Adenomyosis a forgotten cause of infertility

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Abstract

Objectives: To review whether adenomyosis causes infertility or not, the current available methods of its diagnosis, the lines of adenomyosis associated infertility treatment, and why future research is needed.

Materials and methods: Electronic databases for studies on adenomyosis and infertility published between 1995-2020 were searched and reviewed using the PUBMED as a search engine. The following keywords were used: adenomyosis, infertility, ultrasonography, MRI, IVF/ICSI, cytoreductive surgery, GnRHa, NSAIDs and HIFU. No language limitations were applied.

Findings: Adenomyosis is a disease of women in reproductive age and contributes to infertility. It can be accurately diagnosed by non invasive imaging. There are different lines of treatment of adenomyosis associated infertility. However all currently available methods have their limitations. There is a need to expand research in this area to be able to answer the enigma of adenomyosis and infertility.

Conclusion: Reproductive medicine physicians should be aware of the possible contribution of adenomyosis to infertility and look for its presence during infertility workup. This will enable them to properly counsel the patients and choose the most appropriate methods for management of their infertility.

Keywords: adenomyosis, Junctional Zone, infertility, IVF, cytoreductive surgery, IVF/ICSI, ultrasonography, MRI.

INTRODUCTION

Early in the last decade a systematic review of prevalence diagnosis, treatment and fertility outcome, was published from a reputable center of research in one of the top journals of human reproduction, concluded that more studies are needed to determine adenomyosis implications on reproductive outcomes, with or without treatment. The authors suggested until then, there is no indication for finding or treating adenomyosis in women who wish to conceive (1). However with the improvement and wider use of diagnostic imaging and application of various treatment modalities, whether medical, surgical or assisted reproductive technology (ART), it is time to change this metto regarding adenomyosis and infertility. This review addresses the recent developments in the various aspects of adenomyosis and infertility and makes the argument why reproductive medicine physicians should change their old approach to adenomyosis in their infertile patients, and counsel patients accordingly.

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Materials and Methods

The author searched 16 electronic databases for studies published between 1995-2020, using the PUBMED as a searching engine, on the incidence of adenomyosis among infertile patients, whether it causes infertility or not, accuracy of modern non invasive methods of its diagnosis, the current available methods for treatment of patients with adenomyosis associated infertility. The review included systematic reviews, meta-analysis and studies, without language limitations, comparing the outcome of infertile women with and without adenomyosis which accounted for confounders. The following Keywords were used: adenomyosis, infertility, Junctional zone (JZ), ultrasonography, MRI, IVF/ICSI, cytoreductive surgery, GnRHa, NSAIDs and HIFU.

Findings

The author included 112 unique references and assessed 72 full-text articles. It would be appropriate to discuss separately the outcome of search on each of the different items looked at.

Is adenomyosis a disease of older women and is not common among infertile patients?

Though endometriosis was first explained in the Egyptian scrolls in 16th century BC, it was only in 1860 that Rokitansky described adenomyosis as a common gynecological disorder in women aged 40-50 years characterized by the presence of heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia (2,3). With a quoted prevalence ranging from 8-27% based on histological examination of hysterectomy specimen, it was usually thought that adenomyosis is a condition of elderly parous women and an association between subfertility and adenomyosis has not been fully established (1). However today with the development of modern imaging, several authors believe that the disease is no longer considered typical of women over 40 years of age and it affects 20-30% of women in reproductive age (4-7). Punete et al 2016 (8) using 3D ultrasonography reported adenomyosis incidence of 24.4% in patient with repeated implantation failure and recurrent miscarriage. Khandeparker et al (2018) (9) using MRI reported an incidence of 33.3% of adenomyosis among infertile patients. Kunz et al (2005) and Chapron et al (2017) respectively reported an incidence of adenomyosis of 79% and 59.9% among infertile patients when adenomyosis is associated with endometriosis (10, 11). With the use of ultrasonography and MRI for the diagnosis of adenomyosis a new epidemiological scenario had developed with an increasing number of women of reproductive age with adenomyosis due to the wider use of ultrasound and MRI for its diagnosis. (12). Adenomyosis was found in 22% of infertile women less than 40 years old undergoing ART (8). Furthermore with the global delay of the age of women at first child birth, it is not surprising that adenomyosis is likely to be encountered in a substantial percentage of infertile patients (13). Several reports have indicated that between 11.9-31% of women undergoing ART are at the age of >40 (14-17).

Is accurate diagnosis of adenomyosis still only possible by invasive techniques?

In the near past adenomyosis was under diagnosed and the diagnosis was only established at pathological examination of hysterectomy specimens or via invasive diagnostic procedures such as percutaneous or laparoscopic uterine biopsy. In the 1960s when laparoscopy was introduced the diagnosis and management of endometriosis were revolutionalized but leaving behind adenomyosis which continued to be diagnosed retrospectively only in hysterectomy specimens. In the mid 1980s the situation changed dramatically when non invasive imaging techniques became available enabling a prospective diagnosis of adenomyosis. The higher frequencies (5-7MHZ) vaginal ultrasonography made it invaluable in the diagnosis and follow up of patients with adenomyosis due its high accuracy. The use of routine real-time TVS in patients with suspected adenomyosis became highly recommended (18, 13). The 2D ultrasonographic criteria for diagnosis of adenomyosis were described by several authors in the literature. They included; globular enlarged uterus, asymmetrical enlargement of anterior and posterior walls, diffusely irregular myometrial echotexture with hyperechoic

features, subendometrial myometrial cysts and echogenic islands, hypoechoic linear striations within a heterogeneous myometrium, increased blood flow in affected areas, and irregular, ill defined or interrupted junctional zone (JZ) (19-21). A systematic review and a meta-analysis by Champaneria et al 2010 reported a sensitivity and a specificity of 2D US of 72% (95% C/65-79%) and 81% (95% C/77-85%) respectively (22). 3D ultrasonograpy was also successfully used in the diagnosis of adenomyosis. The 3D focuses predominantly on the junctional zone (JZ) as there is a strong association between thickening and disruption of the junctional zone (JZ) and the occurrence of adenomyosis (23,24). In a study on 45 patients who have had hysterectomy for adenomyosis, Exacoustos et al (2011) found that the features with the highest specificity were a junctional zone (JZ) thickness of > 8mm, myometrial asymmetry and hypoechoic striations. When at least 2 of these features are present, the overall accuracy was reported to be 90% with sensitivity and specificity of 92% and 83% respectively (25). Most researchers suggested that 3D US is more accurate than 2D US in the diagnosis of adenomyosis. However a recent meta-analysis by Andres et al (2018) suggested there was no improvement in the overall accuracy in TV US 3D compared with TV US 2D for the diagnosis of adenomyosis (26). The accuracy of diagnosis of adenomyosis by ultrasonography is highly dependent on the experience of the operator, with significant intra-observer and inter-observer variability in the findings and therefore the use of MRI for the assessment and follow up of patients with adenomyosis was recommended (9). High resolution pelvic MRI is now considered the current reference standard for non invasive imaging of adenomyosis due to its multiplanar capabilities, excellent soft tissue resolution, repeatability and reproducibility and less operator dependent with a sensitivity and specifity of 86-100% in asymptomatic patients (27, 9). Several workers reported on the criteria for adenomyosis diagnosis using MRI. These included focal or diffuse thickening of the JZ thickness > 5mm or >12mm, poor definitions of JZ borders, low signal intensity uterine mass with ill defined border, localized high signal foci within an area of low signal intensity, linear striations of increased signal radiating out from the endometrium into the myometrium and bright foci in endometrium isointense with myometrium (28-30, 13). Review of 57 out of 687 articles by Bazot et al 2018 concluded that MRI is more useful than TVS in the diagnosis of subtle nuances of uterine adenomyosis and whether it is internal adenomyosis, adenomyomas or external adenomyosis (21). Very recently Chapron et al 2020 have indicated that imaging techniques, including 2D and 3D US as well as MRI allow proper identification of the different phenotypes of adenomyosis (diffuse and/or focal). However while the diagnosis of diffuse adenomyosis is straight forward, in more limited disease , the diagnosis has poor inter-observer reproducibility leading to extreme variations in the prevalence of disease (12).

Is it true that adenomyosis does not cause infertility, and it is the usually associated reproductive disorders, what cause infertility?

Adenomyosis is frequently associated with fibroids, endometriosis or muscular hypertrophy. MRI can be useful in differentiating the nature of the condition whether adenomyosis alone or whether it is associated with other pathology (31). In the experimental animal the baboon, endometriosis is statistically significantly associated to adenomyosis and adenomyosis is strongly associated with lifelong primary infertility (32), Kunz et al in 2005 suggested that uterine adenomyosis is significantly associated with pelvic endometriosis, yet it constitutes an important factor of sterility in endometriosis presumably by impairing uterine sperm transport (10). Just one year later Kissler et al published their work on the radionuclides transport in women with diffuse adenomyosis and primary infertility. When radionuclides mimicking sperm size were placed into the posterior vaginal fornix, no utero-tubal transport of the radionuclides was detected and radionuclides remained in the uterine cavity in 70% of cases (33). Kusakabe et al in 2005 made the observation that in Knock-out mice their gestational capacity is impaired if these animals are deprived of perforin. Perforin induces apoptosis in target cells. Thickening of the JZ myometrium, a common finding in adenomyosis, occurs in the absence of perforin (34). Several researchers have proved and suggested many factors in the pathophysiolo-

gy of adenomyosis to account for infertility in adenomyosis. These include abnormal concentration of intra-uterine free radicals (35) , abnormal uterine contractility (36) an increase in cytokines and inflammatory mediators, VEGF and microvessel density (37), gene dysregulation (38), impaired implantation due to decrease in HOXA10 (39), altered endometrial function and receptivity (40), immune dysfunction and alterations of adhesion molecules, (41), impaired decidualization due to decreased expression of NR4A nuclear receptors (42,43), possible disturbance of the role of microbiota for a receptive and fertile endometrium (44). Several workers have demonstrated reduced concentrations of various implantation factors in adenomyosis - associated infertility. These included decrease in leukemia inhibitory factor (45, 46) HOXA10, (39) and RCASI (47). Though adenomyosis is frequently associated with other reproductive disorders which could cause infertility, yet adenomyosis by itself could account for infertility in a number of patients. Adenomyosis may also have a deleterious effect on the outcomes of infertility treatment when associated with other reproductive disorders. This concept is supported by research in basic science and has been emphasized by clinical research particularly in assisted reproductive programs. Chapron et al 2020 suggested an integrated non-invasive diagnostic approach of adenomyosis, considering risk factors profile, clinical symptoms, clinical examination and imaging to adequately identify and characterize adenomyosis and its contribution to patients infertility (12).

Are there robust clinical studies to support the negative effect of adenomyosis on fertility and fertility treatment?

A direct causal relationship between adenomyosis and subfertility has been proposed in the literature. However, no robust data is available due to the lack of prospective randomized controlled trials (48). This is mostly because it is extremely difficult to conduct such trials without violating the ethical principles of research. Furthermore with its poorly understood pathogenesis, the impact of the different phenotypes of adenomyosis on reproduction stays unclear. Furthermore, interpretation is rendered difficult because of the high incidence of concomitant pathology as fibroids and endometriosis (49). Nevertheless a lot of evidence is accumulating from basic and clinical studies in ART to support the deleterious effect of adenomyosis on fertility and fertility treatment. An early study in 1998 by Fanchin et al measured the frequency of JZ contractions and its effect on pregnancy rate in IVF program. They found a stepwise decrease in clinical pregnancy rates with increased frequency of JZ contractions. Pregnancy rates decreased from 50% to below 20% when JZ contractions increased from < 3 contractions to >5 contractions per minute $P < 0.001$ (50). Piver studied the JZ thickness and implantation failure in IVF cycles. The pregnancy rate/transfer was 45%, 16% and 5% when JZ thickness was < 10mm, 10-12mm and >12mm respectively (51). MRI evaluation of JZ thickness was the best negative predictive factor of implantation failure in IVF cycles. In another prospective study on 152 patients undergoing IVF, implantation failure was 37.5% and 95.8% when the JZ thickness was <7mm and 7-10mm respectively $P<0.0001$ (52). Thus the increase in JZ thickness can be significantly correlated with implantation failure in IVF independently of the cause of infertility or patient's age. A meta-analysis and systematic review by Vercillini et al on women with adenomyosis undergoing ART (304 patients) showed a 28% reduction in the likelihood of clinical pregnancy and increased miscarriage rates when compared with women without adenomyosis (1262 patients) (48) . A more recent retrospective study of 973 patients undergoing IVF by Sharma et al found adenomyosis adversely affects the life birth rate and miscarriage rate whether alone or when associated with endometriosis. Live birth rate was 27.4%, 26.4%, 11.3% and 12.5% for patients with tubal, endometriosis only, endometriosis+adenomyosis and adenomyosis only respectively. The miscarriage rate was 13%, 14.6%, 35% and 40% for these patients respectively. The differences were statistically significant. The study concluded that screening for adenomyosis might be considered before IVF. Affected couples should be counseled about the reduced success rates after IVF treatment and about the associated complications of pregnancy (53) . Park et al in 2016 performed a retrospective study of 241 IVF cycles for women with adenomyosis

between the years 2006-2012. They compared IVF results in women without versus with GnRHa pretreatment, fresh embryo transfer versus frozen embryo transfer and in women with focal versus diffuse adenomyosis. The clinical pregnancy rate was 25.2% (37/147) in fresh ET without GnRHa pretreatment versus 30.5% (32/105) in fresh ET with GnRHa pretreatment and 39.5% (17/43) in FET with GnRHa pretreatment. The clinical pregnancy rate was 32.9% (23/70) in fresh ET following GnRHa pretreatment in women with focal adenomyosis compared with a pregnancy rate of 25.7% (9/35) in women with diffuse adenomyosis. In FET with GnRHa pretreatment, pregnancy rate was 43.5% (10/23) versus 35% (7/20) in focal and diffuse adenomyosis respectively (54). A recent meta-analysis by Younes et al 2017 compared the effect of adenomyosis on IVF treatment outcomes in 519 patients with adenomyosis versus 1535 patients without adenomyosis (55). They found adenomyosis has a detrimental effect on IVF clinical outcomes concerning live birth rates and miscarriage rates. The use of long term GnRHa or long protocol could be beneficial for women with adenomyosis undergoing IVF. Cumulative spontaneous clinical pregnancy rates in women who underwent surgery for adenomyosis and who did not favoured surgery. Clinical pregnancy rate after fresh ET in women with diffuse adenomyosis was less than in women with focal adenomyosis. Recently Razavi et al performed a systematic review and meta-analysis to study the possible adverse pregnancy outcomes in women with adenomyosis (56). The number of women with adenomyosis was 322 and those without adenomyosis 9420. They found three fold increase in preterm birth rate ($z = 5.47$ $p < 0.00001$), higher incidence of pre-eclampsia ($z = 2.06$ $p = 0.04$), higher incidence of small gestational age ($z = 3.61$ $p = 0.0003$) in women with adenomyosis compared with women who did not have adenomyosis.

Are there standardized guidelines on treatment of infertility associated with adenomyosis?

It is difficult to standardize guidelines on the management of infertility associated with adenomyosis. This is simply because the pathogenic mechanisms of adenomyosis development are still unclear and because there are different phynotypical expressions of adenomyosis. It is not proven yet that all the evidence available may be applied to different forms of the disease (57). Sex steroid hormones, inflammation, neoangiogenesis, growth factors, ECM enzymes and neurogenic factors are key pathogenic mediators of pain, abnormal uterine bleeding and infertility. More research is needed to better understand the pathophysiology and early pathways implicated in the initiation of adenomyosis to develop adequate therapeutic strategies. The current treatment of adenomyosis associated infertility can be summarized as follows:

Medical Treatment

Few RCTs focused on medical treatment for adenomyosis. However, no drug is currently labeled for adenomyosis and there are no specific guidelines to follow for the best management of these patients (58). Adenomyosis is usually associated with chronic pelvic pain and severe dysmenorrhoea which affects quality of life of patients. If the pain is not alleviated for a long time it can change how the brain perceives it and processes signals leading to an amplification of pain (59). It is important to relief the pain and minimize the abnormal uterine bleeding frequently associated with adenomyosis even if the primary complaint of the patient is infertility. (60).

1. Non steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs and acetaminophen remain the first line in the pharmacological management of pain. They may be used alone or in combination with other medications. NSAIDs like ibrufen and naproxen are effective and well tolerated drugs. It is best to schedule the initiation of the medication 1-2 days prior to the onset of bleeding to improve the pain and reduce menstrual flow (60).

2. Suppressive hormonal therapy:

Hormonal suppression is usually a first line treatment of adenomyosis related pain and menstrual bleeding. For the infertile patient it may be the only treatment required for few patients or it may be an adjuvant pretreatment or post treatment to improve the results of other definitive treatments as surgery or IVF.

2.1- Combined estrogen and progesterone therapy (pills, vaginal ring, or transdermal patch).

2.2- Progesterone- only pills or intramuscular depot-medroxy progesterone.

2.3- Levonorgestrel - containing intrauterine device.

These medications lead to atrophy of the intrauterine endometrial tissues and reduction of the size of the adenoma. These various drugs have been shown to be equally effective in several comparative randomized controlled trials. The reproductive medicine physician should choose the treatment option based on cost, side effects and prior experience in individual patient. (61).
2.4- GnRHa produces a hypogonadotropic state by down regulating luteinizing hormone and follicle stimulating hormone: A high proportion of patients develop troublesome side effects including vasomotor symptoms, vaginal atrophy and sleep disturbance. If used for a period of more than 6 months they should be used with adds-on to avoid osteoporosis. They may be used for infertile patients followed by spontaneous pregnancy. More commonly they are used before IVF to improve its results or following surgical treatment for adenomyosis. Long term suppressive therapy with GnRHa before IVF has been shown to improve outcomes (58). Several authors reported on spontaneous successful pregnancies and live births in small series following treatment with GnRHa for adenomyosis in infertile patients (13).

3. Anti coagulation therapy:

Liu et al 2016 had published corroborating evidence for platelets induced epithelial -mesenchymal transition and fibroblast-to-myofibrolast transdifferentiation in the development of adenomyosis. These findings underscore the possibility for the use of anti-coagulation therapy in adenomyosis and holds promise for the development of novel biomarkers for adenomyosis (62).

4. High intensity focused ultrasound (HIFU):

There has been a number of publications on the use of HIFU for the treatment of infertility in patients with adenomyosis (63-67). A review of the literature between 2000- March 2017 by Zhang et al (2017) concluded that HIFU is a non invasive, ablation technique for both focal and diffuse adenomyosis (68). It is associated with a high conception and live birth rates. Zhou et al (2016) reported on 68 patients in whom 54 patient conceived and 21 patients (30.1%) delivered (67). HIFU is associated with a low rate of minor and or major complications. Several factors contribute to its efficacy including distance from the skin to the adenomyoma, volume of the adenomyoma, number of hyperintense foci, location of the uterus and the adenomyoma, and whether it is associated with endometriosis or not. Strict selection criteria have been used to achieve higher success rate. Patients with associated pelvic endometriosis, adhesions between the bowel and uterus and abdominal surgical scar wider than 10mm are relative contra-indication for the procedure.

5. Cytoreductive Surgery:

Cytoreductive Surgery has been used for the treatment of adenomyosis in infertile patients. However, the operation is associated with complications particularly hemorrhage and rupture scar in subsequent pregnancy. Cytoreductive Surgery is feasible for patients with localised or focal adenoma. However, for diffuse adenomyosis the operation is difficult and associated with massive hemorrhage and high incidence of scar rupture in subsequent pregnancy and labour. To reduce the amount of hemorrhage Pitressin is first injected in the uterine wall. This is followed by excision of the adenoma either via laparotomy or possibly laparoscopy in experienced hands. For diffuse adenomyosis the classic V shaped wedge resection is performed followed by suturing the uterine wall. If the lesion is large the uterine muscle flap method is used with asymmetric dissection of the lesion (69). Diffuse adenomyosis may also be excised using the triple flap method which involves extensive dissection of the adenomyosis (69,70). When surgical excision is performed contraception should be administered for periods of 6-24 months depending upon the extent of the dissection and the operative restoration of the uterine wall (69,71). Most publications of cytoreductive surgery for adenomyosis come from Japan. Between the year 1990-2018, 2365 cases were reported globally. 2123 (89.8%) cases were reported from Japan. Pregnancy was reported in 397 (16%) cases which ended in a live birth in 337 (84.89%) cases . Rupture uterus was reported in 23 (5.79%) cas-

es. There was a higher incidence of miscarriage, placenta accrete and percreta compared to CS and myomectomy scars (70).

6. ART:

Based on accumulating evidence from previously published studies, discussed earlier in this review, ART is an important line of treatment to achieve pregnancy in infertile patients with adenomyosis. If medical or surgical treatment failed then IVF becomes an option. In some other cases it may be the first option such as when associated with male factor or tubal factor infertility, advanced maternal age or long duration of infertility. Long term GnRHa pretreatment seems beneficial to improve results of ART. The use of long down regulations GnRHa protocol is preferred to the antagonist or short protocols. Frozen ET with GnRHa pretreatment seems to be superior to fresh ET. The results of ART in patients with focal adenomyosis are likely to be superior to those in patient with diffuse adenomyosis. Adenomyosis seems to have a deleterious effect on the outcome of pregnancy including preterm birth, pre-eclampsia and small gestation for age. Should surgery be performed before ART contraception should be applied for a period of 6-24 months depending on the extent of weakening of the uterine wall. There is no agreement in the literature on guidelines for the treatment of adenomyosis associated infertility. A recent national survey was conducted in Japan as an official project of the Japanese Society of Obstetrics and Gynecology (JSOG) using questionnaires to assess modalities of treatment of adenomyosis associated infertility. Questionnaires were sent to 1149 Japanese medical facilities including 725 institutes that were authorized as training facilities by JSOG and 582 institutes that were registered to JSOG for ART (72). No management policies were found in 106 facilities. The pregnancy rate was 41.7% and abortion rate was 29.8%. Eighty five patients received medications, 89 patients underwent surgery as a pretreatment before infertility treatment and 361 patients had no pretreatment.

Conclusion

Uterine adenomyosis is another enigmatic disease of our time which may cause infertility, repeated implantation failure and recurrent miscarriage. There are different phenotypes of adenomyosis and treatment should be patient centered according to patient's needs and symptoms. Medical pretreatment may improve chances of occurrence of pregnancy and live birth whether spontaneous or following IVF. Long term GnRHa therapy prior to IVF increases pregnancy rate and live birth rate. Though surgical treatment may be beneficial, it is associated with intra operative, post operative, and long term complications. There is an urgent need to establish some systematic classification and research into new molecules in the pathogenic mechanism of adenomyosis to result in guidelines for management of adenomyosis in infertile patients

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