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Fertility, Pregnancy Rate, and Neonatal Outcome of Patient with Adenomyosis

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ABSTRACT

This study aimed to look at the link between adenomyosis and fertility, pregnancy, and neonatal outcomes. Until April 2022, an electronic search was conducted utilizing the Medline, Pubmed, and Cochrane databases. There were seventeen observational studies in total. After assisted reproductive technology, adenomyosis was linked to a reduced clinical pregnancy rate (OR 0.69; 95 percent CI 0.51, 0.94) and a greater miscarriage rate (OR 2.17; 95 percent CI 1.25, 3.79) (ART). The lower clinical pregnancy rate was more substantial in the subset of individuals with brief downregulation regimens. Similar relationships were seen after age adjustment. Preeclampsia, premature delivery, cesarean section, fetal malpresentation, small-for-gestational-age infancy, and postpartum hemorrhage were also substantially linked to adenomyosis, which was confirmed after adjusting for age and mode of conception. Finally, adenomyosis is a disease that affects the muscles.

Keywords: Adenomyosis, fertility, pregnancy rate.

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I. Introduction

Adenomyosis is a perplexing gynecological condition characterized by endometrial epithelial and stromal cells within the myometrium. It is a varied condition in terms of anatomical and clinical phenotype, ranging from a normal-sized uterus to a much-enlarged uterus, with symptoms ranging from heavy dysmenorrhea and hypermenorrhea to no symptoms. It is usually coexisting with endometriosis [1].

In addition to the well-known effects of endometriosis on pain and quality of life, it has recently been discovered that it can severely impact pregnancy and newborn outcomes. The detrimental connection persists even when endometriosis has been surgically removed [2].

In recent systematic research, adenomyosis has also been linked to poor conception, pregnancy, and neonatal outcomes [3]. However, this evaluation did not include all of the eligible papers. No sensitivity analysis was performed to account for potential confounders such as age, the number of previous pregnancies, the previous manner of delivery, and the presence of endometriosis. Most importantly, pregnancy outcomes were not evaluated based on the method of conception, which could be a source of bias given that ART is an independent risk factor for pregnancy issues and that many adenomyosis patients' pregnancies occur only after ART. Finally, ART and the type of stimulation regimen utilized may impact results [4].

Therefore, this study aimed to a) explore the relationship between adenomyosis and reproductive results using the ART stimulation protocol and adjusting for various variables, and b) examine the link between adenomyosis and pregnancy and neonatal outcomes.

II. Materials and Methods

We searched Medline, Pubmed, and Cochrane for all studies that met the criteria. ((pregnancy) OR (fertility) OR (neonatal outcomes) OR (assisted reproductive technologies)) AND (adenomyosis) Studies published in English through April 1, 2022, were included. Reference sections from relevant studies, important publications, and abstracts from the field's major yearly meetings were also looked through. To assess eligibility, the following criteria were used: 1) controlled trials evaluating both cases (women with adenomyosis) and controls, 2) description of adenomyosis diagnosis method and 3) existence of data on

fertility, pregnancy, or neonatal outcomes. Aside from full-text publications, data was acquired from additional sources (reviews, abstracts, oral presentations, and national or local health statistics).

We used a standardized data extraction form to extract information from each study, which included general study characteristics (author, year of publication, country, design, number of patients and controls, method of adenomyosis diagnosis, matching factors, and possible confounders), clinical characteristics of the patients (age, mode of conception, co-existence of endometriosis), and requested outcomes. To resolve differences, the consensus was used. If necessary, communication with the authors was used to complete the data set.

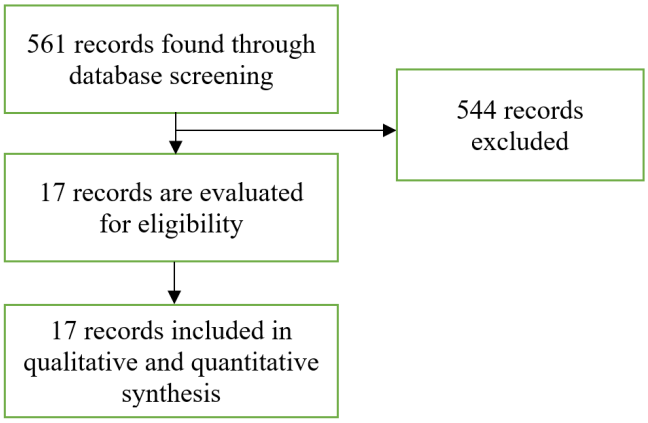

Fig. 1. PRISMA Flow Diagram

A. Fertility Outcomes after ART

According to the ART protocol, we divided eligible studies into subgroups. Only trials with an ultra-long or modified ultra-long pituitary downregulation procedure were included in the first grouping. Only trials with a brief downregulation technique were included in the second subgroup. The third group included trials that used a protracted GnRHa treatment (beginning in the initial mid-luteal phase) and studies that used several protocols.

The clinical pregnancy rate (3 studies, 209 vs. 1039 women, OR 0.78; 95 percent CI 0.45, 1.35), live birth rate (2 studies, 189 vs. 985 women, OR 0.64; 95 percent CI 0.19, 2.14), and miscarriage rate (2 studies, 189 vs. 985 women, OR 0.64; 95 percent CI 0.19, 2.14), as well as the miscarriage rate (3 studies, 209 vs. 10 (3 studies, 68 vs. 4048 pregnancies, OR 1.23; 95 percent CI 0.31, 4.91). The adenomyosis group had a lower clinical pregnancy rate (2 studies, 119 vs. 248 women, OR 0.34; 95 percent CI 0.20, 0.57) and a higher miscarriage rate (2 studies, 36 vs. 129 pregnancies, OR 4.32; 95 percent 1.77, 10.55), while only one study had data on the live birth rate (1 study, 81 vs. 73 women, OR 0.19 95 percent CI 0.19 (0.09, 0.42). There was no difference between the two groups in terms of clinical pregnancy rate (6 studies, 513 vs. 911 women, OR 0.84; 95 percent CI 0.58, 1.21) or live birth rate (3 studies, 145 vs. 270 women, OR 0.82; 95 percent CI 0.27, 2.49) in the third subgroup, but the adenomyosis group had a significantly higher miscarriage rate (5 studies, 410 vs. 643 pregnancies, OR 2.30; 95 percent 0.98, 5.39).

When all studies were taken into account, the adenomyosis group had a significantly lower clinical pregnancy rate (11 studies, 841 vs. 2198 women, OR 0.69; 95 percent CI 0.51, 0.94) and a significantly higher miscarriage rate (10 studies, 514 vs. 1176 women, OR 2.17; 95 percent 1.25, 3.79) and a significantly higher miscarriage rate (10 studies, 514 vs. 1176 women, OR The live birth rate between the two groups was not statistically significant (6 studies, 415 vs. 1328 women, OR 0.58; 95 percent CI 0.29, 1.17).

B. Pregnancy Outcomes

1) Preterm delivery

This result was based on data from six investigations. Two had significant age disparities between groups, although the results could be adjusted based on age [5], [6]. Two [7] and [8] mainly were matched for age, and one had no significant age differences between groups [9]. According to the meta-analysis, the adenomyosis group had a statistically significant greater risk of preterm delivery (6 studies, OR 2.65; 95 percent CI 2.07, 3.39).

2) Severe preterm delivery (< 32 weeks)

There was no significant difference between the two trials [7], [10]. (2 studies, 58 vs. 395 women; OR 2.20; 95 percent 0.45, 14.916).

3) Preeclampsia

Data from four investigations were used to arrive at this conclusion. Two groups were mainly age-matched, with no significant age disparities between them [7], [8]. According to the meta-analysis, women with adenomyosis had a much higher risk of developing cancer (4 studies, 159 vs. 785 women, OR 4.32; 95 percent CI 1.68, 11.09).

C. Obstetric Outcomes

1) Cesaeran section and malpresentation

Women with adenomyosis were shown to have a considerably higher risk in all investigations (4 studies, 462 vs. 101840 women; OR 2.48; 95 percent CI 1.44, 4.26) [6]. It was eliminated from a sensitivity analysis due to the case group's significantly greater age and ART rate, which could not be adjusted. Shin et al. were also eliminated since the case group had a much higher ART rate [9]. The meta-analysis of the remaining two trials [7], [8], which were unaffected by age or mode of birth, revealed that the adenomyosis group had a greater probability of cesarean section (2 studies, 51 vs. 112 women; OR 4.44; CI 2.64, 7.47). According to two studies, women with adenomyosis have a greater chance of prenatal malpresentation (2 studies, 79 vs. 386 women, OR 2.84; 95 percent CI 1.60, 5.81).

2) Operative vaginal delivery

Reference [7] was the only study having data on this outcome. According to the study, there was no statistically significant difference between the two groups (10 women following ART pregnancy vs. 16 women following ART pregnancy; OR 0.49; 95 percent CI 0.02, 13.28). (26 vs. 128 women after natural conception; OR 1.24; 95 percent CI 0.13, 11.57).

3) Postpartum, antepartum hemorrhage

According to the meta-analysis, the adenomyosis group had a considerably increased risk of PPH (3 studies, 101 vs. 637 women; OR 2.90; 1.39, 6.05). According to a single study, there was no significant difference in antepartum

hemorrhage between the two groups (22 vs. 251 women; OR 0.66; 95 percent CI 0.08, 5.17) [10].

D. Neonatal Outcome

1) Small for gestational age

This result was based on data from four investigations. In the study by Hashimoto et al. [8], the groups were matched for age and ART rate. Similarly, the study by [7] was mostly matched for age. However, the outcome could be extracted individually according to the manner of conception after they provided their raw data. Reference [6] gave results corrected for age and mode of conception. At the same time, the groups in [11] study were not substantially different in age and manner of conception. According to a meta-analysis of these four trials, the adenomyosis group had a considerably increased risk (4 studies, OR 2.86, 95 percent CI 1.68, 4.88). Only trials that were matched for endometriosis were included in the sensitivity analysis. In two investigations, SGA risk was considerably increased in patients with endometriosis (2 studies, OR 2.10; 95 percent CI 1.17, 3.77).

2) Low birth weight

A meta-analysis of two studies that included both natural and ART pregnancies found that the adenomyosis group had a higher risk of birth weights of less than 2500g (2 studies, OR 2.82, 95 percent CI 1.20, 6.62) and less than 1500g (2 studies, OR 5.67; 95 percent CI 0.91, 35.34) [6], [9]. Shin et al. looked at the risk of low birth weight (2500gr) in both ART and natural conception pregnancies [9]. In ART pregnancies, the adenomyosis group had a considerably greater risk (25 vs. 187 women; OR 7.69; 95 percent CI 2.56, 35.34). In natural conception pregnancies, however, there was no significant difference between the groups (47 vs. 8057 women; OR 2.16; 95 percent CI 0.67, 7.02).

3) Intrauterine growth restriction

Only one study reported data on this outcome, with the adenomyosis group having a considerably greater risk (22 vs. 251 women; OR 3.40; 95 percent CI 1.13, 10.17) [10].

4) Intrauterine fetal death

There was no difference between the two groups in a meta-analysis of two trials (2 studies, 58 vs. 395 women; OR 1.43; 0.34, 6.04) [7], [10].

III. Discussion

According to this systematic meta-analysis, adenomyosis is linked to a lower clinical pregnancy rate and a greater loss rate after ART, especially when the ovaries are stimulated with a brief GnRH agonist or antagonist protocol. Adenomyosis is linked to premature labor, preeclampsia, cesarean delivery, fetal malpresentation, SGA, low birth weight, and PPH. After accounting for age and mode of conception, the link could be substantiated.

A new systematic meta-analysis looked at adenomyosis patients' reproductive outcomes and discovered that the clinical pregnancy rate was lower [3]. Even though there was a lot of study heterogeneity, some papers were left out, and no subgroup analysis for potential confounders was done. The previous study has shown that the ovarian stimulation technique is critical for adenomyosis patients' reproductive success [12]. GnRHa therapies that last too long produce estrogen deficiency, inactivate adenomyosis for a short time, reduce uterine volume, and restore some altered endometrial functions [12], [13]. This phase of possibly therapeutic estrogen deficiency does not occur in GnRH antagonists or short GnRHa cycles. When brief downregulation approaches are applied by metaanalyzing the ART trials individually based on the stimulation protocol, adenomyosis has a more significant negative impact on the pregnancy rate. When the fertility outcomes were controlled for age, a significant confounder for fertility outcomes, a sensitivity study returned the same results.

Participants in one study were given a COC tablet for 21 days before starting GnRHa medication for at least ten days [14]. A COC-mediated effect on the endometrium may be essential in patients with adenomyosis, even if it is not considered an ultra-long ovarian downregulation. As a result, we classified this trial as a modified ultra-long downregulation study and meta-analyzed it alongside two additional studies [10], [15] that used a standard ultra-long GnRHa pretreatment. Regarding its preventive effect on adenomyosis, the results of the two investigations utilizing the conventional ultra-long GnRHa pretreatment were incongruent.

Furthermore, the results should be viewed with caution because control groups using ultra-long downregulation procedures have a lower clinical pregnancy rate (372/1039, 35.8%) than control groups using short downregulation protocols (2 studies, 120/248, 48%). The disparity in control groups could suggest different demographics or a negative effect of ultra-long GnRHa medication on control patients' pregnancy rate each cycle. Nonetheless, two retrospective controlled trials in patients with adenomyosis comparing GnRHa pretreatment to no treatment before fresh–embryo [16] and frozen–embryo transfer back up the tremendous advantage of ultra-long GnRHa pretreatment before ART [17].

Assume that prior to ART, the favorable effect of extended GnRHa on fertility had been established. In this scenario, concerns about severe ovarian suppression must be addressed, particularly in women with low ovarian reserve. Given recent advances in vitrification technology, which have resulted in higher embryo survival and pregnancy rates [18], it may be possible to vitrify embryos at the blastocyst stage to ensure proper development and then administer prolonged GnRHa before endometrial preparation to inactivate adenomyosis, reduce uterine volume, and possibly normalize some distorted endometrial functions. This would allay fears about severe ovarian suppression while allowing GnRHa to impact fertility positively. It is important to remember that frozen blastocyst transfers are connected to a higher risk of preeclampsia (RR 3.13, 95 percent CI 1.06–9.30, p=0.029) [19]. This danger must be evaluated against the approach mentioned above are possible benefits. Finally, whether alternative drugs with lower adverse effects, such as progestins, could be beneficial before ART is unknown.

Due to the following variables, the increased risk of cesarean birth in endometriosis patients should be approached with caution. The most comprehensive study was based on a patient-reported questionnaire collected during pregnancy for the diagnosis of adenomyosis, with substantial disparities in

age, primiparity, and sterility treatment found between groups [6]. The other studies suffer from the same lack of matching for potential confounders. This calls into question the existence of a different relationship between adenomyosis and the likelihood of cesarean birth. Despite this, a sensitivity analysis that included only two trials with balanced age and method of conception discovered a higher rate of cesarean section. This could be because adenomyosis patients have a higher rate of fetal malpresentation and placental malposition, both of which are causes of elective cesarean birth. It is unclear whether patients with adenomyosis are more likely to have a vaginal delivery fail and have a cesarean surgery.

Adenomyosis is a complex condition with a wide range of lesions, from widespread myometrial hypertrophy to more easily recognizable isolated lesions [20]. Adenomyosis has a varying effect on the reproductive process, depending on the degree of uterine involvement. The pooled findings revealed a statistically non-significant OR of 1.36 in favor of localized adenomyosis (CI: 0.67-2.75) [21]. Another prospective study [22] involved 152 women who underwent an MRI before beginning IVF therapy. A pregnancy rate of 63 percent was found in the group with a maximum junctional zone thickness of 10 mm, compared to 14 percent with a maximum junctional zone thickness of >10 mm. Patients with an average JZ thickness of >7 mm and a peak JZ of >10 mm had a 96 percent implant failure rate, compared to 38 percent in other patient groups. According to this study, the thickness of the JZ is linked to an increase in negative implantation outcomes. Unfortunately, our objective to address this issue was not successfully realized due to the various diagnostic criteria for adenomyosis and insufficient characterization and categorization of adenomyosis in independent investigations. Specific diagnostic criteria for adenomyosis have been established [23], and we strongly recommend their use in future studies to determine which adenomyosis traits are most relevant for the reproductive course. When inspecting and characterizing a uterus with adenomyosis by ultrasound, a recent article recommended looking at seven variables: existence, position, differentiation (focal/diffuse), appearance (cystic/non-cystic), uterine layer involvement, extent, and size of lesion [24]. An MRI-based classification method was used to differentiate internal adenomyosis, exterior adenomyosis, and structural-related adenomyoma subtypes, with a potential therapeutic strategy association [25].

IV. Conclusion

We discovered a relationship between adenomyosis and poor reproductive results, especially after the downregulation of the ART protocol. Although the results are insufficient for a compelling evaluation of the optimum ART technique, this association is less significant or absent in ART with mixed or ultra-long GnRHa protocols. Randomized controlled trials are now underway to provide accurate, definite data on the possible protective function of ultra-long GnRHa downregulation in adenomyosis. Adenomyosis during pregnancy is connected to preterm delivery, preeclampsia, cesarean section, fetal malpresentation, SGA, low birth weight, and PPH. Gynecologists should be aware of these hazards to advise on proper pregnancy management and recognize and treat pregnancy issues early. Matching, controlled trials with correct adenomyosis categorization are needed from fertility to postpartum time until we can study the influence of different adenomyosis subtypes and their therapy in every step of the reproductive course.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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