

## Association of Adenomyosis with Recurrent Miscarriage

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### Editorial

**Introduction:** Adenomyosis is the presence of endometrial glands and stroma within the myometrium. The exact pathogenesis of adenomyosis remains unclear, but several theories have been proposed. Common mechanisms include the invasion of the endometrium into the myometrium and the formation of adenomyotic foci from Müllerian remnants. Clinically, adenomyosis typically presents with heavy menstrual bleeding, dysmenorrhea, and diffuse uterine enlargement. However, definitive diagnosis requires histopathological examination, with adenomyosis findings present in 20–30% of hysterectomy specimens. Since a definitive diagnosis necessitates surgical tissue sampling, the exact prevalence of adenomyosis in the general population remains undetermined [1] ...

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Previous studies suggest that adenomyosis is more prevalent in nulliparous women and increases with age [2,3]. However, these findings may be biased due to diagnostic challenges associated with adenomyosis. Firstly, histopathological examination remains the gold standard for diagnosis, and older women are more likely to undergo surgery. In contrast, less invasive diagnostic tools, such as ultrasound, magnetic resonance imaging (MRI), and hysteroscopy, are preferred for younger women, offering the advantage of concurrent biopsy or treatment [4,5]. Secondly, the clinical manifestations of adenomyosis overlap with other gynecological conditions, such as endometriosis or fibroids, making differential diagnosis challenging. Lastly, no consensus exists regarding ultrasonographic diagnostic criteria for adenomyosis. Consequently, the prevalence of adenomyosis in younger women may be underestimated.

Some studies suggest a causal relationship between adenomyosis and infertility [6,7]. Several reports have highlighted the adverse effects of adenomyosis on assisted reproductive technology (ART) outcomes [8–10]. However, a recent study indicated that while adenomyosis does not impair embryo implantation, it significantly increases miscarriage rates following IVF with egg donation cycles [11].

Recurrent miscarriage (RM) is defined as two or more clinically documented pregnancy losses confirmed by ultrasound or histopathological examination. Possible causes of RM include uterine anomalies, immunological, genetic, endocrine, infectious, environmental, and thrombophilic factors. However, up to 50% of RM cases remain unexplained. Recently, Puente et al. screened a cohort of RM patients for adenomyosis and reported that over one-third of them had the condition. This suggests a possible causal link between adenomyosis and RM, warranting further observational studies [1].

Emerging evidence indicates a strong association between adenomyosis and adverse pregnancy outcomes, particularly RM. Given its significant implications for fertility and pregnancy success,

understanding the underlying mechanisms of adenomyosis-related pregnancy loss and developing effective diagnostic and therapeutic strategies are essential.

Recent studies have identified several pathophysiological pathways through which adenomyosis may contribute to pregnancy loss. First, the condition is associated with a chronic inflammatory response in the myometrium, leading to elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ). This inflammatory environment may create a hostile uterine milieu, disrupting embryo implantation and placental development [12]. Additionally, adenomyosis is linked to increased uterine contractility and structural alterations, which may impair fetal growth and heighten the risk of miscarriage [13].

Furthermore, vascular dysfunction and reduced endometrial receptivity play a crucial role in pregnancy failure among women with adenomyosis. Studies have shown that the expression of key implantation markers, such as leukemia inhibitory factor (LIF) and HOXA10, is altered in adenomyotic uteri, indicating impaired endometrial receptivity [14]. Moreover, abnormal angiogenesis, characterized by increased vascular endothelial growth factor (VEGF) expression, may lead to placental insufficiency and early pregnancy loss [15].

Despite these findings, diagnosing adenomyosis in women with RM remains challenging due to symptom overlap with other uterine disorders. Advances in imaging techniques, particularly high-resolution transvaginal ultrasound and MRI, have improved noninvasive detection of adenomyosis [16]. However, a standardized diagnostic criterion for reproductive-aged women is still lacking.

From a therapeutic perspective, the management of adenomyosis in RM patients remains incompletely defined. Current treatment options include hormonal therapies such as gonadotropin-releasing hormone (GnRH) agonists and dienogest, which aim to reduce inflammatory and excessive contractile responses. Emerging evidence suggests that surgical interventions, such as adenomyomectomy, may improve pregnancy outcomes in select cases [12]. Additionally, adjunctive treatments like low-dose aspirin and heparin have been proposed to address vascular defects and implantation failures in these patients [17].

With growing awareness of adenomyosis as a contributor to RM, larger studies are needed to refine diagnostic criteria, clarify underlying mechanisms, and optimize therapeutic strategies. Identifying at-risk individuals and implementing targeted interventions could improve pregnancy outcomes and enhance the reproductive prospects of women affected by this condition.

## References

1. Atabekoglu, C.S., et al., The association between adenomyosis and recurrent miscarriage. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 2020. 250: p. 107-111.
2. Peric, H. and I. Fraser, The symptomatology of adenomyosis. *Best practice & research Clinical obstetrics & gynaecology*, 2006. 20(4): p. 547-555.
3. Templeman, C., et al., Risk factors for surgically removed fibroids in a large cohort of teachers. *Fertility and sterility*, 2009. 92(4): p. 1436-1446.
4. Di Spiezo Sardo, A., et al., Is hysteroscopy better than ultrasonography for uterine cavity evaluation? An evidence-based and patient-oriented approach. *Journal of Endometriosis and Pelvic Pain Disorders*, 2016. 8(3): p. 87-93.
5. Di Spiezo Sardo, A., et al., The role of hysteroscopy in the diagnosis and treatment of adenomyosis. *BioMed research international*, 2017. 2017(1): p. 2518396.
6. Tomassetti, C., et al. Adenomyosis and subfertility: evidence of association and causation. in *Seminars in reproductive medicine*. 2013. Thieme Medical Publishers.
7. Puente, J., et al., Adenomyosis in infertile women: prevalence and the role of 3D ultrasound as a marker of severity of the disease. *Reproductive Biology and Endocrinology*, 2016. 14: p. 1-9.
8. Maubon, A., et al., Uterine junctional zone at magnetic resonance imaging: a predictor of in vitro fertilization implantation failure. *Journal of Obstetrics and Gynaecology Research*, 2010. 36(3): p. 611-618.
9. Thalluri, V. and K. Tremellen, Ultrasound diagnosed adenomyosis has a negative impact on successful implantation following GnRH antagonist IVF treatment. *Human reproduction*, 2012. 27(12): p. 3487-3492.
10. Youm, H.S., Y.S. Choi, and H.D. Han, In vitro fertilization and embryo transfer outcomes in relation to myometrial thickness. *Journal of assisted reproduction and genetics*, 2011. 28: p. 1135-1140.
11. Martínez-Conejero, J.A., et al., Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation. *Fertility and sterility*, 2011. 96(4): p. 943-950. e1.
12. Vercellini, P., et al., Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. *Human reproduction*, 2014. 29(5): p. 964-977.
13. Tsikouras, P., et al., The Impact of Adenomyosis on Pregnancy. *Biomedicines*, 2024. 12(8).
14. Younes, G. and T. Tulandi, Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. *Fertility and sterility*, 2017. 108(3): p. 483-490. e3.
15. Harada, T., et al., The impact of adenomyosis on women's fertility. *Obstetrical & gynecological survey*, 2016. 71(9): p. 557-568.
16. Kunz, G., et al., Adenomyosis as a disorder of the early and late human reproductive period. *Reproductive biomedicine online*, 2007. 15(6): p. 681-685.
17. Cozzolino, M., et al., The effect of uterine adenomyosis on IVF outcomes: a systematic review and meta-analysis. *Reproductive Sciences*, 2022. 29(11): p. 3177-3193.