Perspective Article

The Art of Managing Infertile Patients with Adenomyosis

Angel Hsin-Yu Pai[1], Liang-Hsuan Chen[1], Shang-Yu Huang[1,2], Hsien-Ming Wu[1,3], Chia-Lin Chang[1], Hong-Yuan Huang[1,2], Yung-Kuei Soong[1], Chyi-Long Lee[2,4]*

[1]Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center, [2]College of Medicine, Chang Gung University, [3]Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, [4]Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center and Chang Gung University, Taoyuan, Taiwan

Introduction

Within the myometrium, the ectopic endometrial tissues, which often migrate from the basalis layer and clonally expand,[1] express diffuse epigenic defects that result in altered responses of estrogens, resistances to progesterone, and other pathophysiology.[1-3] Furthermore, at these sites, through cyclic tissue injury and repair, the tissues are often highly fibrotic.[1] Clinically, adenomyosis often occurs with endometriosis[4] and presents with overlapping symptoms, such as dysmenorrhea, heavy menstrual bleeding, chronic pelvic pain, and infertility. Approximately, 20% of cases of adenomyosis involve women younger than 40 and 80% are aged 40–50 years.[4] With women delaying their child-bearing age and also earlier diagnoses of the disease, associations between adenomyosis and infertility have recently emerged. The objective of this review is to focus on the impacts of adenomyosis on fertility, challenges encountered during antiretroviral therapy (ART) treatments, and current managements for optimizing their reproductive outcomes.

Associations of Adenomyosis and Infertility

When adenomyotic lesion infiltrates into the inner myometrium, it triggers local inflammation that involves platelet aggregation and hypoxia, thereby generating inflammatory cytokines and prostaglandins, as well as increasing local estrogen synthesis.[1] These events may cause uterine hyperperistalsis through estrogen receptor induction of oxytocin signaling and fibrosis due to epithelial–mesenchymal-transition and fibroblast-to-myofibroblast transdifferentiation.[1,5,6] While abnormal contraction waves are thought to interfere with gamete and embryo transport,[7] local inflammation[8] and fibrosis are considered the primary factors leading to an altered uterine milieu.[1,9] Insufficient expression of adhesion molecules (integrins) and implantation markers like leukemia inhibitory factor, along with altered functioning of the embryonic development gene (HOXA10) may impair the implantation process.[10] In addition, current research has found reduced number of luminal microvilli, impaired steroid hormone metabolism, and increased oxidative stress in the endometrium of patients with adenomyosis.[11]

Adenomyosis has also been linked to early pregnancy losses and potentially recurrent pregnancy losses (RPLs).[12] Through altered responses to progesterone,[13,14] impaired expressions of decidualization markers,[15] different immune and cytokine profiles,[16-18] and dysregulated epigenetics and genetics,[19] adenomyosis affects implantation,[18] and placentation quality, thereby increases the risk of miscarriages and RPL.[12] Although the exact mechanisms of each theory still require further elucidations, the clinical presentation of infertility for this specific population of patients poses as a challenge to many clinicians.

Impacts on *In vitro* Fertilization Treatments

In a meta-analysis that incorporated seventeen observational studies,[20] the authors primarily found that among patients undergoing ART, those with adenomyosis were significantly associated with a lower clinical pregnancy rate (CPR) (odds ratio [OR] 0.69; 95% confidence interval [CI] 0.51–0.94)

Article History:
Submitted: 23-Apr-2024
Revised: 23-May-2024
Accepted: 31-May-2024
Published: 21-Oct-2024

Access this article online

Quick Response Code:

Website: https://journals.lww.com/gmit

DOI: 10.4103/gmit.gmit_53_24

Address for correspondence: Prof. Chyi-Long Lee, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center, No. 5, Fuxing St., Guishan Dist., Taoyuan 333, Taiwan.
E-mail: leechyilong@gmail.com

How to cite this article: Pai AH, Chen LH, Huang SY, Wu HM, Chang CL, Huang HY, *et al*. The art of managing infertile patients with adenomyosis. Gynecol Minim Invasive Ther 2024;13:205-8.

and a higher miscarriage rate (OR 2.17; 95% CI 1.25–3.79). Furthermore, in the subgroup of patients undergoing short downregulation protocols, the decrease in CPR was even more significant, despite adjusting for age. They also discovered that adenomyosis was significantly associated with risks of pregnancy-induced hypertension, preterm birth, cesarean section, fetal malposition, low birth weight, and postpartum hemorrhage.

In a systemic review and meta-analysis by Vercellini *et al*.,[4] reduced pregnancy and live birth rates (LBRs) and an increased miscarriage rate were observed in women with adenomyosis. A recent prospective observational cohort study[21] that utilized egg donation and single embryo transfer (ET) cycles in order to focus on infertility-related uterine factors faced by patients with adenomyosis found that although the presence of adenomyosis did not significantly affect the implantation, clinical pregnancy, or LBRs, women with adenomyosis had a significantly higher miscarriage rate than those without (35.4% vs. 18.1%, respectively). Therefore, the negative associations of adenomyosis on fertility outcomes, even after ART treatment, are not to be overlooked or oversimplified.

Current Managements

Drug therapy is often the preferred treatment modality, even for patients who have undergone surgery, as it is necessary to reduce the risk of recurrence. By altering the hormonal profile, drug therapy ultimately aims to create a hypoestrogenic environment.[22] For instance, combined oral contraceptive induces a pseudo-gestational state that eventually leads to endometrial decidualization and atrophy of the endometrium and adenomyotic lesions. The local action of Levonogestrel[23] induces decidualization and atrophy of ectopic endometrial tissue by downregulating estrogen receptors and preventing further estrogenic stimulation. Meanwhile, dienogest, a fourth-generation progestin with a high affinity for progesterone receptors, inhibits systemic gonadotropin secretion and provides additional anti-proliferative and local anti-inflammatory effects on the endometrial tissue.

Gonadotrophin-releasing hormone (GnRH) agonists can serve as a second-line treatment for adenomyosis.[24] Continuous use of GnRH agonists suppresses the secretion of follicular-stimulating hormone and luteinizing hormone. In addition, a significant reduction in uterine volume, as measured by ultrasonography, was observed after 16 weeks of GnRH agonist treatment.[25] Histologically, 3–6 months of GnRH agonist therapy significantly reduced the infiltration of CD68-positive macrophages and the density of von Willebrand factor-positive microvessels.[26] Compared to the untreated group, higher apoptotic indices and quantitative scores of activated caspase-3 were observed in the eutopic endometrium, lesions, and uterine myometrium after GnRH agonist therapy.

When refractory to medical treatments or in severe cases, surgical intervention may be required. Although hysterectomy is the ultimate solution, it is not a possible option for patients desiring fertility.[27] With advances in surgical tools, imaging modalities, and minimal invasive options, the indications and approaches to adenomyomectomy differ depending on the surgeons. Various laparotomic methods have been explored to debulk maximally and minimize risks of uterine rupture.[28] Meanwhile, with appropriate techniques,[29,30] laparoscopic volume reduction of the adenomyotic lesions is feasible without massive blood loss associated complications. With so many options, adequate control of symptoms and ideal physical status are crucial and attainable, even when these patients are seeking or currently under fertility treatments.

The efficacy of pretreatment

A retrospective cohort study[31] included 537 women with adenomyosis, divided into three groups: (Group A) underwent frozen ET (FET) after long-term GnRH agonist pretreatment; (Group B) underwent fresh ET using the ultra-long GnRH agonist protocol; and (Group C) underwent fresh ET using the long GnRH agonist protocol. The authors found that in Group A, the total gonadotrophin dose and stimulation duration were significantly lower than in Groups B and C. In addition, the implantation and LBRs in Group A were significantly higher than in Groups B and C. Increase in implantation rate, CPR, and LBR, along with a decrease in miscarriage rate, were also seen in Group A when compared to Group C. In fresh cycles, the LBR was significantly higher in the ultra-long GnRHa protocol compared to the long GnRHa protocol. Overall, it was observed that FET after long-term GnRHa pretreatment had beneficial effects on pregnancy outcomes for patients with adenomyosis. Interestingly, another retrospective study[32] noticed a higher CPR for patients who had a sevenfold or greater reduction of CA-125 levels after GnRH agonist pretreatment.

Besides GnRH agonists, dienogest[33] or letrozole[34] have also shown comparative efficacies for these patients before their ART treatments. A longitudinal randomized control trial[34] compared patients with adenomyosis who received low-dose letrozole (n = 79) or GnRH agonist (n = 77) before their *in vitro* fertilization (IVF) treatments. Assessments of the patients' symptoms, such as dysmenorrhea and menorrhagia, hemoglobin level, and sonographic features, all showed improvement in both groups, with letrozole therapy being the more cost-effective one. Therefore, for adenomyosis patients preparing to receive IVF treatments, it is imperative to choose a modality most suitable for each patient.

To freeze or not to freeze?

In a recently published single-center observational study analyzing 306 women with adenomyosis undergoing blastocyst ET,[35] the authors found that, compared to fresh ET, the freeze-all group had significantly higher cumulative LBRs (86 individuals, 44.1% vs. 34 individuals, 30.6%) and cumulative ongoing pregnancy rates (88 individuals, 45.1% vs. 36 individuals, 32.4%). Even after multivariate logistic regression analysis, among women with adenomyosis, the freeze-all strategy was associated with a higher likelihood of live birth (OR 1.80; 95% CI 1.02–3.16). The authors suggested that adenomyosis-affected endometrial receptivity may be more significantly impacted by controlled ovarian stimulation (COS), and the freeze-all strategy may be beneficial in avoiding the negative effects of COS on the already compromised uterine cavities.

In addition to the freeze-all strategy, segmented ART protocol had shown encouraging results. It entails initiating IVF by freezing all embryos, followed by administering GnRH agonist or progestin for 3–6 months, and then arranging thaw ET.[22,36] Growing scientific evidence suggests that COS can lead to notable alterations in the endocrine profile of a reproductive cycle, particularly during the crucial early luteal phase.[36] These alterations may adversely impact implantation and early placental development. Therefore, for patients with adenomyosis, who are already more predisposed to these negative impacts, deferring ET to reduce the effects from COS may be a more suitable option for higher ART success.

Optimize outcomes with choices of *in vitro* fertilization protocol

Previously, the use of ultra-long protocol in patients with adenomyosis had shown potential enhancement of CPR or live birth rate (LBR).[37] A widely accepted rationale being that downregulation induced by long-acting GnRH agonist may counteract the hyperestrogenism and progesterone resistance associated with adenomyosis. However, the ultra-long protocol may cause profound suppression of ovarian function, leading to increased duration and dosage of gonadotropin. Moreover, for adenomyosis patients with diminished ovarian reserve, the suppression induced by long-acting GnRH agonists may result in poor ovarian response, characterized by reduced oocyte retrieval and unfavorable pregnancy outcomes. In a retrospective cohort study, Ge *et al*.[38] compared to 257 fresh ET and 305 FET. The authors found that when fresh ET was chosen, more advantageous results were seen in the ultra-long or long protocol, in terms of the number of oocytes retrieved, the number of 2PN, number of high-quality embryos on day 3, implantation rate, CPR, and LBR. Understandably, in a fresh cycle, if an antagonist protocol was used, freeze-all followed by FET was recommended. Meanwhile, in the FET cycles, the choice of protocols did not impact pregnancy outcomes.

Conclusion

Even with the help of ART, infertile patients with adenomyosis have lower implantation rate and LBR and higher miscarriage rate.[20] Currently, many medical, surgical, and non-invasive treatment modalities are available. However, in preparation for or during assisted reproduction treatments, the choice of protocol, fresh or frozen cycle, with or without pretreatment, and other factors play some parts in the pregnancy outcomes. When managing infertile patients with adenomyosis, it is important to monitor and control the disease before, during, and after their IVF treatments to not only optimize their pregnancy outcomes, but also reduce their symptomatic burdens.

Author contributions

Pai AH conceived and designed the paper; collected the data; performed the analysis; and wrote the paper. Chen LH, Huang SY, Wu HM, Chang CL, Huang HY, and Soong YK contributed data. Lee CL designed the paper; contributed data; and helped edit the paper. All authors have read and agreed to the published version of the manuscript.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

Nil.

Conflicts of interest

Prof. Chyi-Long Lee, an editorial board member at *Gynecology and Minimally Invasive Therapy*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

References

1. Khan KN, Fujishita A, Mori T. Pathogenesis of human adenomyosis: Current understanding and its association with infertility. J Clin Med 2022;11:4057.
2. MacLean JA 2nd, Hayashi K. Progesterone actions and resistance in gynecological disorders. Cells 2022;11:647.
3. Pirtea P, de Ziegler D, Ayoubi JM. Endometrial receptivity in adenomyosis and/or endometriosis. Fertil Steril 2023;119:741-5.
4. Vercellini P, Viganò P, Bandini V, Buggio L, Berlanda N, Somigliana E. Association of endometriosis and adenomyosis with pregnancy and infertility. Fertil Steril 2023;119:727-40.
5. Liu X, Shen M, Qi Q, Zhang H, Guo SW. Corroborating evidence for platelet-induced epithelial-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation in the development of adenomyosis. Hum Reprod 2016;31:734-49.
6. Artymuk N, Zotova O, Gulyaeva L. Adenomyosis: Genetics of estrogen

metabolism. Horm Mol Biol Clin Investig 2019;37:20180069. [doi: 10.1515/hmbci-2018-0069].
7. Kissler S, Zangos S, Wiegratz I, Kohl J, Rody A, Gaetje R, *et al.* Utero-tubal sperm transport and its impairment in endometriosis and adenomyosis. Ann N Y Acad Sci 2007;1101:38-48.
8. Carrarelli P, Yen CF, Funghi L, Arcuri F, Tosti C, Bifulco G, *et al.* Expression of inflammatory and neurogenic mediators in adenomyosis. Reprod Sci 2017;24:369-75.
9. Huang Q, Liu X, Critchley H, Fu Z, Guo SW. How does the extent of fibrosis in adenomyosis lesions contribute to heavy menstrual bleeding? Reprod Med Biol 2022;21:e12442.
10. Fischer CP, Kayisili U, Taylor HS. HOXA10 expression is decreased in endometrium of women with adenomyosis. Fertil Steril 2011;95:1133-6.
11. Khan KN, Fujishita A, Suematsu T, Ogawa K, Koshiba A, Mori T, *et al.* An axonemal alteration in apical endometria of human adenomyosis. Hum Reprod 2021;36:1574-89.
12. Pirtea P, Cicinelli E, De Nola R, de Ziegler D, Ayoubi JM. Endometrial causes of recurrent pregnancy losses: Endometriosis, adenomyosis, and chronic endometritis. Fertil Steril 2021;115:546-60.
13. Nie J, Lu Y, Liu X, Guo SW. Immunoreactivity of progesterone receptor isoform B, nuclear factor kappaB, and IkappaBalpha in adenomyosis. Fertil Steril 2009;92:886-9.
14. Nie J, Liu X, Guo SW. Promoter hypermethylation of progesterone receptor isoform B (PR-B) in adenomyosis and its rectification by a histone deacetylase inhibitor and a demethylation agent. Reprod Sci 2010;17:995-1005.
15. Jiang Y, Jiang R, Cheng X, Zhang Q, Hu Y, Zhang H, *et al.* Decreased expression of NR4A nuclear receptors in adenomyosis impairs endometrial decidualization. Mol Hum Reprod 2016;22:655-68.
16. Tremellen KP, Russell P. The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure. II: Adenomyosis and macrophages. J Reprod Immunol 2012;93:58-63.
17. Zhihong N, Yun F, Pinggui Z, Sulian Z, Zhang A. Cytokine profiling in the eutopic endometrium of adenomyosis during the implantation window after ovarian stimulation. Reprod Sci 2016;23:124-33.
18. Bourdon M, Maget AS, Jeljeli M, Doridot L, Marcellin L, Thomas M, *et al.* Reduced fertility in an adenomyosis mouse model is associated with an altered immune profile in the uterus during the implantation period. Hum Reprod 2024;39:119-29.
19. Jiang JF, Sun AJ, Xue W, Deng Y, Wang YF. Aberrantly expressed long noncoding RNAs in the eutopic endometria of patients with uterine adenomyosis. Eur J Obstet Gynecol Reprod Biol 2016;199:32-7.
20. Nirgianakis K, Kalaitzopoulos DR, Schwartz AS, Spaanderman M, Kramer BW, Mueller MD, *et al.* Fertility, pregnancy and neonatal outcomes of patients with adenomyosis: A systematic review and meta-analysis. Reprod Biomed Online 2021;42:185-206.
21. Cozzolino M, Cosentino M, Loiudice L, Martire FG, Galliano D, Pellicer A, *et al.* Impact of adenomyosis on *in vitro* fertilization outcomes in women undergoing donor oocyte transfers: A prospective observational study. Fertil Steril 2024;121:480-8.
22. Chen LH, Lo WC, Huang HY, Wu HM. A lifelong impact on endometriosis: Pathophysiology and pharmacological treatment. Int J Mol Sci 2023;24:7503.
23. Gibbons T, Georgiou EX, Cheong YC, Wise MR. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. Cochrane Database Syst Rev 2021;12:CD005072.
24. Etrusco A, Barra F, Chiantera V, Ferrero S, Bogliolo S, Evangelisti G, *et al.* Current medical therapy for adenomyosis: From bench to bedside. Drugs 2023;83:1595-611.
25. Matsushima T, Akira S, Fukami T, Yoneyama K, Takeshita T. Efficacy of hormonal therapies for decreasing uterine volume in patients with adenomyosis. Gynecol Minim Invasive Ther 2018;7:119-23.
26. Khan KN, Kitajima M, Hiraki K, Fujishita A, Sekine I, Ishimaru T, *et al.* Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy. Hum Reprod 2010;25:642-53.
27. Chen J, Porter AE, Kho KA. Current and future surgical and interventional management options for adenomyosis. Semin Reprod Med 2020;38:157-67.
28. Osada H. Uterine adenomyosis and adenomyoma: The surgical approach. Fertil Steril 2018;109:406-17.
29. Ai G, Ding L, Luo N, Cheng Z. The application of uterine artery occlusion combined with uterine-vaginal nerve block technique in patients with adenomyosis. Gynecol Minim Invasive Ther 2019;8:194-5.
30. Kuo HH, Weng CH, Jaiswal A, Wu KY, Wang CJ, Lee CL, *et al.* Performing laparoscopic adenomyomectomy with the four-petal method. Fertil Steril 2020;114:1352-4.
31. Wu Y, Huang J, Zhong G, Lan J, Lin H, Zhang Q. Long-term GnRH agonist pretreatment before frozen embryo transfer improves pregnancy outcomes in women with adenomyosis. Reprod Biomed Online 2022;44:380-8.
32. Wang Y, Yi YC, Guu HF, Chen YF, Kung HF, Chang JC, *et al.* Impact of adenomyosis and endometriosis on IVF/ICSI pregnancy outcome in patients undergoing gonadotropin-releasing hormone agonist treatment and frozen embryo transfer. Sci Rep 2023;13:6741.
33. Kobayashi H. Efficacy, adverse events, and challenges of dienogest in the management of symptomatic adenomyosis: A comparison with different hormonal treatments. Gynecol Obstet Invest 2023;88:71-80.
34. Sharma S, RoyChoudhury S, Bhattacharya MP, Hazra S, Majhi AK, Oswal KC, *et al.* Low-dose letrozole – An effective option for women with symptomatic adenomyosis awaiting IVF: A pilot randomized controlled trial. Reprod Biomed Online 2023;47:84-93.
35. Bourdon M, Santulli P, Maignien C, Bordonne C, Millischer AE, Chargui A, *et al.* The "freeze-all" strategy seems to improve the chances of birth in adenomyosis-affected women. Fertil Steril 2024;121:460-9.
36. Ozgur K, Humaidan P, Coetzee K. Segmented ART – The new era in ART? Reprod Biol 2016;16:91-103.
37. Hou X, Xing J, Shan H, Mei J, Sun Y, Yan G, *et al.* The effect of adenomyosis on IVF after long or ultra-long GnRH agonist treatment. Reprod Biomed Online 2020;41:845-53.
38. Ge L, Li Y, Guan S, Cui L, Chen ZJ. Effects of ovarian stimulation protocols on outcomes of assisted reproductive technology in adenomyosis women: A retrospective cohort study. Front Endocrinol (Lausanne) 2023;14:1198779.