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Review Article

## Adenomyosis and its impact on fertility

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### ABSTRACT

Adenomyosis is an estrogen dependent benign gynecological disease affecting women of reproductive age causing them to have an adverse effect. Symptoms in these patients include pelvic pain, menorrhagia, abnormal uterine bleeding and infertility. It has a negative impact on a woman's reproductive ability. The gold standard treatment for adenomyosis is hysterectomy for whom fertility is not an issue and for whom future pregnancy has no concerns, however females who wish to retain uterus for child bearing purposes the treatment seems to be very challenging. In this literature we will focus on how adenomyosis affects the reproductive outcome in women and what is its impact on the pregnancy rate also we will enlighten the pregnancy outcomes and pregnancy rate in patient with adenomyosis after various treatment Including the medical, surgical and in-vitro fertilization.

**Keywords:** Adenomyosis, Infertility, IVF, Pregnancy outcome

### INTRODUCTION

Adenomyosis (AD) is one of the most common benign pathological disease found in gynecology department, It can be defined as the presence of ectopic stromal and endometrial gland in the layer of uterus known as myometrium resulting in an enlarged hyper trophic and hyper plastic uterus.<sup>1</sup> Based on the characteristic and growth of adenomyosis it is categorized into two form the focal and the diffuse type, when the growth of ectopic endometrial and stromal glands are within the myometrium of the uterus it is referred to as the focal AD, these are circumscribed and localized lesion can also be called as adenomyoma. When the ectopic endometrial glands and stroma are widely spread or distributed throughout the uterine surface it is referred to as diffuse AD.<sup>2</sup> Since the diffuse type AD involves more than half of the myometrium it causes severe menstrual cramp and

more aggravated symptoms in comparison to the focal type. Involvement in diffuse type of AD requires wide range of excision, Henceforth there are several limitations and complications in the outcomes based on the surgical and medical approach in the course of disease entity. AD generally falls into the population of middle aged females, women of reproductive age and females with multiple gestation, the prevalence rate of adenomyosis in general population accounts for about 18%-66%.<sup>3</sup> Patients with AD often complains of hypermenorrhea (extensive menstruation), dysmenorrhea (painful menstruation) passage of blood clots during menstruation, heavy menstrual bleeding along with abnormal uterine bleeding, pelvic pain and dyspareunia (pain during sexual intercourse), infertility and miscarriage are some of the common symptoms which is experienced by these females. However, heavy bleeding accounts for the most common chief complaint in patients

with AD and it has the greatest impact on the quality of life in these females, making them anemic, fatigue and less enthusiastic to carry out activities of daily life.<sup>4</sup> AD have been reported to have a negative impact on a female's child bearing capacity i.e it decreases the chances of spontaneous pregnancy, increases the frequency of abortion and thus leaves the women infertile, by far there is no evidence that can comply with the increase in pregnancy rate just by giving medical treatment alone to these patients.<sup>5</sup> Treatment in these patients mainly depends upon the symptoms, severity and the desire to preserve fertility for child bearing purposes. Use of non-steroidal anti-inflammatory drugs (NSAIDs), Analgesics, oral contraceptives, progestin, gonadotropin-releasing hormone agonists (GnRH<sub>a</sub>), aromatase inhibitor, tranexamic acid, danazol, levonorgestrel intrauterine system (LNG-IUS), danazol-loaded intrauterine devices, uterine artery embolization are some of the conservative treatment used in these patients.<sup>6</sup> Hysterectomy remains the Gold standard choice in females who don't desire future pregnancy, conservative surgeries such as uterine sparing surgery is also carried out on those females for whom fertility is a concern and those who desire for future pregnancy. The confirmatory histopathology diagnosis can only made after hysterectomy. However, imaging modalities like transvaginal sonography, MRI and 3D TVS are some of the tools used in the initial diagnosis of this disease.

#### ***Reasons for female infertility caused by adenomyosis***

The chances of female getting adenomyosis generally increases when a woman is of advanced maternal age, as this disease affect the middle aged women so chances of it reciprocates. Previous studies have shown the interference of AD with embryo implantation, these females are more susceptible to increased chances of spontaneous abortion, they have comparatively lower chances of getting pregnant due to decreased rate of implantation per embryo transfer.<sup>7</sup> Due to ectopic stromal and endometrial gland there is hypertrophy that changes the morphology of the musculature and the plasticity of the endometrial cavity which have a significant effect on the uterine contraction and fertility which perhaps doesn't result in a successful implantation. The junction zone thickness greatly varies in patient with AD to that in a normal female in whom the junction zone thickness is thin, consistent and regular having a maximum thickness of about (JZ median thickness 5.2) but in AD patients there was significant increment in the myometrium thickness which attributed to increased JZ in return which affects the fertility. When the JZ expands from slight to massive size it results in fibrosis and hyperplasia of the endometrial cavity which result in subsequent changes in the elasticity, plasticity and the contour of the uterine cavity which in turns affect the peristalsis and thus fertility.<sup>8</sup> These changes in the JZ can be best visualized on Trans vaginal ultrasound (TVS), 3D - TVS or MRI.<sup>9</sup> On magnetic resonance image when the thickness of JZ

exceed to at least 12mm or to the cut off value of 10mm, JZ AD is said to be present.<sup>10</sup>

#### ***Adenomyosis and infertility***

*Natural pregnancy rate and infertility rate of adenomyosis.*

Studies have shown a decrease in the pregnancy rate (PR) in patients with AD, some researchers have come to the conclusion that AD adversely affects the probability of getting pregnant and early pregnancy losses have also been significantly reported.<sup>11</sup>

Several studies also brought down to knowledge that the frequent miscarriage rate in patients with AD accounts for about 32% to that in women without AD which is 14%.<sup>12</sup> Preterm delivery, premature birth, premature rupture of membrane (PROM), preterm premature rupture of membrane (PPROM), recurrent implantation failure and spontaneous pregnancy losses are some of the complications whose risk is increased in AD patients. However, those patients who underwent surgery for myometrium resection and whose uterus was reconstructed using a "triple flap method" after a period of one year follow up there was a significant increase in the pregnancy rate of 61.5% and live birth rate of 53.8% with more than 75% pregnancy achieved by In Vitro fertilization no uterine rupture was noted in these patients during the course of pregnancy.<sup>13</sup> Out of 103 Patients who underwent clinical adenomyomectomy, 70 of them conceived with a pregnancy rate of 30% in one year and the pregnancy was achieved with IVF.<sup>14</sup> Studies have also reported the change in endometrial receptive marker in an adenomyotic endometrium thus stands another reason for failed implantation.<sup>15</sup> No studies have shown the natural conception by these patients but have always shown a negative impact of AD on infertility.

#### ***Reproductive outcomes of adenomyosis after surgery***

Gonadotropin-releasing hormone analog (GnRH-a) treatment before surgery or preparing the endometrium with GnRH-a for 24 weeks prior to surgery.

The use of (GnRH-a) in combination with estrogen have shown a positive role in pregnancy and has improved the chances of conception in several patients.<sup>16</sup> As visualized by MRI the adenomyotic lesions have significantly decreased by the use of (GnRH -a).<sup>17</sup> The use of it have also played a positive role on the markers of endometrial implantation.<sup>18</sup> It is believed to decrease the size of Adenomyotic lesion, while the AD patients who underwent frozen embryo transfer whose endometrium was prepared with long term (GnRH-a) therapy before the Implantation showed better pregnancy rate in comparison to those in whom pre-treatment with (GnRH-a) was not given.<sup>19</sup>

### **Cytoreductive surgery**

This surgery approach can be an open surgery or the laproscopic one, the approach to AD tissue is similar to myomectomy which involves the same steps in surgery, after the excision of adenomyotic tissue or AD lesions, the uterine layers are often sutured back to restore the contour of the myometrium, the suture technique greatly varies with different types including the U sutures, the figure of eight or interrupted suture.<sup>20</sup> The incision made for excising the AD lesion also varies which includes the transverse H incision or just a transverse or Longitudinal incision or a wedged shaped incision.<sup>21</sup> The approach and outcome is different in surgery of focal AD versus diffuse AD, unlike the focal AD the adenomyotic lesion is not well circumscribed and doesn't have an obscure boundary it becomes difficult to completely excise the lesion without having to predict no postoperative or intra operative complications. Due to the wide excision in diffuse AD followed by uteroplasty the chances of uterine rupture is very high in comparison to the pregnancy outcome in focal AD patients, where conception outcomes after the cytoreductive surgery were believed to improve. The pregnancy outcome and the delivery rate after cytoreductive surgery was higher and also there was symptomatic relief of the clinical manifestations.<sup>22</sup> Studies also concluded that the pregnancy outcome in older women i.e (more than 40 years old) were poor with very low pregnancy rate and thus infer that cytoreductive surgery have no impact on fertility for those women who are above 40 years old. Women who underwent surgery versus women who were only on (GnRH-a) treatment showed a higher delivery rate of 33% versus 8% in the surgery group.<sup>23</sup> After the surgery the delivery and the pregnancy rate were higher in groups who used IVF/ICSI. Complications such as uterine rupture during pregnancy are most likely to be noticed in those cases when surgery was extensive in AD patients and cases of uterine rupture have been reported. 9-15mm is the optimal wall thickness for prevention of uterine rupture and for conception following a cytoreductive surgery.<sup>24</sup> Thus uterine conservative operative method in AD patient can be useful but uterine rupture and prerequisite management should be taken into consideration while operating such patients and following up these patients postoperatively. In comparison to women who are less than 39 years old versus women who are above 40 years old, the pregnancy rate was 41.3 and 3.7%.<sup>25</sup> The symptoms of painful menstruation ameliorated after conservative surgery from 54.6 to 84.6%, symptoms of menorrhagia bettered from 50-68.8% or even to 73.7%, the pregnancy outcome also up regulated from 46.9% to 60.5%.<sup>26</sup>

### **Reproductive outcomes in adenomyosis after In vitro fertilization**

Pregnancy rate in women of more than 40 years old compared to those in younger women is estimated to be (3.7% versus 41.3%) with probability of 0.05, females

who are younger below the age of 39, the In vitro fertilization rate was 21.3% and the IVF pregnancy rate was 60%, patients with a prior history of IVF failure showed the pregnancy rate of (P =0.02).<sup>27</sup>

### **Reproductive outcomes with the use of medical treatment**

The management of patients with adenomyosis still remains controversial albeit there is no proper guideline to follow as a management for these patients. Medical management have always been useful in alleviating the symptoms but doesn't stand as a treatment in absolute cure, they are generally helpful in ameliorating the symptoms but of course cannot treat the disease. The role of NSAIDs, OCPs, levonorgestrel releasing intra uterine systems (LNG-IUS), progestin such as danazol, dienogest and GnRH analogues have no doubt helped in alleviating the symptoms of menorrhagia and pain, significant reduction in the size of adenomyotic lesion is noted with use of GnRH analogue, none of the medical treatment by far has reported to improve fertility outcome alone , except with the treatment of GnRH in combination with surgery has shown to have a positive result on the pregnancy outcome.

Their role on infertility is also very debatable especially when it comes to the use of GnRH analogue Vs without using GnRH analogue and its impact on fertility. Use of GnRH agonists such as nafarelin acetate or leuprolide acetate for a period of 24 weeks showed a spontaneous pregnancy in women with severe adenomyosis.<sup>28</sup> Despite only being few cases or reports in support of this management there were relatively good results in fertility when GnRH analogues were tested both prior and after the surgery. Studies have shown that the chances of pregnancy in infertile females had drastically increased with the administration of GnRH before the cycles of IVF.<sup>29</sup> Patients undergoing frozen embryo transfer (FET) with long term treatment with GnRH agonists and in whom the endometrium was prepared with hormone replacement therapy showed an improved pregnancy outcome.<sup>30</sup>

There was up-regulation of pregnancy rate after GnRH pre-treatment in women undergoing FET by (39.5%) versus (25.2%) without pre-treatment of GnRH analogue.<sup>31</sup> On the contrary there are also studies that showed there is no improvement with the use of GnRH analogue pre-treatment in patients with IVF. With advantages of GnRH pre-treatment on fertility there is limitation too from its long term use. Mood instability, reduced mineral bone density, atrophy of genitalia, hypoestrogenic side effect such vasomotor syndrome are some of the side effect which is also related to the use of it, making it applicable only for a short period of time, plasma estradiol levels should be well monitored to prevent it from hypoestrogenic state and thus preventing its adverse effect while using the drug simultaneously for the therapeutic effect on adenomyosis.<sup>32</sup>

## DISCUSSION

Adenomyosis is a benign disease of the uterine musculature in which the myometrium is invaginated by endometrial glands and stroma cells causing these women to have abnormal uterine bleeding, dysmenorrhea, heavy menstruation and dyspareunia, it affects women of reproductive age and its most commonly seen in women of 30-40 age group. Adenomyosis have generally a poor pregnancy outcome and therefore it's one of the main causes of infertility. Due to lower implantation rate, increased miscarriage, and poor pregnancy outcome, women with adenomyosis have lower chances to conceive in comparison to non-adenomyotic females. The diagnosis of adenomyosis is confirmed by histopathology following a hysterectomy in women with severe symptoms of menorrhagia, heavy menstrual bleeding and pelvic pain. Concerning the treatment in patients with adenomyosis by far there is no international guideline which is to be followed in due course of the disease, treatments are given based on the severity of the disease, the symptomatic complain of the patients and the wish to conserve the uterus for childbearing purpose. Females dealing with infertility issues, the pretreatment of GnRHa in females undergoing frozen embryo transfer showed the highest chance of pregnancy, study by Niu also showed that pregnancy rates, implantation rate and ongoing pregnancies were higher in females whose endometrium was prepared for 6 months with GnRHa pre-treatment before undergoing frozen embryo transfer, in comparison to those in whom pretreatment of GnRHa was not given.<sup>33</sup> Thus infer us that GnRHa pretreatment have a positive effect on fertility. Study conducted in 2014 regarding the effect of adenomyosis on IVF/ICS. It included 9 studies with IVF/ICS except the two case control study, 306 women out of 1865 were diagnosed with AD, the authors came to the conclusion that AD adversely affect the chances of getting pregnant and increases the pregnancy loses.<sup>34</sup>

A retrospective case control study by Hashimoto A, recently showed AD is associated with increased risk of pre-eclampsia, increased second trimester miscarriage and placental malposition.<sup>35</sup> There is an urgent requirement for a unanimous diagnostic criteria and a proper guideline for management in these patients, which will allow the clinicians and researchers to perform well conducted prospective studies on adenomyosis and its effectiveness of surgical treatment in dealing with pregnancy outcomes and fertility.

## CONCLUSION

The management of adenomyosis is very challenging yet controversial, medical treatment proved to be effective in reducing the symptoms faced by these women in disease entity. Conservative surgery is offered to those for whom pregnancy is a concern on the contrary hysterectomy is the choice for whom fertility is not an issue for future pregnancy and for those who don't want to preserve the

uterus, with concerns to fertility, conservative excisional methods are an option but due to high chance of uterine rupture these should be discussed with the patients beforehand. There is still limitation to support data for surgery effectiveness due to less cases and reports. Till now there is no confirmed treatment that has a direct effect on fertility with AD patients however improvement in the pregnancy outcomes have been noticed with few treatments discussed in this literature. More scientific trials and well-designed studies are required to put into consideration).

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