ISSN: 2576-2842

Research Article

Journal of Gynecology & Reproductive Medicine

Adenomyosis: In-Vitro Fertilization Does Not Improve Pregnancy Outcome as Compared to Conventional Infertility Treatment

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Submitted: 23 Jan 2023; **Accepted:** 26 Feb 2023; **Published:** 06 Mar 2023

Citation: Bagchi, B., Chaudhuri, A. R., Chatterjee, S. (2023). Adenomyosis: In-Vitro Fertilization Does Not Improve Pregnancy Outcome as Compared to Conventional Infertility Treatment. *J Gynecol Reprod Med, 7*(1), 23-28.

Introduction

Adenomyosis is a benign invasion of endometrial glands and stroma into the uterine myometrium. [1, 2]. It can present with heavy and painful menstrual bleeding or be asymptomatic [2-4]. Over last three decades the diagnosis of adenomyosis has been feasible after the introduction of MRI and 3D-TVS. Although there are no international consensus on the diagnostic criteria for adenomyosis with either ultrasound or MRI, the Morphological Uterus Sonographic Assessment (MUSA) consensus statement provides several important ultrasounds features for diagnosis of adenomyosis [5-8]. Heterogeneous and hypoechogenic areas in the myometrium, areas with or without anechoic lacunae or cysts of varying size, linear striation radiating out from the endometrium into the myometrium, poor definition of the junctional zone (JZ), and pseudo-widening of the endometrium (enlargement of uterus with asymmetric thickening of the anterior or posterior walls). On 3D TVS, features linked to adenomyosis were JZmax 8 mm or greater, myometrial asymmetry, and hypoechoic striations [9]. Adenomyosis is often diagnosed with the presence of 3 or more such sonological findings. The prevalence of adenomyosis in women in the general population is about 8–27% of which almost 32% need to undergo assisted reproductive techniques (ART) or In-vitro fertilization (IVF). Direct association of adenomyosis as a sole factor for subfertility is yet to be established; the anatomo-physiopathological conditions can alter the endo-myometrial junctional zone, myometrial contractions or obstruction of the tubal ostia, consequently interfere on sperm and embryo migration resulting in adverse reproductive outcome [9.10]. In the previous literature, adenomyosis has repeatedly been suggested responsible for infertility but any definitive conclusion still lacks adequate evidence [11, 12].

Aim of study; The present study has been performed to find out the pregnancy outcome in subfertile patients with adenomyosis with or without other confounding factors and regarding the necessity of assisted reproductive technique or in-vitro fertilization (IVF) in such patients.

Material and Methods: The present study is a retrospective observational study involving a private fertility clinic with a co-existing ultrasound service. All women aged 18–45 years with complaints of subfertility who underwent an ultrasound between 1st January 1994 and 30th December 2019 were assessed for Sonological Evidence of Adenomyosis (SEOA) as part of a standardized ultrasound evaluation. Those women who then had an episode of fertility treatment and were diagnosed with adenomyosis were included in the study. 42 women (Group A) were included in the study from 1st January 1994 to 31st December 1999, with complaints of infertility and adenomyosis; whereas 376 women (Group B) satisfying the inclusion criteria were studied from 1st January 2000 to 30th December 2019. Using two- and three-dimensional ultrasound SEOA was defined by the presence of any one or more features of MUSA criteria including myometrial cysts, loss of endo-myometrial interface, diffuse course echogenicities, increased vascularity or increased antero-posterior myometrial diameter [9].

Statistical Analysis

The obtained results were analyzed using SPSS Statistics software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Illinois, USA). The comparison between groups was evaluated using the Pearson's Chi-Square test. A p value of <0.05 was considered to be statistically significant.

Results

In Group A among 42 patients with subfertility, 26.1% of patients conceived after treatment in the pre-IVF era.16.9% had live birth and 9.01% patients had miscarriage. In Group B, 376 patients were diagnosed to have infertility with adenomyosis with or without fibroids or endometriosis in the post-IVF era.76 patients with only adenomyotic uterus with no other obvious pathology were

treated and assessed for pregnancy outcome. 25% (19) of such patients conceived spontaneously where as 31.58% (24) of them required IVF-ET for conception; 17.11% (13) and 19.74% (15) patients had live birth in cases of spontaneous conception and the ones who underwent IVF respectively. The miscarriage rates were 7.89% to 11.84% in these group of women respectively **(Table 1)**. When our data was analyzed for women suffering from adenomyosis and endometriosis, 20.45% of 220 patients had spontaneous conception after medical or surgical treatment of their disease and 25.45% were subjected to IVF-ET treatment of which 17.73% had live birth and rest 7.73% had spontaneous abortion. Even in cases of natural conception there was a miscarriage rate of 8.18%. There was no statistical significance in pregnancy outcome of such patients who were diagnosed with adenomyosis having a spontaneous pregnancy or having undergone ART **(Table 2)**. Patients with adenomyosis associated with fibroids complain more of dysmenorrhea and menorrhagia and pregnancy rate, live birth rate and miscarriage rate have no statistical significance in women who had conceived with IVF-ET or had conceived naturally **(Table 3).**

Table 1: Pregnancy Outcome In Adenomyosis

Group B		SPONTANEOUS/ FERTILITY TREATMENT OTHER THAN IVF/ICSI	FERTILITY TREATMENT WITH IVF/ICSI	p Value	Significance
ADENOMYOSIS ONLY	PREGNANCY	19(25)	24(31.58)	0.417	NOT SIGNIFICANT
	LIVE BIRTH	13(17.11)	15(19.74)		
	MISCARRIAGE	6(7.89)	9(11.84)		
Total		76(100)	76(100)		

Data analysis done using Pearson's Chi-Square test

Table 2: Pregnancy Outcome In Adenomyosis With Endometriosis

Group B		SPONTANEOUS/ FERTILITY TREATMENT OTHER THAN IVF/ICSI	FERTILITY TREATMENT WITH IVF/ICSI	p Value	Significance
ADENOMYOSIS WITH ENDOMETRIOSIS	PREGNANCY	45(20.45)	56(25.45)	0.142	NOT SIGNIFICANT
	LIVE BIRTH	27(12.27)	39(17.73)		
	MISCARRIAGE	18(8.18)	17(7.73)		
Total		220(100)	220(100)		

Data analysis done using Pearson's Chi-Square test

Table 3: Pregnancy Outcome In Adenomyosis With Fibroid

Group B		SPONTANEOUS/ FERTILITY TREATMENT OTHER THAN IVF/ICSI	FERTILITY TREATMENT WITH IVF/ICSI	p Value	Significance
ADENOMYOSIS WITH FIBROID	PREGNANCY	18(22.5)	23(28.75)	0.269	NOT SIGNIFICANT
	LIVE BIRTH	12(15)	11(13.75)		
	MISCARRIAGE	6(7.5)	12(15)		
Total		80(100)	80(100)		

Data analysis done using Pearson's Chi-Square test

Table 4: Pregnancy Outcome In Adenomyosis Pre And Post IVF ERA

GROUP		Group A	Group B		
		SPONTANEOUS/FERTILITY TREATMENT PRE-IVF TIMES(1994-1999)	FERTILITY TREATMENT POST-IVF TIMES (2000-2019)	p Value	Significance
ADENOMYOSIS WITH OTHER CONFOUNDING FACTORS	PREGNANCY	11(26.19)	103(27.39)	0.993	NOT SIGNIFICANT
	LIVE BIRTH	7(16.67)	65(17.29)		
	MISCARRIAGE	4(9.52)	38(10.11)		
Total		42(100)	376(100)		

Data analysis done using Pearson's Chi-Square test

Discussion

According to previous literature adenomyosis has been seen to negatively affect fertility [13-15]. It has been proved time and again that factors like distorted anatomy of the uterus, alteration of the myometrial part of the endo-myometrial junctional zone, adenomyomas at different sites of the uterus, excess myometrial contractions, dysperistalsis, excessive inflammation of the endometrial cavity, release of pro-inflammatory cytokines are associated with adenomyosis which hamper reproductive outcome. Our present study has been carried out to re-look into the fact whether adenomyosis alone or the associated factors are responsible for infertility and whether in-vitro fertilization is the only solution to achieve pregnancy [16]. We had assessed two groups of patients over a different time-frame, addressed as pre-IVF era (1994-1999) and post-IVF era (2000-2019). Symptomatic patients diagnosed with adenomyosis suffering from infertility were included in the study from 1994 to 1999, where we had seen 26.1% of patients achieved pregnancy with ovulation induction with or without intrauterine insemination or had spontaneous conception following treatment of adenomyosis.16.9% had live births and 9.01% had first trimester miscarriage. Even in the post-IVF era women with adenomyosis only, who had conceived following in-vitro fertilization and embryo transfer (IVF-ET) were 31.58%, of whom 19.74% had live birth and 11.84% had spontaneous abortion (Table 1).

No statistically significant difference was noted among women with adenomyosis who had conceived with IVF-ET or others who had not required any assistance after treatment of adenomyosis and had had spontaneous conception. Patients suffering from infertility or recurrent pregnancy loss or recurrent implantation failure and in older women seeking assisted reproductive technique (ART) like IVF have been often seen to be associated with adenomyosis [17, 18]. According to the review conducted by Dueholm (2017), miscarriage rate was 32% occurred in women with adenomyosis [19].

The adverse effects of adenomyosis on fertility appears to reduce implantation rates, increased risk of early pregnancy loss and subsequent a decrease in live births rates, which could be directly related to impaired utero-tubal transport, reduced sperm function due to high nitric oxide levels in the uterine cavity, altered uterine contractility, altered endometrial capillary density, excessive angiogenesis mediator secretion, reduced expression of implantation markers, inadequate decidual reaction owing to the overexpression of P450 aromatase, which alters the estrogen/progesterone balance in the secretory phase of the cycle [19-21]. Even when patients were treated with in-vitro fertilization at our center 27.39% patients had attained pregnancy, 17.29% had live birth and 10.11% had spontaneous loss of pregnancy. 63.6% of women with at least one risk factor including adenomyosis have been seen to suffer from recurrent miscarriage as reported by Cem Somer Atabekoğlu et al. [20].

As per previous literature by Sharma S. et al, clinical pregnancy rate was 36.62% in women with endometriosis alone, 22.72% in women with endometriosis and adenomyosis, 23.44% in women who only had adenomyosis and 34.55% in controls. Miscarriage rates were as follows: 14.62%, 35%, 40% and 13.04%, respectively. Live birth was observed to be less in adenomyosis groups compared with controls and women with only endometriosis, which again shows adverse reproductive outcome in adenomyotic women [15]. HOXA10 is up-regulated in response to estrogen and progesterone and its levels increase dramatically during the mid-secretory phase in the glands. In adenomyosis, the decreased expression of both HOXA10 and LIF changes the endometrial molecular environment which plays a role in impaired implantation and receptivity. In endometriosis as well, an epigenetic change mediated through methylation of the HOXA10 promoter, has been noticed [22]. Abnormal expression of integrin β3 and osteopontin (OPN) in the endometrium of adenomyosis may contribute to infertility in some patients. The mRNA and immunostaining intensity of integrin β3 and OPN were significantly lower in the adenomyosis patients than in the controls [23].

A meta-analysis performed by few authors concluded that while adenomyosis appeared to hamper IVF outcomes, larger studies were needed to confirm this adverse effect [24]. Following this review, the same group of researchers published a contradictory study that demonstrated asymptomatic adenomyosis had not ad-

versely affected implantation. [25]. According to previous literature, infertile women with adenomyosis associated with fibroids has been seen to have poor reproductive outcome [26]. Similarly when we had analyzed our data it appeared adenomyosis associated with confounding factors like fibroids had 22.5% spontaneous pregnancy with 15% live births and 7.5% miscarriage rate. Patients who underwent IVF-ET attained a pregnancy rate of 28.75%, 13.75% had live births and 15% had miscarriage (Table 3).

Majority of studies investigate the impact of adenomyosis on fertility in women undergoing IVF, a recent cross-sectional study by Hashim et al., focused on analyzing the prevalence of this in infertile young women [27]. Women with adenomyosis have usually been seen to have a higher average age, a higher BMI, more dysmenorrhea complaints and a higher incidence of ovarian endometriomas, than those without adenomyosis. Thus, the hypothesis that adenomyosis may cause changes to the uterine environment that hinder embryonic implantation in natural conceptions and that, if present, may also influence if the patient is subjected to IVF.

Women suffering from adenomyosis and infertility were treated with different medications in pre-IVF era and had attained pregnancy. Gonadotrophin-releasing hormone (GnRH) analog alone, conservative surgery, or combined therapy have been used by many clinicians since decades to treat such women. Three women had been treated with monthly intramuscular injections of 3.75 mg leuprolide acetate for 5months and one of them had delivered a healthy male baby after conservative treatment of severe adenomyosis [28]. As has been suggested by Nelson and Corson, patient with histologically diagnosed adenomyosis who underwent a long-term course and 2 women with adenomyosis who underwent 6 months treatment with of GnRH-a (buserelin) conceived shortly after cessation of treatment [29, 30]. A small Japanese study, in which 3 of 4 infertile patients successfully conceived after using a danazol intra-uterine device (IUD), is also additional evidence to link adenomyosis and infertility [31].

Combination treatment like fertility sparing laparoscopic cytoreductive surgery or partial adenomyomectomy, along with GnRH-a administration, in sub fertile women with adenomyosis also had been seen to have significant benefits for controlling symptoms of adenomyosis and increases the pregnancy rate compared with GnRH-a alone. [32-36]. The cumulative 3-year clinical pregnancy rate and final successful delivery rate were also found to be higher in this cohort. Hence conservative management of adenomyosis with GnRH-agonist pretreatment or using antagonist might help in reducing uterine size and improve elasticity, consequently facilitating conception; but miscarriage rate also increases. [17-38]. As has been noticed in our data pregnancy outcome in patients with adenomyosis who had conceived spontaneously after treatment of adenomyosis or who have attained pregnancy with IVF, have no statistically significant difference (Table 4). As has been demonstrated in previous studies, fertility treatment for females with adenomyosis is extensive, but even in ART after pituitary downregulation with GnRH, the rate of clinical pregnancy achieved is still controversial since studies find both lower rate and no significant difference between females with or without the disease [39].

Conclusion

The need of the hour is to carry out randomized, large scale clinical studies, with well-defined and standardized selection criteria to conclude about the association of adenomyosis with a poor reproductive outcome is undeniable. Adenomyosis appears to have adverse effects on IVF results, clinical pregnancy rates, live birth rates and pregnancy loss rates. We have to establish a standardized diagnostic protocol , seeing that screening for adenomyosis must be considered before assisted reproductive treatment, both for treating women with adenomyosis as well as for elucidating the prognosis. Even though MRI can theoretically provide better information than TVUS, the latter should be preferred for screening, since it has greater availability and is inexpensive. The selection of ideal evidence-based treatment options for adenomyosis in fertility clinics is difficult, due to the lack of evidence that there is a relation between fertility and the degree of adenomyosis, reinforcing, once again, the need for standardized studies.

Acknowledgement

We acknowledge the contribution of Mr. Souvik Datta, our learned statistician who has helped us in analysis of data obtained.

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