322 cases and 9420 controls) were eligible for inclusion in the meta-analysis. Women with adenomyosis had an increased likelihood of preterm birth (OR, 3.05; 95% CI, 2.08–4.47; $P<0.001$), small for gestational age (OR, 3.22; 95% CI, 1.71–6.08; $P<0.001$), and pre-eclampsia (OR, 4.35; 95% CI, 1.07–17.72; $P=0.042$).

Conclusion: Adenomyosis seems to have a detrimental impact on pregnancy outcomes, resulting in a higher likelihood of preterm birth, small for gestational age, and pre-eclampsia.

KEYWORDS

Adenomyosis; Pre-eclampsia; Premature birth; Preterm birth; Preterm delivery; Small for gestational age

1 | INTRODUCTION

In adenomyosis, endometrial glands and stroma develop ectopically within the myometrium.[1] Among infertile women, the prevalence of adenomyosis is reported to range from 10% to 90%.[2–4] Adenomyosis is mostly diagnosed in parous women aged 40–50 years, although asymptomatic adenomyosis is sometimes observed among women with a gynecologic disease such as leiomyoma or cervical intraepithelial neoplasia.[5,6] Traditionally, the diagnosis was based on histopathologic findings, but magnetic resonance imaging (MRI) and high-quality transvaginal ultrasound (TVUS) are now used to diagnose the disorder non-invasively with an accuracy of 80%–90%.[5,7,8]

Adenomyosis causes various symptoms including dysmenorrhea, heavy menstrual bleeding, and infertility. The number of pregnancies complicated by adenomyosis has increased in recent years, alongside the trend in delayed pregnancy and advances in infertility treatment.[2,9] Furthermore, the disorder has been associated with poor pregnancy outcomes, including spontaneous abortion, preterm birth, preterm

premature rupture of membranes (PPROM), pre-eclampsia, and fetal growth restriction.[10–12]

Several studies have investigated the maternal and neonatal complications of adenomyosis among infertile women. In addition, two systematic reviews and meta-analyses have assessed the adverse effects of adenomyosis on the success of infertility treatment and pregnancy outcomes among affected women;[4,13] however, the potential impact of adenomyosis on the outcomes of spontaneous pregnancy remains unclear. Pregnancies achieved via assisted reproduction technologies (ART) are confounded by several obstetric complications, including hypertensive disorders of pregnancy and placental malposition.[14–16] Thus, it is important to evaluate pregnancy outcomes for women who conceive spontaneously, and to assess the associations between adenomyosis and spontaneous pregnancy outcomes. The aim of the present study was therefore to conduct a systematic review and meta-analysis to evaluate the effect of adenomyosis on maternal and neonatal outcomes in spontaneous pregnancy.

2 | MATERIALS AND METHODS

2.1 | Protocol

The systematic review and meta-analysis was carried out by using a pre-specified protocol in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) consensus statement.

2.2 | Eligibility criteria

Primary studies were included in the review if they met the following criteria: they were a cohort or case–control study with medically confirmed pregnancy outcomes as the endpoints; they recruited pregnant women who had ultrasonographic and/or histologic diagnosis of focal or diffuse adenomyosis prior to conception; they recruited women with a spontaneously conceived singleton pregnancy; and they reported the risk ratio, odds ratios (OR), or hazard ratio, or data to calculate these risks, of pregnancy outcomes. Studies were excluded if they had a non-observational design (randomized controlled trial, quasi-experimental), or there were inadequate details of the methodology or results. In addition, abstracts with no follow-up report of findings, ongoing clinical studies, review papers, letters to the editor, and editorials were excluded.

2.3 | Search strategy

The following electronic databases were searched: PubMed (1950 to March 2018), Embase (1980 to March 2018), Scopus (2004 to March 2018), and Web of Science (1945 to March 2018). In addition, the references and citation lists of retrieved articles were manually searched to identify further articles and unpublished data. Two authors (MS and AA-H) conducted the search independently. Language restrictions were not applied. The keywords/terms and database-specific indexing terminology used in the search are summarized in Table S1.

2.4 | Study selection

Two independent researchers (two of MS, AM, and MR) examined the titles and abstracts of all identified papers. The full text was retrieved if the study was considered potentially relevant. Discrepancies were settled by discussion with a third researcher not involved in the reviewing process. If additional information about a potential study was required, the corresponding author was contacted.

2.5 | Data extraction

Relevant data, including study characteristics, quality, and endpoints were extracted from the selected articles by two independent investigators. The primary endpoints for the meta-analysis were preterm birth (babies born alive before 37 completed weeks of gestation), pre-eclampsia (defined as hypertension and significant proteinuria in a previously healthy woman on or after 20 gestational weeks); small for gestational age (SGA; defined as birth weight below the 10th percentile for gestational age); fetal malpresentation (defined as abnormal position of the fetal head vertex relative to the maternal pelvis); low birth weight (LBW; less than 2500 g regardless of gestational age); and gestational diabetes mellitus (GDM; any degree of glucose intolerance with onset during pregnancy).

2.6 | Methodologic quality

The quality of the selected studies was assessed using the Newcastle–Ottawa quality assessment scale for case–control and cohort studies.[17] The following items were assessed: selection of the study groups, comparability of study groups, and ascertainment of exposure and outcome. Two independent researchers (MS and AA-H) evaluated the risk of bias in the selected studies. Discrepancies were resolved by discussion with a third researcher.

2.7 | Data analysis

Statistical analyses were performed by using RevMan version 5.3 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). For each adverse pregnancy outcome, the OR with corresponding 95% confidence interval (CI) was calculated for case (or exposed) women versus control (or unexposed) women. A random effects model was used to pool OR data. Weighting of studies included in the meta-analyses was calculated via the Mantel-Hansel method. Heterogeneity was tested by the Cochrane χ^2 test, and the degree of heterogeneity was quantified via the I^2 statistic. A P value of less than 0.05 was considered statistically significant. The likelihood of publication bias was assessed by Egger test, with a P value of less than 0.10 considered to indicate statistically significant publication bias.

To investigate whether the results of the meta-analysis were dependent on a specific study, the meta-analysis statistic was recalculated after omitting one study at a time (sensitivity analysis). All comparisons were two-tailed, and a P value of less than 0.05 was considered statistically significant.

3 | RESULTS

In total, 1296 publications were retrieved from the database searches: 700 from PubMed, 1009 from Embase, 1149 from Scopus, and 679 from Web of Science. After screening the titles and abstracts, six studies (involving 322 cases and 9420 controls) were potentially eligible for inclusion in the meta-analysis. The process of study selection is shown in Figure 1.

Table 1 outlines the main characteristics of the included studies. The six studies were conducted between 2006 and 2018, and four were published after 2015. The studies were conducted in Japan (n=2),[11,18] Turkey (n=1),[12] Italy (n=1),[19] Taiwan (n=1),[10] and Korea

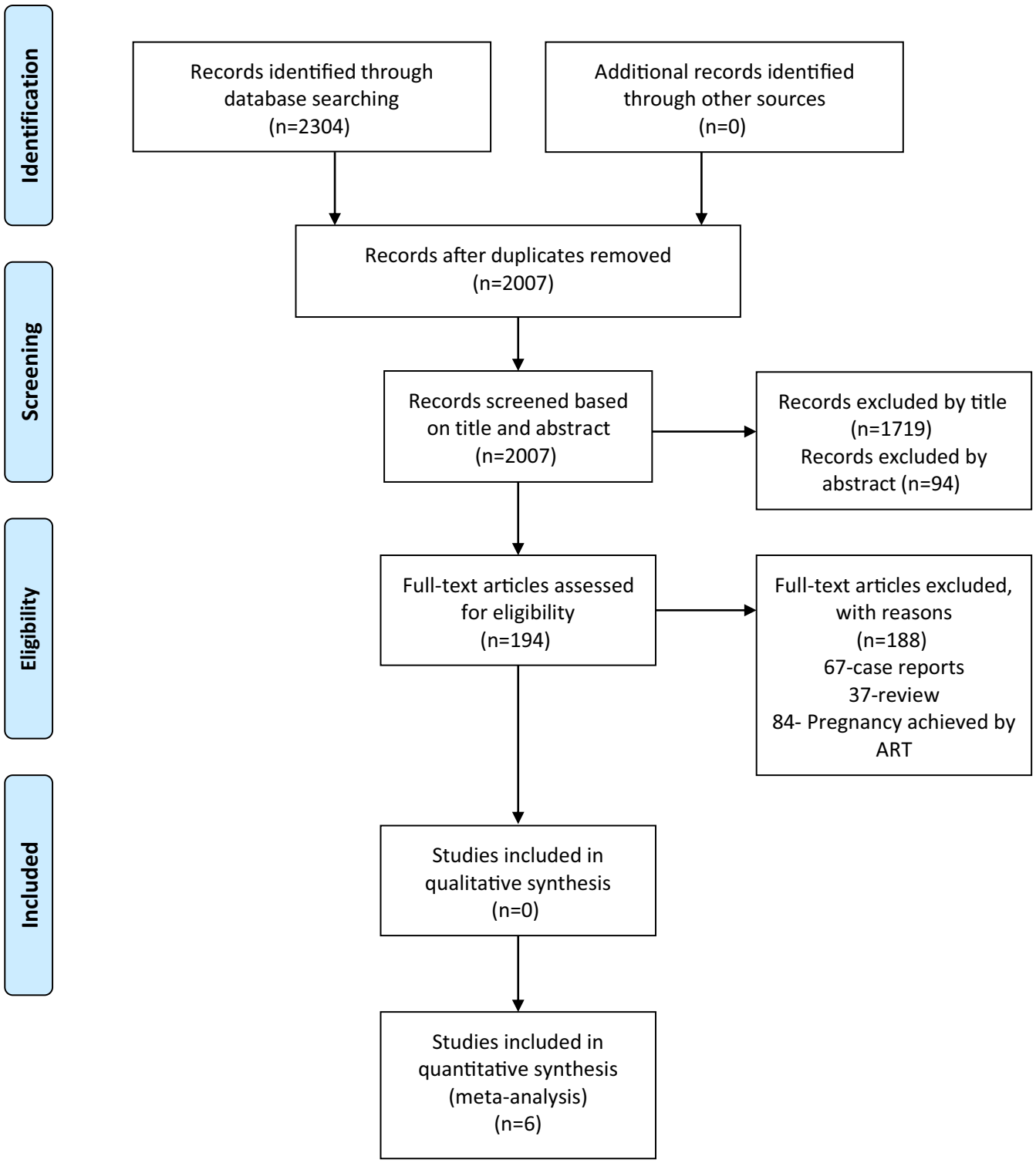

FIGURE 1 Flowchart showing the study selection process.

TABLE 1 Characteristics of the studies included in the systematic review.

Study	Country	Study design	Study population	No. of women with adenomyosis	No. of women without adenomyosis	Method of diagnosis	Reported pregnancy outcomes
Exacousto, 2016[19]	Italy	Cohort	Singleton pregnancy women with adenomyosis	61	500	TVUS	Preterm birth, SGA
Hasdemir, 2016[12]	Turkey	Case–control	Women with diagnosis of pre-eclampsia	59	10	MRI	Pre-eclampsia
Hashimoto, 2018[18]	Japan	Case–control	Singleton pregnancy women with adenomyosis	49	245	MRI and TVUS	Abortion, pre-eclampsia, gestational hypertension, placental malposition, GDM, fetal malpresentation, preterm delivery
Juang, 2006[10]	Taiwan	Case–control	Singleton pregnancy women with adenomyosis	35	277	MRI and TVUS	Preterm delivery
Mochimaru, 2015[11]	Japan	Case–control	Women diagnosed with adenomyosis before pregnancy	36	144	MRI and TVUS	Preterm delivery, PPROM, pre-eclampsia, fetal malpresentation, postpartum hemorrhage, SGA, IUFD, NICU admission
Shin, 2018[20]	Korea	Retrospective cohort	Singleton pregnancy women with adenomyosis	82	8244	TVUS	Preterm birth, LBW, VLBW

Abbreviations: GDM, gestational diabetes mellitus; IUFD, intrauterine fetal demise; LBW, low birthweight; MRI, magnetic resonance imaging; NICU, neonatal intensity care unit; PPROM, preterm premature rupture of membranes; SGA, small for gestational age; TVUS, transvaginal ultrasound; VLBW, very low birthweight.

(n=1).[20] The sample size ranged from 69[12] to 8326[20] women. Four of the six studies were designed as case–control studies and two as cohort studies. Adenomyosis was diagnosed by MRI in one, TVUS in two, and a combination of TVUS and MRI in three studies. The critical appraisal of the included studies is shown in Table S2. Two studies were scored as satisfactory, two as good, one as very good, and one as unsatisfactory.

Five studies (261 cases and 8841 controls) evaluated the association between adenomyosis and preterm birth with ORs ranging from 1.96 (95% CI, 1.23–3.12) to 5.00 (95% CI, 2.20–11.36). The sensitivity analysis indicated that no single study substantially influenced the pooled estimate, which showed that adenomyosis was associated with a three-fold increase in the likelihood of preterm birth (OR, 3.05; 95% CI, 2.08–4.47; $P<0.001$) (Fig. 2). Among the five studies, there was no heterogeneity among the five studies ($P=0.25$, $I^2=26\%$) or evidence of publication bias (Egger regression intercept, 9.99; 95% CI, −1.76 to 21.76; $P=0.073$).

Subgroup analysis of cohort and case–control studies showed a significant association between adenomyosis and preterm birth for both types of study (OR, 3.73; 95% CI, 2.12 to 6.57, $P<0.001$, $I^2=0\%$; and OR, 2.87; 95% CI, 1.60–5.17; $P<0.001$; $I^2=50\%$, respectively) (Fig. 2). The pooled OR of preterm birth was 3.73 (95% CI, 2.12–6.57; $P<0.001$; $I^2=0\%$) in the two studies that used TVUS for diagnosis, and 2.87 (95% CI, 1.60–5.17; $P<0.001$; $I^2=50\%$) in the three studies that used TVUS and MRI for diagnosis (Fig. 3).

Three studies assessed the association between adenomyosis and pre-eclampsia with ORs ranging from 1.66 (95% CI, 0.42–6.50) to 18.15 (95% CI, 4.73–69.64). Women with adenomyosis demonstrated higher odds of developing pre-eclampsia relative to women without adenomyosis (OR, 4.35; 95% CI, 1.07–17.72; $P=0.042$; $I^2=70\%$) (Fig. 4). There was no evidence of publication bias (Egger regression intercept, 10.29; 95% CI, −109.82 to 130.40; $P=0.748$).

Three studies including 1035 women (585 cases and 450 controls) evaluated the association between adenomyosis and SGA, two of which found a significant association (OR, 3.22; 95% CI, 1.71–6.08; $P<0.001$) (Fig. 5). There was no heterogeneity among the studies included in the analysis ($P=0.35$, $I^2=4\%$), and no evidence of publication bias (Egger regression intercept, 25.61; 95% CI, −15.98 to 67.22; $P=0.081$).

Two studies assessed the association between adenomyosis and fetal malpresentation among 474 participants (85 cases and 389 controls). Women with adenomyosis demonstrated a similar likelihood of developing fetal malpresentation as compared with women without the disorder (OR, 2.35; 95% CI, 0.69–8.04; $P=0.17$) (Fig. 6). Non-significant heterogeneity was observed among the two studies ($P=0.092$, $I^2=64\%$).

Only one study assessed the association between adenomyosis and GDM with 294 participants (49 cases and 245 controls).[18] There was a significant difference in the occurrence of GDM between women with and those without adenomyosis (OR, 2.84; 95% CI, 1.35–5.97; $P=0.006$).

Only Shin et al.[20] assessed the association between adenomyosis and LBW in a study of 8316 women (72 cases and 8244 controls).

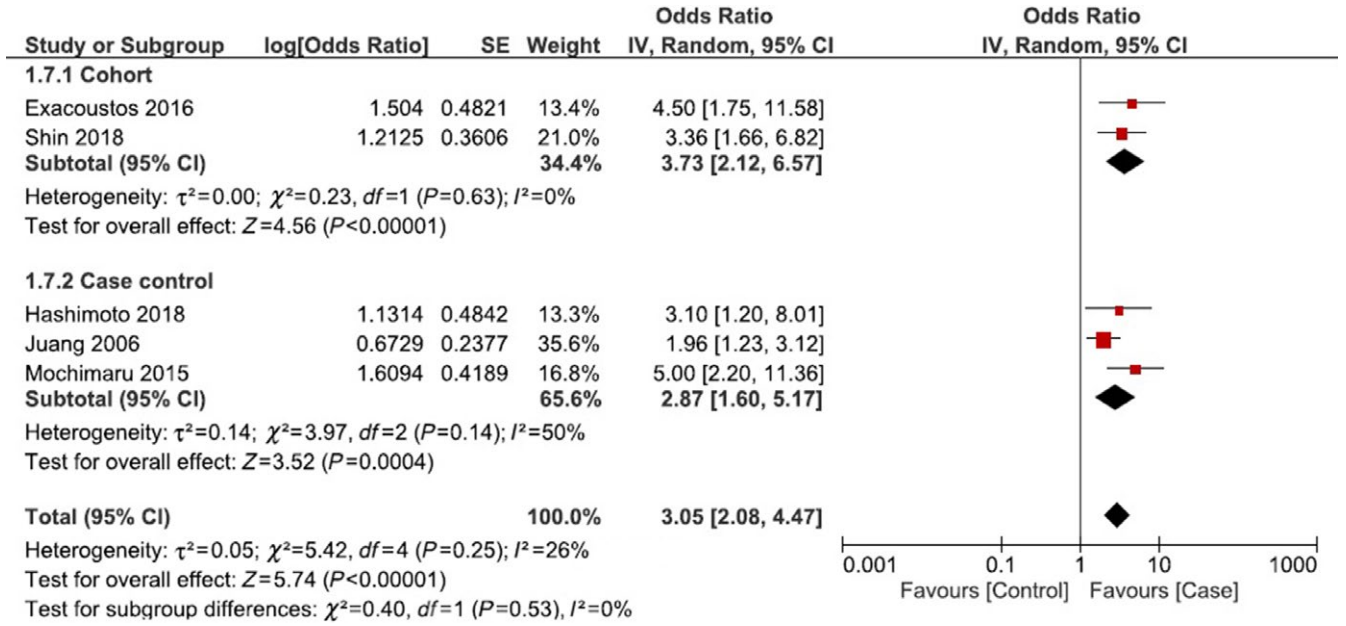

FIGURE 2 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in cohort and case–control studies that evaluated the likelihood of preterm birth among pregnant women with a diagnosis of adenomyosis.

They reported a strong association between LBW and adenomyosis (OR, 5.05; 95% CI, 2.56–9.96; *P*<0.001).

Only Hashimoto et al.[18] reported the association between adenomyosis and spontaneous abortion with 294 participants (49 cases and 245 controls). There was a significant difference in the occurrence of abortion between women with and those without adenomyosis (OR, 11.2; 95% CI, 2.2–71.2; *P*<0.001).

Only one study assessed the association between adenomyosis and PPROM with 180 participants (36 cases and 144 controls).[11] There was a strong association between PPROM and adenomyosis (OR, 5.5; 95% CI, 1.7–17.7; *P*=0.012).

4 | DISCUSSION

The present systematic review and meta-analysis, including six studies with 9742 women (322 cases and 9420 controls), investigated whether adenomyosis is associated with adverse pregnancy

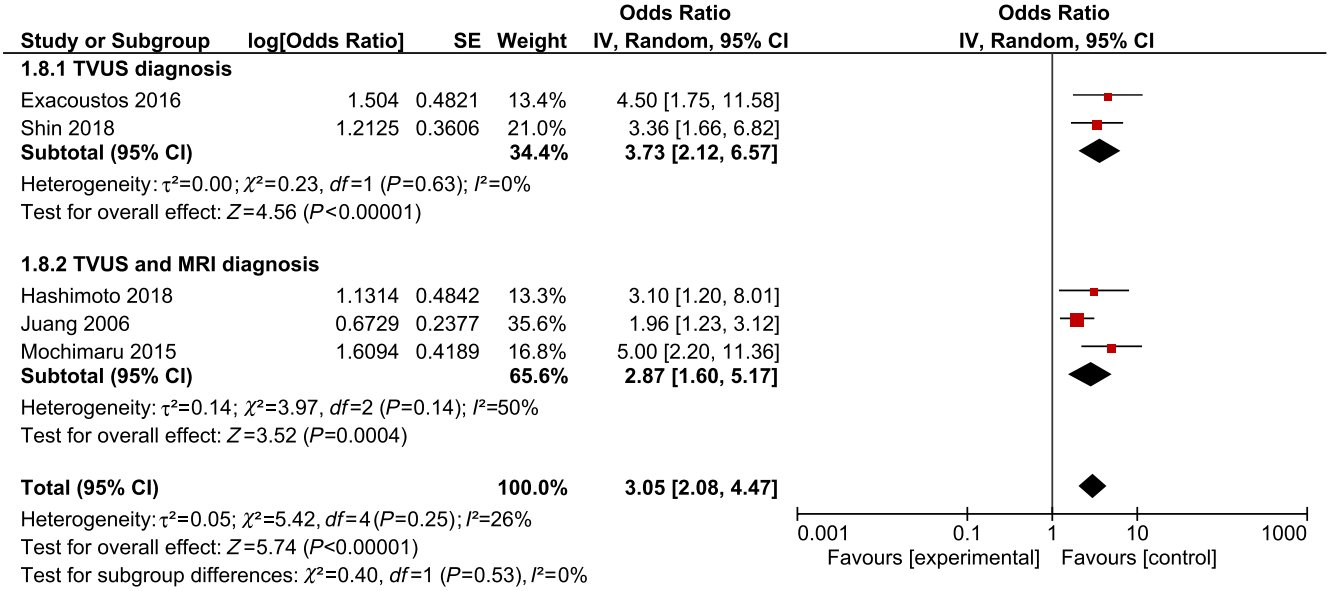

FIGURE 3 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of preterm birth among pregnant women with a diagnosis of adenomyosis determined by magnetic resonance imaging (MRI) or transvaginal ultrasonography (TVUS).

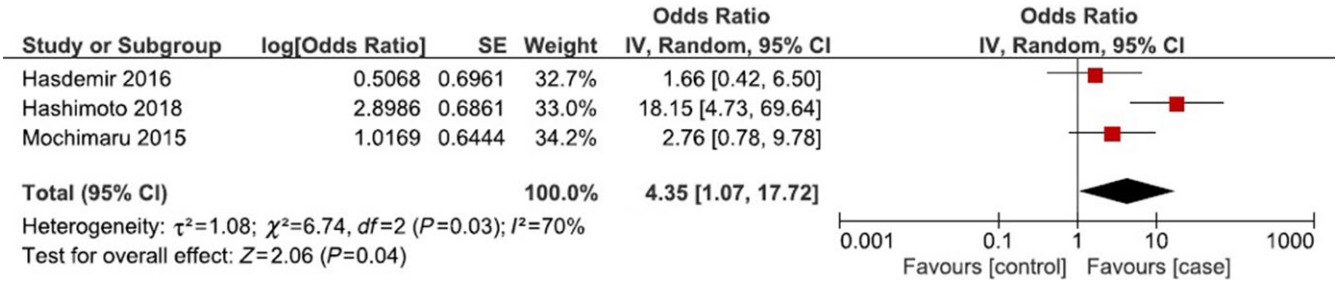

FIGURE 4 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of pre-eclampsia among pregnant women with a diagnosis of adenomyosis.

outcomes. Overall, women with adenomyosis were found to have an increased likelihood of preterm birth, PPROM, spontaneous abortion, GDM, SGA, and pre-eclampsia as compared with women without adenomyosis. However, there was no evidence for the association of adenomyosis with fetal malpresentation. Data from a single study also demonstrated that the likelihood of LBW was significantly higher for women with adenomyosis.

The study has some limitations. Although the pooled estimates did not change with the exclusion of any of the studies, they should be considered with caution owing to the small number of included studies, misclassification bias based on the diagnostic method, and the significant heterogeneity between the studies. In addition, the majority of studies were designed as low-quality case–control studies with small sample sizes. Subgroup analysis was conducted to decrease the impact of heterogeneity; however, it was not possible to perform subgroup analysis for pre-eclampsia, fetal malpresentation, or SGA because of the low number of studies included in the final meta-analysis. In the subgroup analysis of diagnostic method and study design, no visual influence on the likelihood of preterm birth was observed (Figs 2 and 3).

Selection bias due to control selection and confounding processes must also be considered. The six studies had a considerable number of confounding factors and, without controlling for these factors, the potential to draw robust conclusions is limited. Furthermore, the review was based on data from observational studies, which have a higher risk of bias as compared with randomized controlled trials. Controlling for potential confounding variables is a fundamental challenge in observational studies, although some factors can be controlled by adjustment after study completion using multivariate analysis.[21] In terms of adenomyosis, many variables such as maternal age, parity, gestational age at delivery, and previous medical history might confound the association with undesirable pregnancy outcomes. However, it was not possible to perform a meta-analysis on adjusted ORs because only one study considered a strategy to control for such variables. The relative rarity of the pregnancy outcomes might explain why multivariate models were not used in the studies included in the review.

In the present meta-analysis, adenomyosis was associated with a higher likelihood of preterm birth. A higher likelihood was observed in both cohort and case–control studies, but the size of the effect was higher in cohort studies. In the hierarchy of evidence-based medicine, well-designed cohort studies provide level II evidence, whereas well-designed case–control studies provide level III evidence.[22] Case–control studies might be more vulnerable to unpredictable confounding factors and selection bias as compared with cohort studies.

In a cohort study, an at-risk population is first selected by the exposure of interest and followed in time until the outcomes of interest occur. Since exposure occurs before the outcome, this design has a temporal framework to assess causality; therefore, these studies are at a higher level to provide accurate scientific evidence.[23] In contrast, a case-control study compares patients who have a disease interest (cases) with patients who do not have the disease (controls). However, despite the methodologic convenience of this method, validity issues may arise. The most important point in this study is the selection of the control group. An important principle is that the distribution of other covariates should be identical among cases and controls; in other words, both cases and controls should stem from the same source population.[24,25] In general, the findings obtained from cohort studies are more accurate and more reliable than case-control studies.

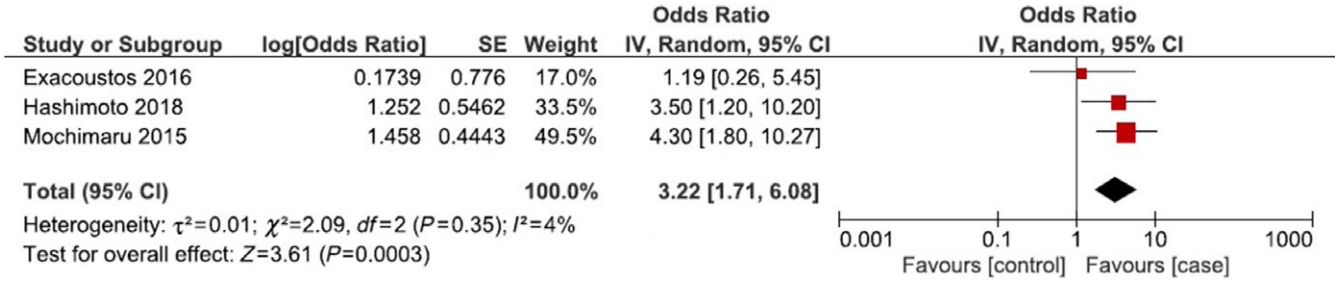

FIGURE 5 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of small gestational age among pregnant women with a diagnosis of adenomyosis.

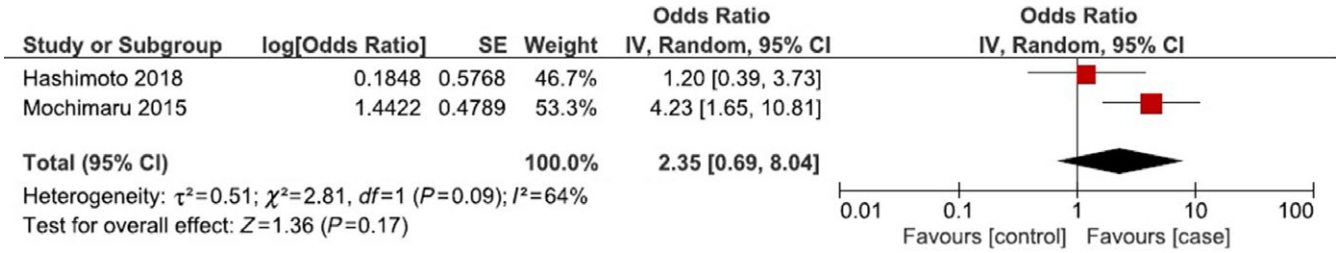

FIGURE 6 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of fetal malpresentation among pregnant women with a diagnosis of adenomyosis.

The likelihood of preterm birth for women with adenomyosis was higher among the studies that used a combination of MRI and TVUS for diagnosis than for those that used only TVUS. As compared with TVUS, MRI has been shown to have better discrimination between women with adenomyosis and those without adenomyosis.[26] This non-differential misclassification of disease produces a bias toward the null finding[27] and, in studies based on TVUS, it might lead to the inclusion of women with minor forms of adenomyosis in the control group, leading to underestimation of the association between adenomyosis and adverse pregnancy outcome. Two of the studies in the present systematic review used TVUS alone as a diagnostic method, and might be affected by misclassification bias.

Convincing clinical and evidence-based experimental studies support the concept that some pathogenic processes lead to a common final biological pathway resulting in spontaneous preterm birth with or without PROM. The four pathogenic processes are immature activation of the maternal or fetal hypothalamic–pituitary–adrenal axis; exaggerated inflammatory condition or infection; abruption or decidual hemorrhage; and pathologic uterine distention.[28] The association between adenomyosis and preterm birth might be due to the condition of exaggerated inflammation or infection. Levels of proinflammatory mediators in the amniotic fluid are significantly higher among women who undergo preterm delivery with intact membranes than among women with term delivery.[29,30]

In a systematic review and meta-analysis including 6270 asymptomatic women, elevated cervicovaginal and amniotic fluid levels of interleukin-6 at mid-gestation were associated with an increased likelihood of preterm birth (OR, 3.05; 95% CI, 2.00–4.67; number needed to treat=7).[31] The activation of pro-inflammatory mediators such as prostaglandin E_2, cyclooxygenase-2, and interleukin-8 is necessary for childbirth. Local and systematic inflammation triggers myometrial vasoconstriction and stimulates cervical ripening. Levels of prostaglandins and cytokines in the peritoneal fluid are higher among women with adenomyosis than among control women.[32] Previous studies have reported an association between adenomyosis and ART outcomes.[4,33] It thus seems logical to infer that impaired implantation constitutes a pathogenic mechanism leading to preterm birth.

There are many similarities between adenomyosis and endometriosis. In both cases, the inner layer of the myometrium (or junctional zone) changes, although these changes are more pronounced in adenomyosis. Poor functioning of the immune system, apoptosis, molecular adhesion, and cell proliferation are obvious in both conditions. In addition, increased levels of inflammatory factors, cytokines, oxidative stress, and free radicals lead to changes in uterine receptivity. Previous studies have shown that both disorders have an epigenetic origin and are affected by steroid hormones.[34–36] Because adenomyosis is a type of endometriosis that is limited to the myometrium, the occurrence of many adverse pregnancy outcomes might be the same in both conditions.

A known pathophysiologic mechanism for many adverse pregnancy outcomes, such as pre-eclampsia, preterm delivery, and fetal growth restriction, is an implantation and placentation defect.[37] It has been shown that a deep placentation defect, caused by the failure of spiral artery remodeling in the myometrial junctional zone, is associated with these complications. During normal pregnancies, the cytotrophoblast of the developing placenta cells invades both the endothelium and uterine spiral arteries, transforming the endothelial layers of these small muscular arterioles into large capacitance vessels of low resistance; in pre-eclampsia, by contrast, infiltration of the decidual portion of the spiral arteries is limited to the proximal decidua, and the major part of the spiral arteries of the placental bed escape endovascular trophoblast remodeling. This failure of uterine spiral artery remodeling prevents an appropriate response to the increased fetal demands for blood flow that occur as gestation progresses.[38] Although the pathophysiology of the effects of uterine adenomyosis on SGA is unclear, Yorifuji et al.[39] demonstrated blood flow in the adenomyosis lesion rather than in the placenta, suggesting vascular stealing by uterine adenomyosis is among the possible pathophysiology mechanisms of SGA.[39]

5 | CONCLUSION

It seems that adenomyosis has a detrimental impact on pregnancy outcomes, increasing the likelihood of preterm birth, SGA, and pre-eclampsia; however, the potential confounding effects of other variables such as maternal age, parity, gestational age at delivery, and previous medical history could not be assessed. The findings of the systematic review suggest the advantages of closer prenatal monitoring of pregnant women for adenomyosis to prevent adverse pregnancy outcomes.

AUTHOR CONTRIBUTIONS

MRa and MRe contributed to conceiving and planning the review; performing study selection, data extraction, quality assessment, and

meta-analyses; assessing evidence quality; and drafting the manuscript. AM contributed to performing study selection, data extraction, quality assessment, and meta-analyses; assessing evidence quality and analyses; and revising the manuscript. MS and AA-H contributed to assessing evidence quality and analyses; and revising the manuscript. SR contributed to analyses and revising the manuscript. All authors read and approved the submitted manuscript and accept responsibility for its publication.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. Benagiano G, Brosens I. History of adenomyosis. *Best Pract Res Clin Obstet Gynaecol*. 2006;20:449–463.
2. Azziz R. Adenomyosis: Current perspectives. *Obstet Gynecol Clin North Am*. 1989;16:221–235.
3. Yeniel O, Cirpan T, Ulukus M, et al. Adenomyosis: Prevalence, risk factors, symptoms and clinical findings. *Clin Exp Obstet Gynecol*. 2007;34:163–167.
4. Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: A systematic review and meta-analysis. *Hum Reprod*. 2014;29:964–977.
5. Maheshwari A, Gurunath S, Fatima F, Bhattacharya S. Adenomyosis and subfertility: A systematic review of prevalence, diagnosis, treatment and fertility outcomes. *Hum Reprod Update*. 2012;18:374–392.
6. Kunz G, Beil D, Huppert P, Noe M, Kissler S, Leyendecker G. Adenomyosis in endometriosis—prevalence and impact on fertility. Evidence from magnetic resonance imaging. *Hum Reprod*. 2005;20:2309–2316.
7. Reinhold C, McCarthy S, Bret PM, et al. Diffuse adenomyosis: Comparison of endovaginal US and MR imaging with histopathologic correlation. *Radiology*. 1996;199:151–158.
8. Dueholm M, Lundorf E. Transvaginal ultrasound or MRI for diagnosis of adenomyosis. *Curr Opin Obstet Gynecol*. 2007;19:505–512.
9. Pontis A, D'Alterio M, Pirarba S, De Angelis C, Tinelli R, Angioni S. Adenomyosis: A systematic review of medical treatment. *Gynecol Endocrinol*. 2016;32:696–700.
10. Juang CM, Chou P, Yen MS, Twu NF, Horng HC, Hsu WL. Adenomyosis and risk of preterm delivery. *BJOG*. 2007;114:165–169.
11. Mochimaru A, Aoki S, Oba MS, Kurasawa K, Takahashi T, Hirahara F. Adverse pregnancy outcomes associated with adenomyosis with uterine enlargement. *J Obstet Gynaecol Res*. 2015;41:529–533.
12. Hasdemir P, Farasat M, Aydin C, Ozyurt B, Guvenal T, Pekindil G. The role of adenomyosis in the pathogenesis of preeclampsia. *Geburtshilfe Frauenheilkd*. 2016;76:882.
13. Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: A meta-analysis. *Fertil Steril*. 2017;108:483–490.e483.
14. Shevell T, Malone FD, Vidaver J, et al. Assisted reproductive technology and pregnancy outcome. *Obstet Gynecol*. 2005;106(5, Part 1):1039–1045.
15. Takemura Y, Osuga Y, Fujimoto A, et al. Increased risk of placenta previa is associated with endometriosis and tubal factor infertility in assisted reproductive technology pregnancy. *Gynecol Endocrinol*. 2013;29:113–115.
16. Toshimitsu M, Nagamatsu T, Nagasaka T, et al. Increased risk of pregnancy-induced hypertension and operative delivery after conception induced by in vitro fertilization/intracytoplasmic sperm injection in women aged 40 years and older. *Fertil Steril*. 2014;102:1065–1070.e1061.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605.
18. Hashimoto A, Iriyama T, Sayama S, et al. Adenomyosis and adverse perinatal outcomes: Increased risk of second trimester miscarriage, preeclampsia, and placental malposition. *J Matern Fetal Neonatal Med*. 2018;31:364–369.
19. Exacoustos C, Lauriola I, Lazzeri L, De Felice G, Zupi E. Complications during pregnancy and delivery in women with untreated rectovaginal deep infiltrating endometriosis. *Fertil Steril*. 2016;106(1129–1135):e1121.
20. Shin YJ, Kwak DW, Chung JH, Kim MY, Lee SW, Han YJ. The risk of preterm births among pregnant women with adenomyosis. *J Ultrasound Med*. 2018;37:1937–1943.
21. Westfall J, Yarkoni T. Statistically controlling for confounding constructs is harder than you think. *PLoS ONE*. 2016;11:e0152719.
22. Sackett DL, Rosenberg WM, Gray JM, Haynes RB, Richardson WS. Evidence based medicine: What it is and what it isn't. *BMJ*. 1996;312:71–72.
23. Vandenbroucke JP, Von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *PLoS Med*. 2007;4:e297.
24. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies: II. Types of controls. *Am J Epidemiol*. 1992;135:1029–1041.
25. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies: III. Design options. *Am J Epidemiol*. 1992;135:1042–1050.
26. Maubon A, Faury A, Kapella M, Pouquet M, Piver P. Uterine junctional zone at magnetic resonance imaging: A predictor of in vitro fertilization implantation failure. *J Obstet Gynaecol Res*. 2010;36:611–618.
27. Jurek AM, Greenland S, Maldonado G. Brief report: How far from non-differential does exposure or disease misclassification have to be to bias measures of association away from the null? *Int J Epidemiol*. 2008;37:382–385.
28. Moroz LA, Simhan HN. Rate of sonographic cervical shortening and biologic pathways of spontaneous preterm birth. *Am J Obstet Gynecol*. 2014;210:555.e551–555.e555.
29. Pierce BT, Pierce LM, Wagner RK, et al. Hypoperfusion causes increased production of interleukin 6 and tumor necrosis factor α in the isolated, dually perfused placental cotyledon. *Am J Obstet Gynecol*. 2000;183:863–867.
30. Zeitlin J, Ancel P, Saurel-Cubizolles M, Papiernik E. The relationship between intrauterine growth restriction and preterm delivery: An empirical approach using data from a European case-control study. *BJOG*. 2000;107:750–758.
31. Wei S-Q, Fraser W, Luo Z-C. Inflammatory cytokines and spontaneous preterm birth in asymptomatic women: A systematic review. *Obstet Gynecol*. 2010;116(2, Part 1): 393–401.
32. Ota H, Igarashi S, Sasaki M, Tanaka T. Distribution of cyclooxygenase-2 in eutopic and ectopic endometrium in endometriosis and adenomyosis. *Hum Reprod*. 2001;16:561–566.
33. Dueholm M. Uterine adenomyosis and infertility, review of reproductive outcome after in vitro fertilization and surgery. *Acta Obstet Gynecol Scand*. 2017;96:715–726.
34. Benagiano G, Brosens I, Habiba M. Structural and molecular features of the endomyometrium in endometriosis and adenomyosis. *Hum Reprod Update*. 2013;20:386–402.
35. Brosens J, Verhoeven H, Campo R, et al. High endometrial aromatase P450 mRNA expression is associated with poor IVF outcome. *Hum Reprod*. 2004;19:352–356.

36. Ishihara H, Kitawaki J, Kado N, Koshiba H, Fushiki S, Honjo H. Gonadotropin-releasing hormone agonist and danazol normalize aromatase cytochrome P450 expression in eutopic endometrium from women with endometriosis, adenomyosis, or leiomyomas. *Fertil Steril*. 2003;79:735–742.
37. Conti N, Cevenini G, Vannuccini S, et al. Women with endometriosis at first pregnancy have an increased risk of adverse obstetric outcome. *J Matern Fetal Neonatal Med*. 2015;28:1795–1798.
38. Stocks G. Preeclampsia: Pathophysiology, old and new strategies for management. *Eur J Anaesthesiol*. 2014;31:183–189.
39. Yorifuji T, Makino S, Yamamoto Y, Sugimura M, Kuwatsuru R, Takeda S. Time spatial labeling inversion pulse magnetic resonance angiography in pregnancy with adenomyosis. *J Obstet Gynaecol Res*. 2013;39:1480–1483.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search strategy.

Table S2. Critical appraisal of the studies included in the review.