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Changes in adenomyosis following elagolix vs leuprolide treatment in a patient with pelvic pain and infertility: A case report

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ABSTRACT

Adenomyosis is a uterine form of endometriosis that poses unique challenges in the management of infertility. Severe pelvic pain and menorrhagia associated with these conditions are commonly managed with intramuscular injections of a gonadotropin-releasing hormone agonist (leuprolide acetate). Since receiving approval by the US Food and Drug Administration in 2018, a novel oral gonadotropin-releasing hormone antagonist, elagolix, has also been increasingly used to manage endometriosis-associated pain. However, the efficacy of elagolix in the treatment of adenomyosis and infertility remains uncertain. In this clinical case of an infertile patient with endometriosis and diminished ovarian reserve, treatment with elagolix effectively controlled her severe endometriosis-related pelvic pain but, surprisingly, failed to prevent concurrent progression of adenomyosis. Subsequently, elagolix was changed to treatment with leuprolide acetate, which led to improvement of adenomyosis in preparation for an embryo transfer during an in vitro fertilization cycle. Women's health providers should be aware that elagolix may not as effectively suppress adenomyosis as leuprolide acetate, particularly in infertility patients undergoing treatment with assisted reproductive technologies.

1. Introduction

Endometriosis and adenomyosis are benign gynecological conditions that present unique challenges to the treatment of infertility in women of reproductive age. Both often manifest with chronic pelvic pain and heavy menstrual bleeding, which significantly impair women's quality of life. Endometriosis occurs in 10–15% of women of reproductive age. However, it affects 70% of women with chronic pelvic pain and the incidence is as high as 50% in women with infertility. [1,2]

Adenomyosis, a uterine form of endometriosis, is defined as endometrial tissue invading at least 2.5 mm into the myometrium. [3,4] It presents unique challenges for assisted reproductive technologies (ART), especially for embryo implantation, due to its active inflammatory nature. Thus, adenomyosis decreases clinical pregnancy rates and increases risk of early pregnancy loss. [5] Adenomyotic lesions proliferate in a high estrogen state and regress with estrogen deprivation. As such, it is theorized that this ectopic endometrial tissue should regress in response to therapies that inhibit ovulation and reduce estrogen production. [4] This inhibition is commonly achieved with intramuscular leuprolide acetate, a long-acting gonadotropin-releasing hormone (GnRH) agonist, which suppresses the HPG axis and leads to decreased estrogen-driven endometriosis proliferation. In turn, such inhibition leads to improvement of embryo implantation and pregnancy outcomes in infertile women with adenomyosis undergoing ART treatment. [6,7]

In 2018, the oral short-acting GnRH antagonist elagolix was approved by the US FDA for treatment of moderate to severe pain associated with endometriosis. However, its efficacy in the treatment of infertile women with adenomyosis is unclear, with only two case reports suggesting reduction in adenomyomatous lesions. [8,9]

This report presents the clinical case of a patient with infertility and endometriosis who received elagolix for management of pelvic pain while she postponed infertility management to focus on education. Surprisingly, when the patient returned to infertility treatment, there was a significant progression of adenomyosis on elagolix, despite adequate control of pelvic pain.

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- CD 1-2
  - Leuprolide Acetate 20 units (40 μg) subcutaneously twice a day
- CD 3-14
  - Leuprolide Acetate 20 units (40 μg) subcutaneously twice a day
  - Recombinant FSH 375 IU subcutaneously daily
  - Purified gonadotropin 75 IU subcutaneously daily
  - Serial US and estradiol monitoring of ovarian response
- CD 15
  - Choriogonadotropin Alfa (HCG injection)
- CD 17 Retrieval

Fig. 1. Ovulation induction protocol.
Abbreviations: CD – cycle day, IU – international units, FSH – follicle-stimulating hormone, US – ultrasound, HCG – human chorionic gonadotropin.

2. Case Presentation

A 34-year-old woman, G1P0010, with laparoscopically confirmed severe endometriosis, remote history of intrauterine synechiae (status - post successful hysteroscopic resection), secondary infertility and diminished ovarian reserve (AMH 0.6μIU/mL) presented for fertility counseling and treatment. The patient's first pregnancy followed an intrauterine insemination (IUI) but resulted in first-trimester missed abortion, for which she underwent an uncomplicated dilation and curettage. Her gynecologic history was notable for remote chlamydial infection and an abnormal pap smear managed with cervical cryotherapy with normal screening thereafter. She had had a laparoscopic diagnosis of moderate pelvic endometriosis at the age of 27 when evaluated for chronic pelvic pain. Due to returning symptoms, she underwent repeat laparoscopy with chromopertubation at the age of 32, with findings of endometriosis progression, pelvic adhesive disease, an intramural fundal leiomyoma and left fallopian tube with partial strictures. At the same time, hysteroscopic excision of a small intrauterine synechiae was performed. Her medical history included depression and nephrolithiasis treated with lithotripsy.

In the course of fertility treatment, the patient underwent elective embryo cryopreservation, with plan for a frozen embryo transfer after completing her education. The microflare protocol with high dose of gonadotropins was used for ovarian stimulation followed by oocyte retrieval and embryo development (Fig. 1). Three good-quality blastocysts were cryopreserved. During the patient's educational pause, her endometriosis-related severe pelvic pain was successfully managed with elagolix, 150 mg PO daily.

She returned one year later for frozen embryo transfer. A preparatory uterine evaluation with saline sonohysterogram (SIS) revealed surprising findings of progression of adenomyosis with irregular endometrium (Fig. 2). Elagolix was discontinued and she was subsequently managed with intramuscular injections of leuprolide acetate 3.75 mg monthly for three months. The follow-up SIS revealed significant reduction in adenomyosis and normalization of the endometrium (Fig. 3). The patient then underwent an elective single frozen embryo transfer; however, she

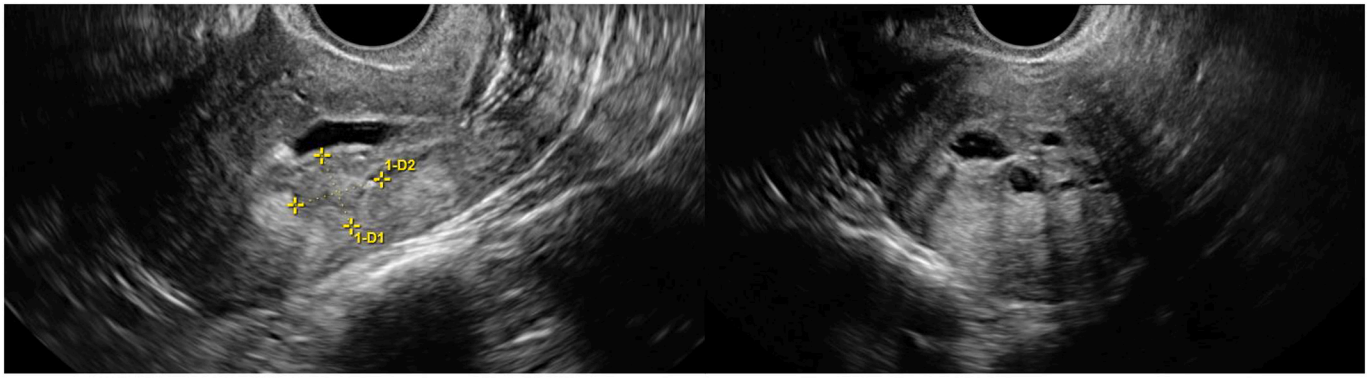

Fig. 2. Saline sonohysterogram after treatment with Elagolix
A. Diffuse adenomyosis and posterior adenomyoma
B. Subendometrial cystic lesions of adenomyosis and endometrial irregularities.

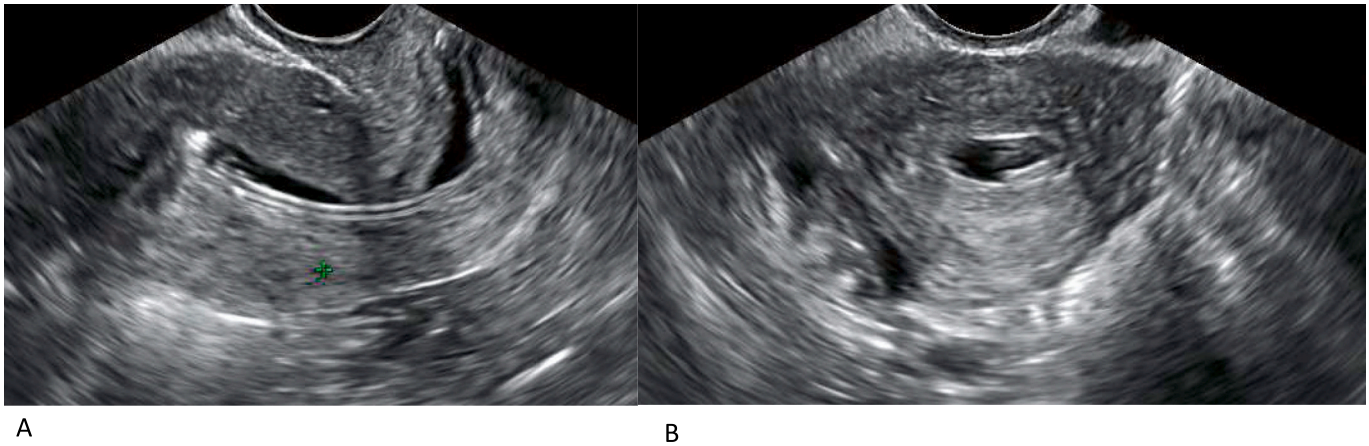

Fig. 3. Saline sonohysterogram after treatment with Leuprolide Acetate.
A. Decrease of diffuse adenomyosis and posterior adenomyoma.
B. Resolution of subendometrial cystic lesions and endometrial irregularity.

did not conceive and was considering the use of a gestational carrier for her remaining embryos.

3. Discussion

It has been demonstrated that adenomyosis negatively impacts the success rate of ART treatments. Specifically, adenomyosis was associated with a 28% reduction in the clinical pregnancy rate in infertile women who underwent in vitro fertilization (IVF) independent of embryo or oocyte quality. [5,6] Leuprolide acetate is a mainstay treatment for various clinical manifestations of endometriosis, in the setting of both pelvic pain and infertility. It has also been shown that pretreatment with leuprolide acetate of infertile women with adenomyosis improves ART outcomes such as embryo implantation, clinical pregnancy rates and live birth rates. [7] Conversely, elagolix has been convincingly demonstrated to treat only endometriosis related pelvic pain and heavy menstrual bleeding. Along these lines, a preferred medical treatment for adenomyosis has not yet been established, with most medications being used off label. Little data exist regarding the efficacy of GnRH antagonists in treating adenomyosis and improving infertility. [10] With regard to elagolix specifically, data evaluating its effect on adenomyosis is insufficient and there is no clinical or scientific evidence of its use in ART.

There are only two published case reports demonstrating the effect of GnRH antagonists on adenomyosis, but both concern non-infertile women. The first describes a 41-year-old patient with a fundal adenomyoma that regressed in size (3.9 cm to 2.7 cm) after three months on elagolix 150 mg per day. [8] The second case reports a patient with an adenomyomatous uterus that reduced in size (875 cm^3 to 290 cm^3) after a 12-week course of another oral GnRH antagonist, linzagolix 200 mg per day. [9] In both cases, the patients reported decreased pelvic pain with improved quality of life. Additionally, in an open-label pilot study of 8 women with MRI-diagnosed adenomyosis, 12 weeks of once-daily linzagolix 200 mg followed by 100 mg daily for an additional 12 weeks resulted in a 32% reduction in adenomyotic uterine volume ($p = 0.0057$) and improved associated symptoms. [11] While these results are encouraging, they are not applicable to women with adenomyosis and endometriosis-related infertility undergoing ART management. Additionally, the overall utility of GnRH antagonists in treating adenomyosis cannot be determined without larger, randomized studies. [12]

Of note, a double-blind, randomized, controlled trial was performed by Muneyyirci-Delale et al., which compared the effectiveness of elagolix with add-back therapy to placebo in reducing heavy menstrual bleeding in 786 women with uterine fibroids and coexisting adenomyosis. They found that, compared with placebo, elagolix significantly reduced bleeding. [13] However, given that all participants in this study had both fibroids and adenomyosis, it is unknown whether the findings can be generalized to women with adenomyosis who do not have fibroids.

There is evidence to suggest that a GnRH antagonist may be as effective as a GnRH agonist during 10–14 days of IVF ovarian stimulation though no scientific data exist comparing the two as pretreatments for endometriosis and adenomyosis prior to ART. Evaluating a group of infertile women with adenomyosis, Zhang et al. found that, in comparison with GnRH agonist IVF cycles, GnRH antagonist cycles resulted in similar clinical pregnancy rates and cumulative live birth rates. [14] Some have also speculated that, given the flexibility of oral administration of GnRH antagonists, "the use of linzagolix might be superior or preferable to current treatments for adenomyosis before ART." [15] Given that the understanding of these new medications in the setting of ART is based on very limited data, it is clear that further investigation in this area is necessary.

In conclusion, this case report demonstrates progression of adenomyosis while using elagolix to manage pelvic pain in a patient with endometriosis-related infertility. Leuprolide acetate treatment for three months resulted in regression of adenomyosis in preparation for embryo transfer in an ART cycle. Taken together with the other limited data in this area, the efficacy of elagolix in the treatment of adenomyosis and infertility remains uncertain. This clinical case raises awareness that despite effective pian relief, elagolix may not as effectively suppress progression of adenomyosis as leuprolide acetate does, particularly in women with infertility undergoing ART management. As such, the hope is that large-scale studies will be conducted in the area to help elucidate the utility of elagolix and other GnRH antagonists in management of women with infertility in a setting of adenomyosis and endometriosis.

Contributors

Mariam Barseghyan, the primary author, was involved in the conception of the case report, analysis and interpretation of data, drafting the initial manuscript, and editing the manuscript.

J. Graham Theisen was involved in the conception of the case report, acquisition, analysis and interpretation of data, drafting the initial manuscript, and revising the manuscript.

Clara Wang was involved in the conception of the case report, analysis and interpretation of data, drafting the initial manuscript, and revising the manuscript.

Larisa Gavrilova-Jordan was the attending physician involved in patient care, was involved in the conception of the study, acquisition, analysis and interpretation of data, and revising the manuscript.

All authors approved the final submission.

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Patient consent

Obtained. The patient provided informed consent for publication of her case and related images.

Provenance and peer review

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Conflict of interest statement

The authors declare that they have no conflict of interest regrading publication of this case report.

References

[1] J.E. Carter, Combined hysteroscopic and laparoscopic findings in patients with chronic pelvic pain, J. Am. Assoc. Gynecol. Laparosc. 2 (1994) 43–47, https://doi.org/10.1016/s1074-3804(05)80830-8.

[2] L.C. Giudice, L.C. Kao, Endometriosis, Lancet 364 (2004) 1789–1799, https://doi.org/10.1016/S0140-6736(04)17403-5.

[3] J.M. Puente, A. Fabris, J. Patel, A. Patel, M. Cerrillo, A. Requena, J.A. Garcia-Velasco, Adenomyosis in infertile women: prevalence and the role of 3D ultrasound as a marker of severity of the disease, Reprod. Biol. Endocrinol. 14 (2016) 60, https://doi.org/10.1186/s12958-016-0185-6.

[4] J. García-Solares, J. Donnez, O. Donnez, M.-M. Dolmans, Pathogenesis of uterine adenomyosis: invagination or metaplasia? Fertil. Steril. 109 (2018) 371–379, https://doi.org/10.1016/j.fertnstert.2017.12.030.

[5] P. Vercellini, D. Consonni, D. Dridi, B. Bracco, M.P. Frattaruolo, E. Somigliana, Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis, Hum. Reprod. 29 (2014) 964–977, https://doi.org/10.1093/humrep/deu041.

[6] J.-J. Li, J.P.W. Chung, S. Wang, T.-C. Li, H. Duan, The investigation and management of adenomyosis in women who wish to improve or preserve fertility, Biomed. Res. Int. 2018 (2018) 1–12, https://doi.org/10.1155/2018/6832685.
[7] G. Younes, T. Tulandi, Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis, Fertil. Steril. 108 (2017) 483–490.e3, https://doi.org/10.1016/j.fertnstert.2017.06.025.
[8] S.K. Kavoussi, A.S. Esqueda, L.M. Jukes, Elagolix to medically treat a uterine adenomyoma: a case report, Eur. J. Obstet. Gynecol. Reprod. Biol. 247 (2020) 266–267, https://doi.org/10.1016/j.ejogrb.2020.02.027.
[9] O. Donnez, J. Donnez, Gonadotropin-releasing hormone antagonist (linzagolix): a new therapy for uterine adenomyosis, Fertil. Steril. 114 (2020) 640–645, https://doi.org/10.1016/j.fertnstert.2020.04.017.
[10] A.G. Cope, A.J. Ainsworth, E.A. Stewart, Current and future medical therapies for adenomyosis, Semin. Reprod. Med. 38 (2020) 151–156, https://doi.org/10.1055/s-0040-1719016.
[11] J. Donnez, O. Donnez, M. Brethous, E. Bestel, E. Garner, S. Charpentier, A. Humberstone, E. Loumaye, Treatment of symptomatic uterine adenomyosis with linzagolix, an oral gonadotrophin-releasing hormone antagonist: a pilot study, Reprod. BioMed. Online 44 (2022) 200–203, https://doi.org/10.1016/j.rbmo.2021.09.019.
[12] F.I. Sharara, M.H. Kheil, A. Feki, S. Rahman, J.S. Klebanoff, J.M. Ayoubi, G. N. Moawad, Current and prospective treatment of adenomyosis, J. Clin. Med. 10 (2021) 3410, https://doi.org/10.3390/jcm10153410.
[13] O. Muneyyirci-Delale, D.F. Archer, C.D. Owens, K.T. Barnhart, L.D. Bradley, E. Feinberg, V. Gillispie, S. Hurtado, J.H. Kim, A. Wang, H. Wang, E.A. Stewart, Efficacy and safety of elagolix with add-back therapy in women with uterine fibroids and coexisting adenomyosis, F S Rep. 2 (2021) 338–346, https://doi.org/10.1016/j.xfre.2021.05.004.
[14] L. Zhang, H. Cai, X. Liu, Y. Xiong, X. Liang, J. Shi, Comparison of pregnancy outcomes between GnRH antagonist protocol with freeze-all strategy and long-acting GnRH agonist protocol in women with adenomyosis undergoing IVF/ICSI: a propensity-score matching analysis, BMC Pregnan. Childbirth 22 (2022) 946, https://doi.org/10.1186/s12884-022-05276-9.
[15] A. Borini, G. Coticchio, Gonadotropin-releasing hormone antagonist linzagolix: possible treatment for assisted reproduction patients presenting with adenomyosis and endometriosis? Fertil. Steril. 114 (2020) 517–518, https://doi.org/10.1016/j.fertnstert.2020.06.003.