CASE REPORT

An unexpected diagnosis of adenomyosis in the subfertile woman

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SUMMARY

A 38-year-old nulliparous female presented to an assisted conception clinic with subfertility and a long-standing history of dysmenorrhoea. Transvaginal ultrasound revealed two lesions in the body of the uterus, which were presumed to be fibroids. A decision was made to remove these lesions prior to attempting in vitro fertilisation (IVF). However, on laparotomy, deeply penetrating adenomyosis was discovered, resulting in an unexpected hysterectomy and significant blood loss. Based on our experience, we highlight the importance of suspecting a diagnosis of adenomyosis preoperatively and the methods by which this diagnosis can be made, in order to avoid potential unforeseen outcomes as described in this case. We discuss conservative management options for this condition, particularly in women wishing to preserve fertility.

BACKGROUND

Adenomyosis was historically believed to be a disease of multiparous women. However, with advances in diagnostic technology and the rising age at which women approach motherhood, it is being increasingly seen in women attending fertility clinics.¹ Histologically, it is identified as the presence of heterotopic endometrial glands and stroma within the myometrium with adjacent hyperplasia of the myometrium.² Adenomyosis can be diffuse or focal. Diffuse disease is most commonly located in the posterior uterine wall, where it can be subdivided into superficial and deep (extending more than one-third of the way into the myometrium) disease. Adenomyosis can also be focal, characterised by nodules in the junctional zone (JZ—junction between endometrium and inner myometrium) or myometrium (adenomyoma). It is usually diagnosed between 40 and 50 years, with the most common presenting symptoms being dysmenorrhoea, menorrhagia and subfertility.³

Adenomyosis is notoriously difficult to diagnose clinically and in the past has been diagnosed on histology after hysterectomy.⁴ Adenomyosis is often misdiagnosed as multiple uterine leiomyomata, which have different prognosis and management options. With greater awareness of the condition and more expert use of technology, such as MRI, the disease is now more commonly diagnosed prior to invasive surgery.³ This is important as it can avoid potential unexpected outcomes, as demonstrated in the case below.

CASE PRESENTATION

A 38-year-old nulliparous female presented to an assisted conception clinic with subfertility. Her husband had two children from a previous marriage and had a vasectomy 8 years previously. An attempt at Testicular Sperm Aspiration and Percutaneous Epididymal Sperm Aspiration (TESA-PESA) with a view to performing intracytoplasmic sperm injection had been successful. Thus she was hoping to conceive via in vitro fertilisation (IVF). She had a history of subfertility with severe dysmenorrhoea and regular cycles. She denied any menorrhagia. Her medical history was otherwise unremarkable and she did not take any regular medications. She had no significant smoking or alcohol history. Pelvic examination revealed a bulky uterus.

INVESTIGATIONS

In terms of subfertility investigations, her biochemistry was normal and her fallopian tubes were patent. A transvaginal ultrasound (TVUS) was performed demonstrating an 8 cm reasonably well-defined mass in the body of the uterus and possibly a further 3 cm mass to the left of the body. It was unclear if this was attached to the left ovary or the actual body of the uterus. The right ovary was seen distinctly and appeared normal. Based on these findings, a presumed diagnosis of uterine leiomyomata (fibroids) was made and no further investigations were performed at this stage.

DIFFERENTIAL DIAGNOSIS

- ▶ Leiomyomata
- ▶ Endometriosis
- ▶ Adenomyosis

TREATMENT

A decision was made to attempt to remove the lesions prior to attempting IVF and the patient proceeded directly to surgery. However, on laparotomy, it was discovered that both ovaries and tubes were stuck down in the Pouch of Douglas with endometriosis. The mass seen on the left on ultrasound scan was in fact an endometrioma on the left ovary that was ruptured during the blunt dissection. Both ovaries were freed and the endometrioma was biopsied. The remainder of the internal aspect of the cavity was diathermied. On dissecting what was thought to be a fibroid out from the posterior aspect of the uterus, it became evident that the whole uterus was enlarged and deformed from adenomyosis. It was impossible to remove the adenomyotic area without completely destroying the

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endometrial cavity. There was haemorrhage from the right uterine vein and left pelvic sidewall, with approximately 2 L of blood loss; the surgeon proceeded to a subtotal hysterectomy. The decision was made in light of significant blood loss and the presumed negligible probability of successful IVF as a result of the extensive adenomyosis.

OUTCOME AND FOLLOW-UP

Histology demonstrated the presence of deeply penetrant adenomyosis within the uterine wall. There was no evidence of endometrial hyperplasia or malignant change. The left ovarian biopsy demonstrated endometriosis. The patient recovered well postoperatively after transfusion of 2 units of packed red blood cells and is now pursuing surrogacy options. Although the patient was understandably shocked at the outcome of the operation, at follow-up she was relieved that she no longer suffered from severe dysmenorrhoea.

DISCUSSION

This case highlights the need to consider adenomyosis preoperatively in the subfertile woman with an abnormal ultrasound scan. If a diagnosis is made, conservative management options can be considered as an attempt to avoid radical surgery.

Clinical findings

In retrospect, one could note that leiomyoma are more likely to be associated with menorrhagia rather than dysmenorrhoea alone. Additionally, on examination, a bulky uterus was noted rather than a nodular uterus, which is more frequently the case with leiomyoma.⁵

Moreover, distinguishing superficial from deep adenomyosis remains a challenge, but one that is the key to appropriate management of the condition. Clinically, distinguishing the two remains difficult due to the absence or non-specific nature of symptoms. It is hypothesised that superficial adenomyosis is more commonly associated with abnormal uterine bleeding, whereas the deeper disease is thought to cause more pain, heavier bleeding and dyspareunia. On examination, the uterus is globular and painful on mobilising.⁶

Imaging

In terms of imaging, a pelvic ultrasound scan remains the first-line investigation as this alone may lead to a diagnosis—anechoic subendometrial cysts in the myometrium (approximately 2–4 mm diameter) are pathognomonic (specificity 98%).⁷ Other signs include a heterogenous appearance of the myometrium, an enlarged but smooth contoured uterus (as opposed to irregular contours associated with uterine leiomyomata) and asymmetrical myometrial walls, suggesting muscle hypertrophy.⁶ With three-dimensional ultrasound scan, the most sensitive feature is a difference in JZ thickness ≥ 4 mm as well as JZ distortion and infiltration.⁷

In terms of differentiating between leiomyoma and adenomyosis on ultrasound scan, the former is associated with defined margins, round lesions causing mass effect with calcification and peripheral vascularisation. However, adenomyosis is characterised by lesions of varying shape with poorly defined margins with no calcification. There is a rectilinear pattern of vascularisation which crosses the hypertrophied endometrium.⁶

Significant training is required to recognise the ultrasound features of adenomyosis and as a result, there is substantial inter-observer variation. In 2001, Dueholm and colleagues conducted a double-blind study of 22 patients and found that MRI was superior to TVUS in the diagnosis of adenomyosis, having a

similar sensitivity but greater specificity (MRI 0.86 (0.76–0.93) and TVUS 0.65 (0.50–0.77)). This is partly due to its excellent soft tissue differentiation and it is less user dependent. A combination of both modalities produced greater sensitivity (0.89 (0.64–0.98)) but lower specificity (0.66 (0.44–0.73)). The diagnostic accuracy of MRI was improved by excluding uteri with a volume greater than 400 mL and by calculating the maximum difference between the thinnest and thickest JZ.⁸ A later review by Dueholm confirmed that MRI was useful in confirming indefinite ultrasound findings and is recommended when coexisting pathologies, such as myomas and severe endometriosis, exist.⁹ This is due to the fact that acoustic shadowing can limit further evaluation of the uterus on TVUS in the presence of fibroids.¹⁰ Endometriosis is thought to coexist with adenomyosis in 54–90% of cases, with some individuals hypothesising that the two conditions are different stages of the same disease process.¹ Hence, in cases of dysmenorrhoea with endometriosis and ill-defined lesions on ultrasound scan, adenomyosis should be strongly suspected.

Many of the identifying features on MRI are similar to those found on ultrasound—an enlarged uterus with irregular margins, asymmetrical myometrial thickening and thickening of the JZ.¹¹ However, JZ thickness varies with age, position in menstrual cycle, during pregnancy and menopause and with hormone usage; hence, one must be aware of these factors.¹² Additionally, Maheshwari *et al*¹ make an important point that exact criteria for diagnosing adenomyosis, with both TVUS and MRI, vary between studies in the literature. Furthermore, the criteria for histological diagnosis are also inconsistent.

Adenomyosis and infertility

Although no direct epidemiological studies exist linking adenomyosis to infertility, a strong argument can be made linking the two from indirect studies. Early data from de Souza *et al*¹³ demonstrated a 54% incidence of JZ thickening (strong evidence for adenomyosis) in subfertile patients with symptoms of menorrhagia and dysmenorrhoea. In 2013, Tomasetti and colleagues concluded that adenomyosis confers lifelong infertility in baboons and a poorer outcome after assisted reproduction techniques. They also reported a dose effect relationship between the extent of adenomyosis and abnormal contractility of the uterus and fallopian tubes. However, the group highlighted the difficulty in assessing the relationship between adenomyosis and subfertility due to the confounding effect of endometriosis that often coexists.¹⁴

Furthermore, it has been suggested that adenomyosis may be a cause of recurrent implantation failure. A 2011 case series identified four women, with recurrent implantation failure during IVF, as having a diagnosis of adenomyosis. Adenomyosis is thought to cause inflammatory changes in the endometrium and have adverse effects on the composition of the endometrial fluid, both of which may adversely affect implantation.¹⁵ In fact, in IVF therapy, an inverse relationship has been found between JZ thickness and implantation rate.¹⁶ This has important clinical implications, which will be discussed later.

Management

The overall management approach for adenomyosis depends on the patient's age, symptoms, associated pathology and her desire for future pregnancies. Classical treatment for severe adenomyosis includes endometrial ablation and hysterectomy.¹⁷ In women who wish to conceive, however, conservative approaches must be considered. Furthermore, treatment for adenomyoma and diffuse adenomyosis will vary. Unfortunately to date, the majority of studies examining the impact of treatment

of adenomyosis on fertility have been uncontrolled, including a number of case series; thus, the true impact of the interventions described below is unclear.¹

Vessel embolisation

A number of studies have been conducted examining the effect of uterine artery embolisation (UAE) on adenomyosis. However, due to lack of control or randomisation, high-quality data is lacking. Kim *et al* conducted the largest study of 54 patients with a 3-year follow-up. In total 57.4% of patients demonstrated long-term success in terms of reduction in menorrhagia and dysmenorrhoea symptoms. Nineteen patients had recurrence, occurring between 4 and 48 months (mean 17.3 months). Four patients underwent hysterectomy due to recurrence of symptoms.¹⁸ A 2009 study of 27 women with symptomatic adenomyosis diagnosed on MRI demonstrated a 79% improvement in menorrhagia symptoms at 12 months. However, at 3 years, 45.5% of women available for follow-up (n=14) reported deterioration in symptoms, suggesting that UAE is effective only in the short term.¹⁹

Hormonal therapy

In terms of medical management of adenomyosis, oral progestones are often used to control menometrorrhagia owing to their ability to cause endometrial atrophy. Their efficacy in the treatment of endometriosis is well known. However, data validating their use in this condition is lacking.²⁰

Gonadotrophin-releasing hormone (GnRH) and antioestrogens such as danazol can also be used. However, their use is partly limited by side effects including mood swings, hot flushes and osteoporosis in the long term.¹⁴ GnRH agonists cause hypoestrogenism. This reduces JZ thickness, uterine size and endometrial deposits, which produce the symptoms of dysmenorrhoea.¹⁸ A number of studies have reported successful pregnancy outcome following treatment with GnRH.^{21–24} However, in this particular case, the size of the lesions would likely limit the effectiveness of GnRH alone.

There are two case series reports in the literature examining the effect of a danazol-loaded intrauterine device²⁵ and vaginal ring²⁶ in patients requiring fertility-preserving treatment of adenomyosis. The pregnancy rate of both studies combined was 41% (16 of 39).

The levonorgestrel-releasing intrauterine system has also been shown to be effective in the treatment of adenomyosis in infertility. In one study of 25 women, it led to a 9.8% reduction in uterine size at 12 months and abolished symptoms of menorrhagia.²⁷

Combined surgical and hormonal treatment

In 2009, Wang *et al*²⁸ carried out a study to evaluate the role of surgery in the management of severe symptomatic adenomyosis. This was a retrospective study analysing outcomes in 65 women treated with conservative surgery (adenomyomectomy) with or without 6 months of GnRH agonist (group A) or 6 months of GnRH alone (group B). Outcome was measured both subjectively in terms of symptom control, and objectively using Ca125 levels and uterine size. The women in group A had more infertile years, a larger uterine size and higher Ca125 levels, although this group reported better symptom control over the 36-month follow-up. Clinical pregnancy rates and successful delivery rates at 3 years were significantly higher in group A (46.4% vs 10.8% ($p<0.002$) and 32.1% vs 8.1% ($p=0.022$)). These results suggest that conservative surgery or combination therapy is more effective than medical therapy alone in terms of

symptom control and reproductive outcome in patients with adenomyosis.

Conservative surgery alone

A recent review identified three case studies examining the effect of conservative surgery alone. The surgery itself consisted of excision of the adenomyotic tissue and hysteroplasty (via laparoscopy or laparotomy). Two studies reported live birth rates^{29–30} and one reported successful clinical pregnancy.³¹

A recent study by Kishi and colleagues examined the determinants of successful pregnancy following laparoscopic adenomyomectomy. Women were divided into two groups by age— ≤ 39 and ≥ 40 years. Rate of clinical pregnancy was 41.3% and 3.7%, respectively, suggesting that age plays a significant role for likelihood of successful outcome. Factors favouring a positive outcome included a history of IVF treatment and posterior wall involvement. In the ≤ 39 years group, 60.8% of women who had experienced previous failed IVF became pregnant after this conservative surgical approach.³²

MRgFUS

MRI-guided focused ultrasound (MRgFUS) is another developing treatment modality for adenomyosis. It has been used to treat focal adenomyosis with a resulting successful pregnancy.³³ Kim *et al* showed that MRgFUS provided significant symptomatic relief up to 6 months post-treatment for 35 women with adenomyosis. However, further studies are required to further evaluate this form of treatment and there is limited data on its effectiveness in women undergoing IVF.³⁴

Adenomyosis and IVF treatment

With a JZ thickness >10 mm on MRI, strong consideration should be given to treatment with GnRH prior to the start of IVF. The treatment protocol aims to reduce the effects of adenomyosis on the endometrium and endometrial fluid, and hence increase the chances of embryo implantation. This has been proven to be effective in patients with endometriosis.³⁵ A 2011 case series demonstrated successful pregnancy in four women with adenomyosis after an ultra-long pituitary downregulation regime. A GnRH agonist was administered (Zoladex injection or Syneral nasal spray) for 6–8 weeks before gonadotrophin stimulation. Additionally, women received 15 mg prednisolone daily, from day 7 of gonadotrophin stimulation until the start of the second trimester, to limit inflammatory activity in the endometrium.¹⁵

In 2013, Niu *et al*³⁶ examined the effect of long-term pituitary downregulation on pregnancy outcomes with frozen embryo transfer in patients with adenomyosis. This was a retrospective study of 339 women—194 received GnRH agonist and hormone replacement therapy (HRT), and 145 received HRT only. On the day of progesterone administration, serum progesterone and endometrial thickness were greater in the HRT-only group. The combined GnRH and HRT group demonstrated better outcomes in terms of clinical pregnancy, implantation and ongoing pregnancy rates (51%, 33% and 49% vs 24%, 16% and 21%). These results suggest that a pituitary downregulation protocol should be strongly considered in patients with adenomyosis pursuing IVF techniques.

In the current case, preoperative investigations were insufficient. It would have been wise to perform MRI prior to surgery. This may have led to a diagnosis of adenomyosis and conservative treatment options being pursued as opposed to laparotomy and the resulting subtotal hysterectomy, which resulted in the patient being unable to conceive. Alternatively, the above protocol could have been attempted prior to IVF.

Learning points

- ▶ Adenomyosis is a common condition present in approximately 1% of women and a high index of suspicion should be observed in the subfertile woman with a bulky uterus. This may avert potential unfavourable outcomes as described in the above case.
- ▶ There are features that can be used to differentiate leiomyomas from adenomyosis on transvaginal ultrasound. However, if diagnosis is in doubt, further investigation should be undertaken—MRI should be strongly considered. However, there are no internationally agreed criteria for diagnosing adenomyosis with either modalities or histological specimen. These are in need of standardisation.
- ▶ There is no definitive treatment that can be recommended in women with adenomyosis wishing to preserve fertility due to a lack of good quality prospective studies. Every suspected case should be discussed as part of a multidisciplinary team with interventional radiologists in order to proceed with the most appropriate treatment for the individual case.
- ▶ In patients presenting with fertility issues and recurrent implantation failure, consideration should be given to suppressing MRI-proven adenomyosis prior to IVF, and to use steroids during the stimulation phase and early pregnancy in these patients to reduce the inflammatory disturbance that adenomyosis may cause in the endometrium.

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