Received: 27 December 2022 | Revised: 1 April 2023 | Accepted: 5 April 2023

DOI: 10.1111/aogs.14580

SYSTEMATIC REVIEW

Different subtypes of ultrasound-diagnosed adenomyosis and in vitro fertilization outcomes: A systematic review and meta-analysis

Xia-Li Wang[1,2] | Zi-Wei Xu[1] | Yan-Yan Huang[1] | Shu Lin[3,4] | Guo-Rong Lyu[1,2]

[1]Department of Ultrasound, Second Affiliated Hospital of Fujian Medical University, Quanzhou, China

[2]Department of Clinical Medicine, Quanzhou Medical College, Quanzhou, China

[3]Center of Neurological and Metabolic Research, Second Affiliated Hospital of Fujian Medical University, Quanzhou, China

[4]Diabetes and Metabolism Division, Garvan Institute of Medical Research, Darlinghurst, Sydney, Australia

Correspondence
Guo-Rong Lyu, Department of Ultrasound, Second Affiliated Hospital of Fujian Medical University, No. 34 North Zhongshan Road, Quanzhou 362000, Fujian Province, China.
Email: lgr_feus@sina.com

Funding information
Quanzhou City Science and Technology Bureau, Grant/Award Number: 2020CT003; Quanzhou City Science & Technology Program of China, Grant/Award Number: 2020N057s

Abstract

Introduction: Adenomyosis prevalence among women with infertility is increasing; their management during in vitro fertilization is usually based on ultrasound diagnosis alone. Herein, we summarize the latest evidence on the impact of ultrasound-diagnosed adenomyosis on in vitro fertilization outcomes.

Material and methods: The study was registered with The International Prospective Register of Systematic Reviews (CRD42022355584). We searched PubMed, Embase, and Cochrane Library databases from inception to January 31, 2023, for cohort studies on the impact of adenomyosis on in vitro fertilization outcomes. Fertility outcomes were compared according to the presence of adenomyosis as diagnosed by ultrasound, concurrent endometriosis and adenomyosis, and MRI-based or MRI- and ultrasound-based adenomyosis diagnosis. Live birth rate was the primary outcome while clinical pregnancy and miscarriage rates were secondary outcomes.

Results: Women diagnosed with adenomyosis by ultrasound had lower live birth (odds ratio [OR] = 0.66; 95% confidence interval [CI]: 0.53–0.82, grade: very low), lower clinical pregnancy (OR = 0.64; 95% CI: 0.53–0.77, grade: very low), and higher miscarriage (OR = 1.81; 95% CI: 1.35–2.44, grade: very low) rates than those without adenomyosis. Notably, symptomatic and diffuse, but not asymptomatic adenomyosis as diagnosed by ultrasound, adversely affected in vitro fertilization outcomes, with lower live birth (OR = 0.57; 95% CI: 0.34–0.96, grade: very low), clinical pregnancy (OR = 0.69; 95% CI: 0.57–0.85, grade: low), and miscarriage (OR = 2.48, 95% CI: 1.28–4.82, grade: low) rates; and lower live birth (OR = 0.37; 95% CI: 0.23–0.59, grade: low) and clinical pregnancy (OR = 0.50; 95% CI: 0.34–0.75, grade: low), but not miscarriage rate (OR = 2.18; 95% CI: 0.72–6.62, grade: very low), respectively. Concurrent adenomyosis in endometriosis is associated with a significantly lower live birth rate (OR = 0.44; 95% CI: 0.26–0.75, grade: low) than endometriosis alone. Finally,

Abbreviations: CI, confidence interval; CPR, clinical pregnancy rate; GnRH, gonadotrophin releasing hormone; IVF, in vitro fertilization; LBR, live birth rate; MR, miscarriage rate; MRI, magnetic resonance imaging; OR, odds ratio; TVUS, transvaginal ultrasonography; US, ultrasound.

the use of MRI-based or MRI- and ultrasound-based adenomyosis diagnosis showed no significant association with in vitro fertilization outcomes (grade: very low for all outcomes).

Conclusions: Considering ultrasound findings, symptoms, and different subtypes of adenomyosis may aid in offering personalized counseling, improving treatment decisions, and achieving better outcomes of in vitro fertilization.

KEYWORDS
adenomyosis, assisted reproduction, endometriosis, infertility, ultrasound

Key message

Adenomyosis possibly remains a priority consideration when planning IVF treatment, even when comorbid with endometriosis. Different treatment regimens for symptomatic vs asymptomatic patients with US-diagnosed adenomyosis may contribute to better counseling for IVF. Furthermore, a comprehensive classification of adenomyosis is warranted.

1 | INTRODUCTION

Adenomyosis, characterized by the presence of islands of endometrial tissue within the myometrium surrounded by hypertrophic smooth muscle cells, may be associated with a significant symptom burden, primarily painful or heavy menstrual periods and chronic pelvic pain. The disease is also associated with reduced fertility and poor reproductive and obstetric outcomes.[1]

With the introduction of transvaginal ultrasonography (TVUS) and MRI, adenomyosis, once diagnosed only by histopathological examination, is increasingly diagnosed in patients with infertility, suggesting that the condition may be linked to subfertility or infertility. Furthermore, a recent meta-analysis reported that adenomyosis had a negative impact on in vitro fertilization (IVF) outcomes; the live birth rate (LBR), clinical pregnancy rate (CPR), and ongoing pregnancy rate were lower, while the miscarriage rate (MR) was higher in patients with adenomyosis than those in the control group.[2] However, a considerable proportion of patients with adenomyosis do not experience adverse IVF outcomes. Thus, adenomyosis remains an enigmatic disorder with poorly understood pathogenesis and pathophysiology.[3]

Existing evidence on the association of adenomyosis with IVF outcomes and related risk factors remains scarce and controversial due to the lack of standardized imaging diagnostic criteria.[4] Moreover, sonographic markers of adenomyosis in asymptomatic patients do not seem to be associated with adverse outcomes in clinical practice, and different types of adenomyosis (focal and diffuse) appear to have different impacts on fertility. In addition, young women are only diagnosed and treated for adenomyosis, while endometriosis may not be recognized and treated.[5] Adenomyosis continues to stagger scientists, gynecologists, and patients, and the standardization of ultrasound (US) diagnosis may be a top priority in addressing this dilemma.

Therefore, we conducted a systematic review and meta-analysis to (1) investigate the impact of adenomyosis diagnosis by US on IVF outcomes, including the effect of the adenomyosis type and symptoms; (2) explore the impact of concurrent endometriosis; and (3) assess the predictive power of MRI or MRI combined with TVUS for better management of women with infertility with US-diagnosed adenomyosis planning to undergo IVF.

2 | MATERIAL AND METHODS

2.1 | Study design

A panel of five US experts formulated four clinical questions including "whether ultrasonographic adenomyosis negatively impacted IVF outcomes," "does concurrent endometriosis have a negative impact on the IVF outcomes in adenomyosis," "does concurrent adenomyosis have a negative impact on the IVF outcomes in endometriosis," and "whether MRI or MRI combined with US-diagnosed adenomyosis has an impact on IVF outcomes" through detailed discussions and communication. Expertise was defined as the performance and interpretation of at least 1000 gynecological TVUS examinations. We registered our study with the International Prospective Register of Systematic Reviews (CRD42022355584) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.

2.2 | Search strategy and selection criteria

We searched PubMed, Embase, and Cochrane Library (CENTRAL) databases from inception to January 31, 2023, for cohort studies on

the impact of adenomyosis diagnosis by US on IVF outcomes. The following search terms were used: "adenomyosis" and "ultrasound" or "MRI" and "endometriosis" and "IVF." After removing duplicate records with EndNote X9, two reviewers (W. X. and X. Z.) independently screened the retrieved studies, first the title and abstract, and then the full article text. Studies were considered eligible if they enrolled patients with infertility diagnosed with adenomyosis who were planning to undergo IVF regardless of the stimulation protocols they accepted. Any discrepancies were referred to a third reviewer (H. Y.) and resolved by consensus. The following data were extracted: year of publication, study design and setting, study population, patients' baseline characteristics, number of patients and cycles, diagnostic method and criteria, treatment protocol, and outcomes (Table S1).

To investigate the impact of US-diagnosed adenomyosis on IVF outcomes, we analyzed all relevant articles, including all studies comparing the clinical outcomes of IVF treatment between two infertility groups (women with and without adenomyosis as diagnosed by US). Studies that included patients who underwent MRI or both MRI and TVUS and those with a statistically significant number of endometriosis cases and in either group were excluded. Furthermore, studies were excluded when the included patients did not match by age or the difference between the two groups was not adjusted in the statistical analyses.

To explore the impact of concurrent endometriosis on the IVF outcomes of adenomyosis, we analyzed studies comparing IVF outcomes between adenomyosis combined with endometriosis (study group) and adenomyosis alone or endometriosis alone (control group), regardless of the radiographic method used for the diagnosis of adenomyosis.

Finally, to investigate the predictive power of MRI-based diagnosis of adenomyosis for IVF treatment outcomes, we analyzed all studies in which patients underwent MRI or both MRI and TVUS.

2.3 | Study outcomes

The primary outcome was the LBR, while the CPR and MR were secondary outcomes. All outcomes were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Live birth was defined as any birth event in which at least one baby was born alive. Clinical pregnancy was defined as the presence of at least one intrauterine gestational sac as visualized by US. Miscarriage was defined as the loss of a clinical pregnancy before 12 weeks of gestation. All the included studies defined one of the three outcomes and were excluded if they did not adhere to the definition or did not define their outcomes.

2.4 | Data analysis

Data were analyzed using Review Manager, version 5.3 (The Cochrane Collaboration, Software Update, London, UK). Dichotomous variables were analyzed using ORs. The significance level was set at $p < 0.05$.

Study heterogeneity was evaluated using I^2 statistic and rated as follows: $I^2 < 30\%$, low; $I^2 = 30\%–50\%$, moderate; or $I^2 > 50\%$, high. If the heterogeneity was low, the fixed-effects model was used to analyze the overall effect; otherwise, the random-effects model was used. To further observe the heterogeneity, forest plots were generated.

We also performed prespecified subgroup analyses of the following baseline variables: asymptomatic vs symptomatic vs combined asymptomatic and symptomatic adenomyosis; and definite diffuse adenomyosis vs focal and diffuse adenomyosis.

Two reviewers (W. X. and X. Z.) independently judged the methodological quality of the included studies using the Newcastle-Ottawa scale (Table S2). To assess the quality of the studies, we assigned stars to indicate their risk of bias, with the highest quality studies receiving up to nine stars. We awarded in three domains: (1) selection of study groups (4 points), (2) comparability of groups (2 points), and (3) ascertainment of exposure and outcomes (3 points) for case control and cohort studies, respectively. For ranking the adequacy of comparability, we awarded one star to studies if the case group and the control group were matched by age or there was no statistical difference between the two groups. Furthermore, studies controlling for other significant confounders or comparisons of other significant confounders between the two groups of population were not statistically different; another star was awarded. We considered studies with a total score of seven or more stars as high quality, a score between four to six as moderate quality and one to three as low quality of assessment.

We evaluated the quality of the body of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) handbook.[6] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

3 | RESULTS

The process of literature identification and study selection is shown in Figure 1. A total of 477 potentially relevant studies were identified through a literature search. After removing 302 duplicates and excluding 97 studies based on the title and abstract screening, 78 articles were fully reviewed, of which 18 were deemed eligible for final quantitative analysis. The US features used in the diagnosis of adenomyosis in the included studies were as follows: myometrial cysts (12/13), myometrial wall asymmetry (9/13), irregular endometrial–myometrial junction (9/13), heterogeneous echogenicity (9/13), linear striations radiating out from the myometrium (9/13), global uterine enlargement (5/13), fan-shaped shadowing (3/13), ill-defined myometrial lesions (1/13), subendometrial echogenic nodules (1/13), hyperechoic islands (1/13), and adenomyomas (1/13).[7–19] Furthermore, only two studies used three-dimensional US and only one study descripted sonographic features in accordance with terms defined by the morphological uterus sonographic assessment

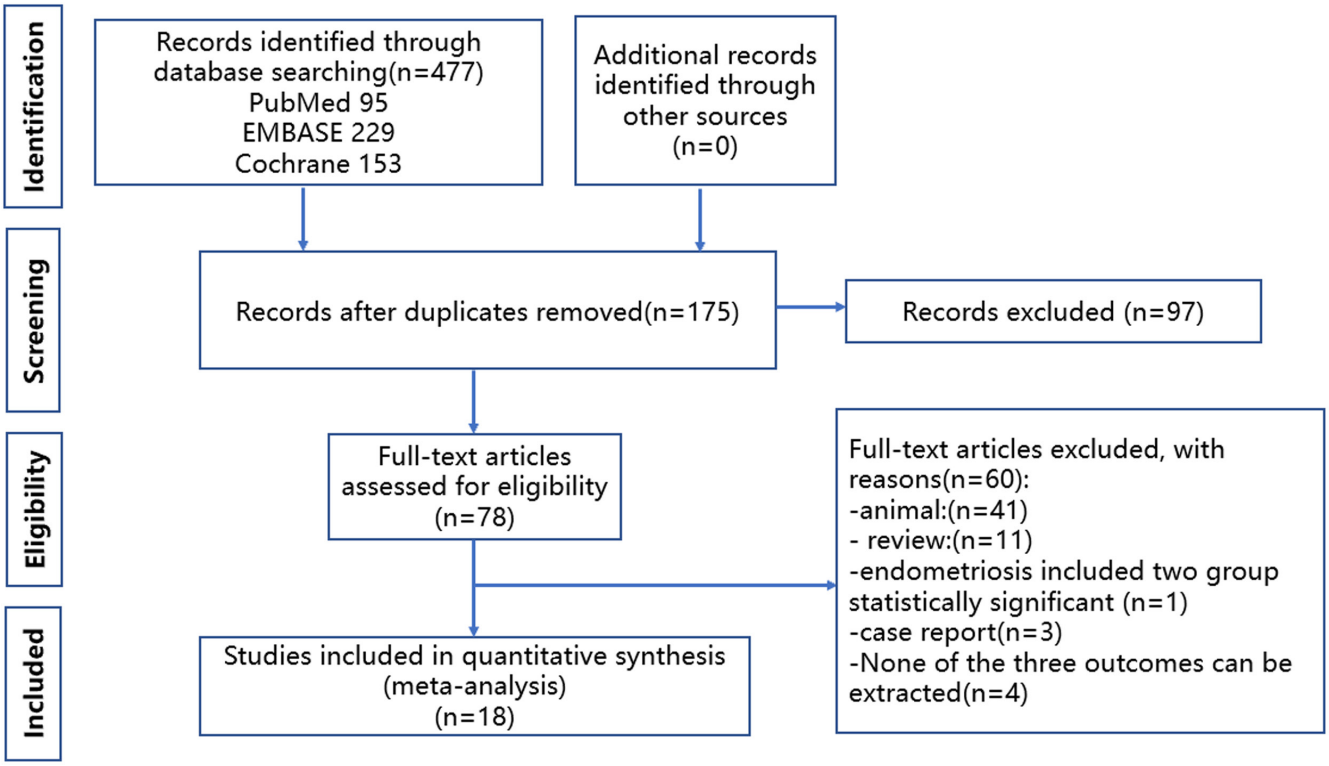

FIGURE 1 PRISMA flow diagram.

(MUSA) group. The characteristics of the studies included in the quantitative analysis are summarized in Table 1.

For the analysis of the impact of adenomyosis as diagnosed by US on IVF outcomes, data from nine studies that included 2240 women with and 15022 women without adenomyosis as diagnosed by US were included for LBR analysis, while data from 13 studies that included 2758 women with and 16536 women without adenomyosis as diagnosed by US were included for CPR and 1806 women with and 13040 women without adenomyosis as diagnosed by US were included for MR analysis.

Compared with women without adenomyosis as diagnosed by US, those with adenomyosis as diagnosed by US had a lower LBR (random-effects OR = 0.66; 95% CI: 0.53–0.82; $p < 0.0001$, grade: very low, Figure 2A), lower CPR (random-effects OR = 0.64; 95% CI: 0.53–0.77; $p < 0.0001$, grade: very low, Figure 2B), and higher MR (random-effects OR = 1.81; 95% CI: 1.35–2.44; $p < 0.0001$, grade: very low, Figure 2C). All related studies had high or moderate heterogeneity, with an I^2 of 70, 70, and 59%, respectively. However, the subgroup analysis according to symptoms showed that asymptomatic adenomyosis as diagnosed by US was not associated with the LBR (OR = 1.46; 95% CI: 0.75–2.86, grade: low), CPR (OR = 1.48; 95% CI: 0.94–2.32, grade: low), or MR (OR = 1.24; 95% CI: 0.65–2.35, grade: low), while symptomatic adenomyosis as diagnosed by US had a negative effect on IVF outcomes, with lower LBR (OR = 0.57; 95% CI: 0.34–0.96, grade: very low), lower CPR (OR = 0.69; 95% CI: 0.57–0.85, grade: low), and higher MR (OR = 2.48; 95% CI: 1.28–4.82, grade: low). In the subgroup analysis according to the type of adenomyosis (diffuse vs. all types), diffuse adenomyosis as diagnosed by US was associated with a lower LBR (OR = 0.37; 95% CI: 0.23–0.59, grade: low) and lower CPR (OR = 0.50; 95% CI: 0.34–0.75, grade: low), but showed no association with the MR (OR = 2.18; 95% CI: 0.72–6.62, grade: very low). The above results are shown in Figure 2 and the grade evidence profile for outcomes are shown in Table S3.

For the analysis of the impact of concurrent endometriosis on the IVF outcomes of adenomyosis, data from two studies that included 121 women with adenomyosis and endometriosis and 149 women with adenomyosis alone were included for LBR and CRP analysis, while those of 53 women with adenomyosis and 100 women without adenomyosis were included for MR analysis. Four studies investigated the effect of adenomyosis in patients with endometriosis; data from two studies that included 230 women with endometriosis and adenomyosis and 117 women with endometriosis alone were included for LBR analysis, data from three studies that included 126 women with endometriosis and adenomyosis and 168 women with endometriosis alone were included for CPR analysis, while those of 96 women with endometriosis and adenomyosis and 90 women with endometriosis alone were included for MR analysis.

The results showed that concurrent endometriosis had no effect on the IVF outcomes in women with MRI- or TVUS-diagnosed adenomyosis: LBR (OR = 1.45; 95% CI: 0.55–3.81, grade: low), CPR (OR = 1.47; 95% CI, 0.58–3.78, grade: very low), and MR (OR = 0.77; 95% CI: 0.27–2.20; grade: low).[10,20] The above results are shown in Figure 3. However, the presence of adenomyosis in patients with endometriosis resulted in a lower LBR (OR = 0.44; 95% CI: 0.26–0.75, grade: low) than that in women with endometriosis alone but

TABLE 1 Main characteristics of the included studies.

Study	Study design	Age (years)	Stimulation protocol	Symptoms	Diagnostic method and criteria	Subtypes of AM	Outcomes	Quality of evidence[a]
Impact of transvaginal US diagnosis of AM on IVF outcomes								
Benaglia et al. (2014)[6]	Prospective cohort study	35 ± 4 (AM+) vs. 35 ± 4 (AM−)	Long protocol GnRHa, short protocol, and others	Asymptomatic	2D-US/AM was diagnosed when asymmetrical thickening of the anterior and posterior walls of myometrium was identified or irregular cystic areas were found within the myometrium or linear striations radiating out from the myometrium or irregular EMJ was observed.	Focal ($n = 24$) and diffuse ($n = 25$)	LBR CPR MR	9
Neal et al. (2020)[7]	Prospective cohort study	37.1 ± 5.2 (AM+) vs. 35.9 ± 4.6 (AM−)	Synthetic/ natural/ long protocol GnRHa	Asymptomatic	3D-US/MUSA group: global uterine enlargement, myometrial wall asymmetry, heterogeneous echogenicity, irregular EMJ, myometrial cysts, fan-shaped shadowing and ill-defined myometrial lesions, as the presence of ≥1 sonographic feature has been diagnosed as AM.	N/A	LBR CPR MR	8
Hou et al. (2020)[8]	Retrospective cohort study	31.8 (29–34) (AM+) vs. 31.6 (29–34) (AM−)	Long or ultra-long GnRH agonist treatment	Symptomatic progressive, secondary dysmenorrhea, and menorrhagia	2D-US/The diagnostic criteria for AM included clinical symptoms, clinical signs, and more than two of the following five features (no distinction of the EMJ; asymmetry of the anterior and posterior myometrium; subendometrial myometrial striations; myometrial cysts and fibrosis; and heterogeneous myometrial echotexture)	N/A	LBR CPR MR	8
Sharma et al. (2019)[9]	Retrospective cohort study	32.8 ± 2.9 (AM+) vs. 33.0 ± 3.4 (AM−)	Long protocol GnRHa	Symptomatic	2D-US/AM was diagnosed when at least three sonographic criteria, such as globular uterus; asymmetrically thickened anterior or posterior myometrial wall; poorly defined EMJ; presence of heterogeneous myometrial area and myometrial cysts.	Diffuse	LBR CPR MR	8
Chiang et al. (1999)[10]	Prospective cohort study	36.0 ± 2.6 (AM+) vs. 35.4 ± 2.8 (AM−)	Long protocol GnRHa and short protocol	N/A	2D-US/The presence of a diffusely enlarged uterus and one or more heterogeneous myometrial areas not encapsulated and within round anechoic areas 1–3 mm in diameter.	Diffuse	LBR CPR MR	7
Costello et al. (2011)[11]	Retrospective cohort study	39.0 (27–42) (AM+) vs. 34.6 (18–42) (AM−)	Long agonist	N/A	2D-US /The presence of AM according to the following criteria: (i) subjective enlargement of the uterine corpus, (ii) heterogeneity of myometrium/hypoechoic striations, (iii) asymmetrically thickened myometrium between anterior and posterior walls, (iv) myometrial cysts, or (v) poor definition of EMJ. Criteria (i) and (ii) were mandatory for a diagnosis of AM. The remainder of the criteria were used to confirm the presence of AM and not all were required for a diagnosis of AM.	N/A	LBR CPR MR	7

(Continues)

TABLE 1 (Continued)

Study	Study design	Age (years)	Stimulation protocol	Symptoms	Diagnostic method and criteria	Subtypes of AM	Outcomes	Quality of evidence[a]
Youm et al. (2011)[15]	Retrospective cohort study	33.6 ± 3.7 (AM+) vs. 33.0 ± 3.7 (AM−)	Short agonist	N/A	2D-US/The sonographic findings suggestive of AM such as myometrial striations, heterogeneous myometrium, myometrial cysts, and poor definition of the EMJ, were examined.	Diffuse	LBR CPR MR	7
Zhang et al. (2021)[16]	Prospective cohort study	34.0 ± 4.0 (AM+) vs. 33.7 ± 3.6 (AM−)	Short GnRHa, GnRHa, or long GnRHa protocol	N/A	2D-US/AM could be diagnosed if US showed three or more of the following features: uterine enlargement, asymmetrical myometrial thickening, presence of heterogeneous myometrial areas, findings of myometrial cysts, presence of echogenic striations in the subendometrium, subendometrial echogenic nodules, irregular EMJ, and poor definition and thickening of the EMJ.	N/A	LBR CPR MR	8
Trinchant et al. (2022)[18]	Retrospective multicenter, cohort study	42.6 (42.1–43.1) (AM+) vs. 41.3(41.2–41.5) (AM−)	Oocyte donation protocol with HRT	N/A	2D-US/Diffuse AM was diagnosed when irregular EMJ, ill-defined myometrial heterogeneity, presence of round anechoic myometrial cysts, and/or asymmetrical thickening of anterior and posterior walls of myometrium were detected.	Focal ($n = 24$) and diffuse ($n = 155$)	LBR CPR MR	9
Martínez-Conejero et al. (2011)[12]	Retrospective cohort study	40.5 (39.8–41.3) (AM+) vs. 40.9 (40.3–41.6) (AM−)	Oocyte donation protocol with HRT	N/A	2D-US/The criteria for sonographic diagnosis of AM included hypoechogenic and heterogeneous areas with decreased echogenicity associated with elliptic intramyometrial lakes of more than 2 mm in diameter in a globular-appearing uterus.	N/A	CPR MR	8
Mavrelos et al. (2017)[13]	Prospective cohort study	36.0 (33.0–38.7) (AM+) vs. 34.0 (31.0–37.0) (AM−)	Long GnRHa protocol	N/A	2D-US and 3D-US/ a patient could be diagnosed with AM if ultrasound imaging showed one or more of the following criteria: (i) asymmetrical myometrial thickening; (ii) parallel shadowing; (iii) linear striations; (iv) myometrial cysts; (v) hyperechoic islands; (vi) adenomyomas; (vii) irregular EMJ.	N/A	CPR MR	7
Salim et al. (2012)[14]	Prospective cohort study	34.6 ± 4.1 (AM+) vs. 34.0 ± 3.7 (AM−)	Long GnRHa protocol	Menorrhagia (3), dysmenorrhea (3), and asymptomatic (13)	2D-US/AM was only diagnosed when there was asymmetrical thickening of the myometrium, irregular cystic areas within the myometrium and linear striations radiating out from the myometrium.	N/A	CPR MR	7
Thalluri et al. (2012)[17]	Retrospective cohort study	35 (32.7–37.3) (AM+) vs. 33 (30–36) (AM−)	Antagonist protocol	N/A	2D-US/The presence of an enlarged "globular" uterus in the absence of fibroids, asymmetric thickening of the anterior or posterior myometrial wall, heterogeneous poorly circumscribed areas within the myometrium, anechoic myometrial blood-filled lacunae or cysts of varying sizes, increased echo-texture of the endometrium and subendometrial linear striations.	N/A	CPR MR	7

TABLE 1 (Continued)

Study	Study design	Age (years)	Stimulation protocol	Symptoms	Diagnostic method and criteria	Subtypes of AM	Outcomes	Quality of evidence[a]
Comparing IVF outcomes between women with AM or AM combined with EM								
Rees et al. (2022)[19]	Retrospective cohort study	33.7 ± 3.6 (AM+ and EM+) vs. 31.4 ± 4.4 (AM+)	Gonal-F, Menopurfostimon and others	Dysmenorrhea (8), asymptomatic (15), not reported (13)	MRI/MRI criteria for the presence of AM were focal or diffuse JZ thickening >12 mm, JZ/myometrium ratio > 40%, and/or presence of high signal intensity myometrial foci on T1/T2 corresponding to an adenomyotic cyst (>2 mm in diameter).	Focal ($n = 16$) and diffuse ($n = 5$)	LBR CPR MR	9
Comparing IVF outcomes between women with EM or EM combined with AM								
Bourdon et al. (2022)[20]	Retrospective cohort study	N/A	N/A	N/A	MRI/AM was defined by the association of the following two criteria: a JZmax of at least 12 mm and a ratio max >40% or disseminated and localized subendometrial lesions without JZ hypertrophy (<12 mm).	Unambiguous data cannot be extracted	LBR	7
Mijatovic et al. (2010)[21]	Retrospective cohort study	N/A	Long GnRHa protocol	N/A	2D-US/The diagnosis of AM was established by applying three or more of the following sonographic features: asymmetry of uterine walls without the presence of leiomyomas; myometrial areas of heterogenous echogenicity with poorly defined borders; minimal mass effect on the endometrium or the serosa which is relative to the size of the myometrial lesion; small myometrial cysts or hemorrhagic foci within the heterotopic endometrial tissue; echogenic nodules or linear striations radiating out from the endometrium into the myometrium; absence of circular vascularization (determined by color Doppler) at the border of the lesion.	N/A	CPR MR	7
Ballester et al. (2012)[22]	Prospective multicenter cohort study	N/A	Long GnRHa, short GnRHa and antagonist protocol	N/A	MRI/AM was defined by: (i) maximal EMJ (EMJ max) of at least 12 mm, (ii) ratiomax (JZ max/myometrial thickness). 40% and (iii) punctate high-density myometrial foci.	Unambiguous data cannot be extracted	CPR	7
Impact of MRI or MRI combined with US for diagnosis of AM on IVF outcomes								
Stanekova et al. (2018)[23]	Retrospective cohort study	37.0 ± 4.0 (AM+) vs. 35.9 ± 4.6 (AM−)	Ultra-long GnRH agonist	N/A	2D-US combined with MRI/enlarged globular uterus, heterogenous myometrium, subendometrial myometrial striations and cysts, asymmetrical thickening of uterine walls, poorly defined (EMJ) and with an area of 2 cm or more of AM being required for a positive diagnosis. In the event of uncertainty, a pelvic MRI was performed to confirm or refute the diagnosis of AM (JZ 12 mm or greater, subendometrial cysts).	N/A	LBR CPR MR	8

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; AM, adenomyosis; CPR, clinical pregnancy rate; EM, endometriosis; EMJ/JZ, endometrial–myometrial junction/junctional zone; GnRHa, gonadotrophin releasing hormone analog; HRT, assisted reproductive technology; IVF, in vitro fertilization; LBR, live birth rate; MR, miscarriage rate; MUSA group, morphological uterus sonographic assessment group; N/A, not applicable; US, ultrasound.

[a]1 to 3-low quality; 4 to 6-moderate quality; 7 to 9-high quality of assessment.

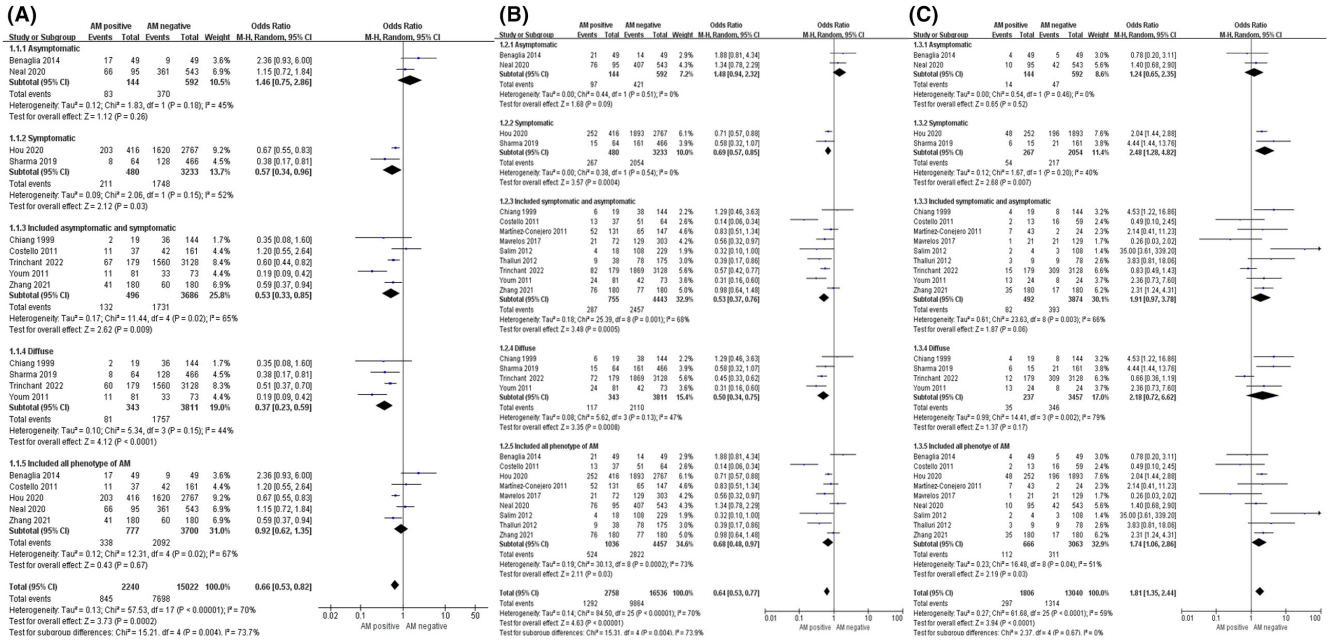

FIGURE 2 Association between in vitro fertilization outcomes and ultrasound-diagnosed adenomyosis. (A) Live birth rate, (B) clinical pregnancy rate, and (C) miscarriage rate. Women with adenomyosis as diagnosed by ultrasound (US) had lower LBRs and CPRs and higher MRs than women without adenomyosis as diagnosed by US. However, asymptomatic adenomyosis as diagnosed by US was not associated with IVF outcomes, while symptomatic adenomyosis as diagnosed by US had a negative effect on IVF outcomes, with lower LBRs and CPRs and higher MRs. In addition, diffuse adenomyosis as diagnosed by US was associated with lower LBRs and CPRs, but not with the MR. CPR, clinical pregnancy rate; IVF, in vitro fertilization; LBR, live birth rate; MR, miscarriage rate; US-diagnosed AM, ultrasound-diagnosed adenomyosis.

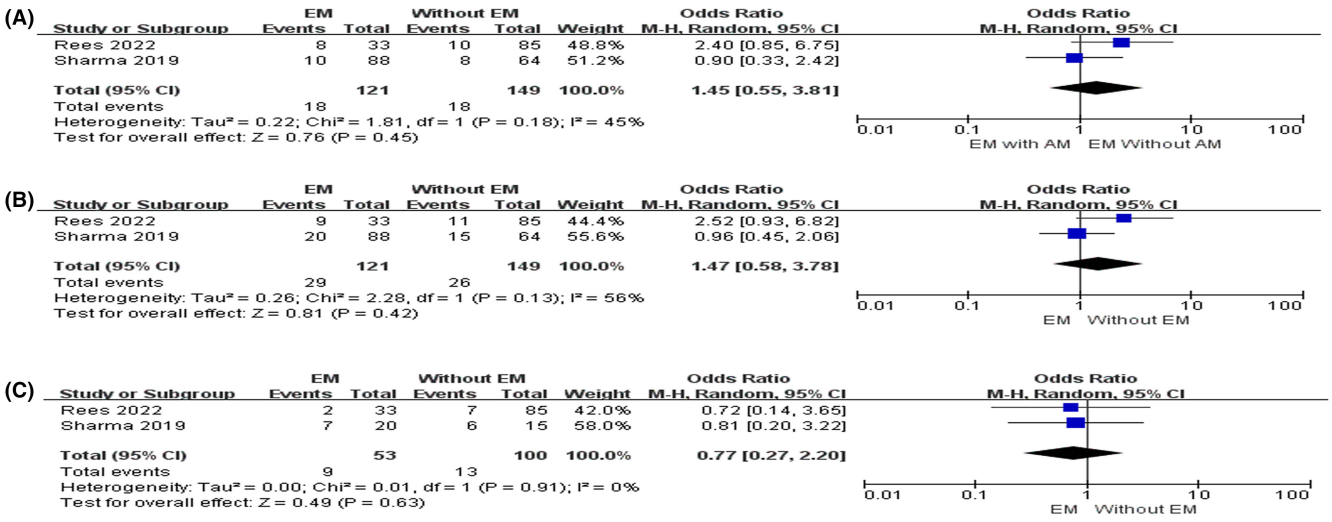

FIGURE 3 Comparison of in vitro fertilization outcomes between women with adenomyosis combined with endometriosis and those with adenomyosis alone. (A) Live birth rate, (B) clinical pregnancy rate, and (C) miscarriage rate. There was no significant difference in the LBR, CPR, or MR according to the presence of endometriosis. CPR, clinical pregnancy rate; IVF, in vitro fertilization; LBR, live birth rate; MR, miscarriage rate.

showed no association with the CPR (OR = 0.51; 95% CI, 0.20–1.29, grade: very low) and MR (OR = 1.24; 95% CI: 0.32–4.79; grade: low).[20–23] The above results are shown in Figure 4 and the grade evidence profile for outcomes are shown in Table S3.

For the analysis of the impact of MRI-based diagnosis of adenomyosis on IVF outcomes, two studies were included, with data from 67 women with and 190 women without adenomyosis for LBR and CPR analysis; of these 52 women with and 169 women without adenomyosis were included in the MR analysis.

Adenomyosis diagnosed by MRI or both MRI and TVUS was not associated with the LBR (OR = 0.43; 95% CI: 0.11–1.69, grade: very low), CPR (OR = 0.46; 95% CI: 0.11–1.84, grade: very low), or MR (OR = 1.78; 95% CI: 0.42–7.59; grade: very low).[20,24] The above results are shown in Figure 5 and the grade evidence profile for outcomes are shown in Table S3.

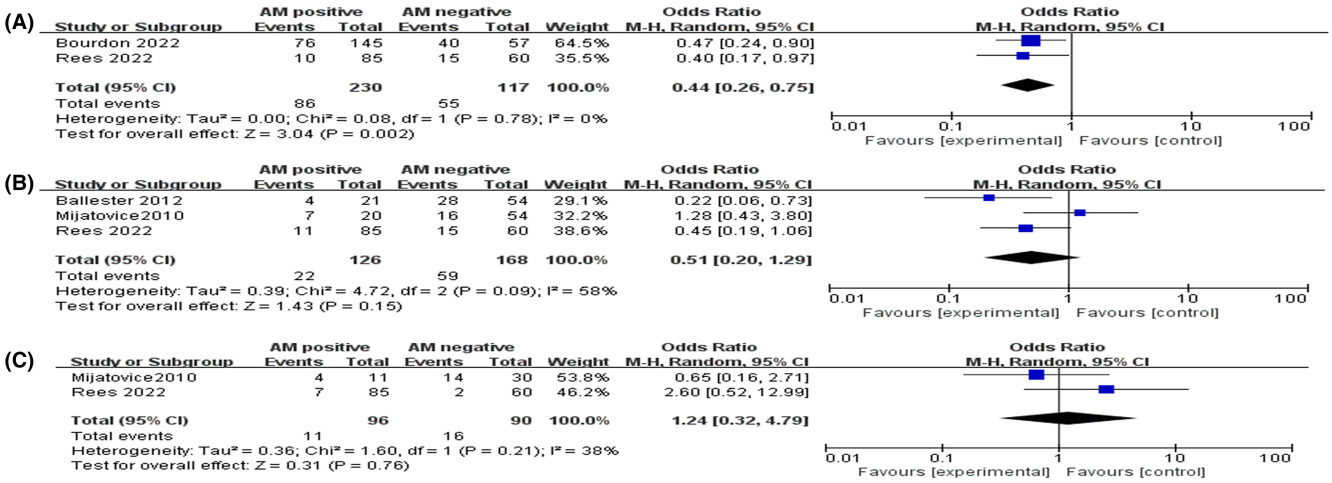

FIGURE 4 Comparison of in vitro fertilization outcomes between women with endometriosis combined with adenomyosis and those with endometriosis alone. (A) Live birth rate, (B) clinical pregnancy rate, and (C) miscarriage rate. Women with endometriosis and concurrent adenomyosis had a lower LBR than those with endometriosis alone. CPR, clinical pregnancy rate; IVF, in vitro fertilization; LBR, live birth rate; MR, miscarriage rate.

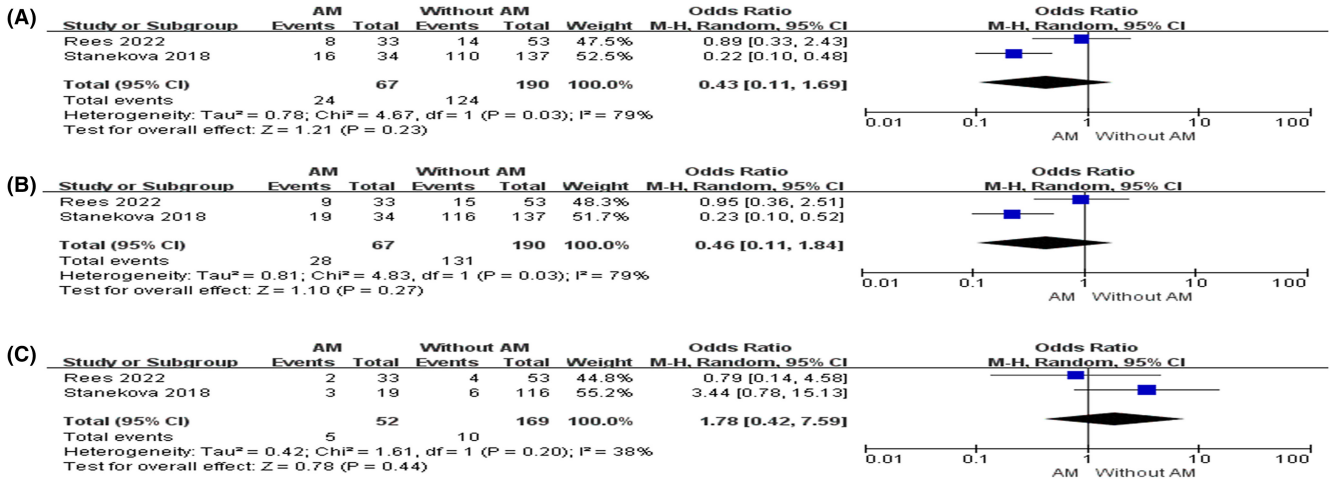

FIGURE 5 Overall association between in vitro fertilization outcomes and MRI or MRI combined with ultrasound (US) in the diagnosis of adenomyosis. (A) Live birth rate, (B) clinical pregnancy rate, and (C) miscarriage rate. Diagnosing adenomyosis using MRI or MRI combined with US did not have a significant effect on IVF outcomes. CPR, clinical pregnancy rate; IVF, in vitro fertilization; LBR, live birth rate; MR, miscarriage rate.

4 | DISCUSSION

The key findings of our study indicate that patients diagnosed with adenomyosis by US may have poorer IVF outcomes than those without the condition. Our analysis also reveals that symptomatic and diffuse adenomyosis, but not asymptomatic adenomyosis diagnosis by US, may adversely impact IVF outcomes. Furthermore, concurrent adenomyosis in women with endometriosis may affect the LBR; however, concurrent endometriosis in women with adenomyosis may have no negative effect on IVF outcomes. Finally, MRI or MRI combined with US used for the diagnosis of adenomyosis was not associated with IVF outcomes.

With the increasing availability of imaging techniques, the prevalence of adenomyosis has been estimated not only in patients undergoing hysterectomy, but also in patients undergoing gynecological TVUS examination. Most patients with adenomyosis undergoing IVF receive medical treatment and have no histological evidence of the disease. Presently, adenomyosis diagnosis is based on features of two-dimensional (or three-dimensional) TVUS, although there is no consensus on the TVUS features of adenomyosis.[25] Therefore, TVUS is crucial for the diagnosis and IVF treatment in adenomyosis. However, from a clinical perspective, an optimal imaging technique should help determine the best treatment modality, besides facilitating accurate diagnosis.

We agree with other groups that adenomyosis should be part of the differential diagnosis in patients with infertility at the first consultation. While there may be benefits from surgical treatment of adenomyosis before IVF, resection may be incomplete in case of lack of capsule, and the risk of uterine rupture during pregnancy may

be higher.[26] Therefore, surgery may not be recommended for patients with infertility without symptoms. Furthermore, several studies demonstrated no difference in pregnancy outcomes between women with and those without US-diagnosed adenomyosis undergoing long-term downregulation ovarian stimulation.[7] In addition, a systematic review and meta-analysis targeting IVF outcomes reported that symptomatic patients with adenomyosis had lower CPRs and higher MRs, which is consistent with our results.[27] Hence, in our opinion, women with asymptomatic US-diagnosed adenomyosis should be appropriately reassured that this finding may be incidental.

In the present study, patients with adenomyosis had poorer IVF outcomes than those without adenomyosis, which is in accordance with the findings of a preceding meta-analysis, but with higher heterogeneity of the included studies.[2] Notably, our study has an important difference from the previous meta-analysis. Namely, our subgroup analysis findings demonstrated for the first time that asymptomatic adenomyosis diagnosed by US may not have a significant impact on the chances of IVF success, which supports the negative impact of symptomatic adenomyosis diagnosed by US on IVF outcomes, as indicated by lower LBRs, CPRs, and higher MRs. Therefore, we concluded that additional therapy may not be necessary for asymptomatic adenomyosis diagnosed by US may not affect the chances of IVF success. Based on our findings, different treatment regimens for symptomatic vs asymptomatic patients with US-diagnosed adenomyosis may contribute to better counseling for couples with infertility planning IVF. Patients with symptomatic adenomyosis, may benefit from an ultra-long gonadotrophin releasing hormone-agonist protocol, despite experiencing stronger pituitary inhibition and lower ovarian responses than those treated with a long gonadotrophin releasing hormone-agonist protocol. These findings suggest that the former protocol may result in better IVF outcomes. However, large, well-designed multicenter randomized controlled trials for adenomyosis are required in the future.

Advances in TVUS have facilitated the diagnose of different phenotypes of adenomyosis (diffuse or focal).[28] In this study, we attempted to extract data on diffuse adenomyosis, and the subgroup analysis results demonstrated a significant decrease in overall heterogeneity. Diffuse adenomyosis had an association with lower LBRs and CPRs. The differences in biological properties between focal and diffuse adenomyosis are not well understood and information is scarce. A study attempting to elucidate the mechanism of hormonal resistance in adenomyosis reported the absence of reduced estrogen and progesterone receptor expression in response to gonadotrophin releasing hormone agonists in adenomyotic tissues in women with diffuse adenomyosis, while those with focal adenomyosis responded to the treatment, which supports our findings. The 2015 MUSA criteria provide detailed, comprehensive, and unified definitions of diffuse, focal, and mixed-type adenomyosis.[29] Unfortunately, no studies to date have investigated the impact of different subtypes of US-diagnosed adenomyosis on IVF outcomes based on these criteria. In our opinion, a comprehensive, clear, and universal classification of adenomyosis, including pattern, location, and histological variation, is warranted. Sonographers and clinicians should be more aware of subtypes of adenomyosis based on US in patients undergoing infertility testing in preparation for IVF.

Furthermore, adenomyosis often coexists with endometriosis. Our results showed that the existence of endometriosis in women with adenomyosis as the primary complaint does not increase the risk of negative IVF outcomes. However, in women with endometriosis as the primary complaint, concurrent adenomyosis was associated with a lower LBR than that in endometriosis alone. Thus, adenomyosis may be a crucial factor to be considered when combined with endometriosis. Endometriosis-related infertility may be associated with ovarian damage, while adenomyosis may lead to infertility by disturbing the endometrial environment by causing aberrant uterine contractions, abnormal myometrial activity, and deranged endometrial milieu with altered expression of implantation factors. Considering that patients undergoing IVF treatment have adjusted to good ovarian function, adenomyosis seems to affect fertility even in the absence of endometriosis. Hence, our findings suggest that adenomyosis possibly remains a priority consideration for obstetricians and gynecologists when planning IVF treatment, even when comorbid with endometriosis.

In a prior meta-analysis, Liu et al. demonstrated that both TVUS and MRI had high and comparable accuracy in diagnosing adenomyosis.[30] In this study, we found that using MRI or MRI combined with TVUS did not negatively affect IVF outcomes; however, it was also not conducive to predicting IVF outcomes in women with adenomyosis. Although the available evidence was of a very low-grade and insufficient (only two studies), the results are still promising. TVUS may have better sensitivity in diagnosing adenomyosis, while MRI has more advantages in diagnosing endometriosis. Based on the available data, adenomyosis may be an important factor that should be considered for IVF treatment. Therefore, improving the diagnostic accuracy of TVUS for adenomyosis may be a possible breakthrough point for future research. We speculate that standardized US according to internationally recognized criteria would be more beneficial for the diagnosis of adenomyosis. For better patient management, we reiterate the importance of TVUS in the assessment of adenomyosis, while MRI should be recommended if screening for endometriosis is necessary.

The strength of our study is that it is the first meta-analysis to date to analyze the impact of adenomyosis on IVF outcomes in consideration of the adenomyosis type, symptoms, and diagnostic methods. However, there are also some limitations to this analysis. First, the results on the effect of MRI or MRI combined with US on IVF outcomes when used for adenomyosis diagnosis should be interpreted with caution because the statistical power was limited and data on adenomyosis subtypes were unavailable. Second, we did not determine the impact on IVF outcomes in focal US-diagnosed adenomyosis because there were no available data that clearly focused on focal adenomyosis. Third, as the analysis of the effect of concurrent endometriosis was based on limited studies, further research is needed to draw firm conclusions. Fourth, because of the observational nature of the included studies, residual or unmeasured

confounding factors cannot be excluded, which limits any conclusions on the causality of the identified associations. Fifth, the inclusion of studies that did not report live births as the primary outcome may constitute a major source of bias, given that live birth rate was the primary outcome of interest. Sixth, even transient changes in the myometrium can simulate adenomyosis, making the interobserver agreement about the sonographic diagnosis very poor. Last, there is no consensus on the diagnostic criteria for adenomyosis, and as the diagnostic criteria are not well defined, this issue can result in heterogeneity.

5 | CONCLUSION

Our findings suggest that asymptomatic adenomyosis diagnosed by TVUS may not have a significant impact on IVF outcomes indicating that additional therapy for this condition may not be necessary. Furthermore, adenomyosis possibly remains a priority consideration for obstetricians and gynecologists when planning IVF treatment, especially in the presence of endometriosis. Moreover, diffuse and symptomatic adenomyosis may have important implications for the IVF outcomes in patients with adenomyosis. Evaluation of individual MUAS criteria and adoption of standardized reporting guidelines in the assessment of adenomyosis using TVUS may contribute to improving individualized treatment, determining the correct approach to IVF treatment, and favorable pregnancy outcomes.

AUTHOR CONTRIBUTIONS

SL, GL and XW conceived and designed the study; XW, ZX, and YH screened and selected the articles; XW and ZX extracted the data; XW and YH assessed the risk of bias; XW analyzed the data; ZX and YH supervised the data analyses and rated the certainty of evidence; XW and SL interpreted the data; XW drafted the manuscript; SL and GL revised the manuscript for important intellectual content. All authors have access to all study data and agree to the decision to submit the manuscript for publication.

FUNDING INFORMATION

This work was supported by the Quanzhou City Science and Technology Program of China (grant no. 2020N057s) and Quanzhou City Science and Technology Bureau (grant no. 2020CT003).

CONFLICT OF INTEREST STATEMENT

The authors declare there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The analytic dataset is available on request by contacting the corresponding author.

ORCID

Guo-Rong Lyu https://orcid.org/0000-0003-3123-1138

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SUPPORTING INFORMATION

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

How to cite this article: Wang X-L, Xu Z-W, Huang Y-Y, Lin S, Lyu G-R. Different subtypes of ultrasound-diagnosed adenomyosis and in vitro fertilization outcomes: A systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2023;102:657-668. doi:10.1111/aogs.14580