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Case Study

Uterine Adenomyosis Relationship with Gravidity, Parity, and Abortion in Women with a History of Infertility: A Case-Control Retrospective Study

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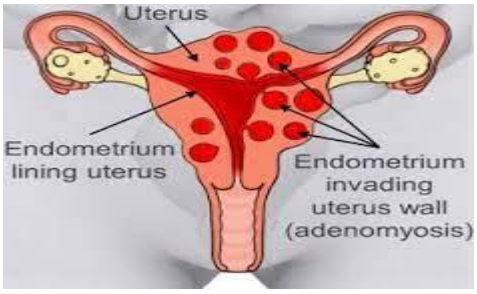
ABSTRACT

Introduction: Adenomyosis is reported to be increasingly diagnosed in young women and affects 20 to 35% of women of reproductive age. This study aimed to evaluate the relationship between the types of uterine adenomyosis and infertility, abortion results in adenomyotic and non-adenomyotic women with a history of infertility.
Methods: In this case-control study, 50 infertile women of reproductive age of 18-40 years old in the Gynecology Clinic in Jahrom city were included in the study. Among the participants, infertile women were respectively selected in case of having an adenomyosis diagnosis, and the control group was selected from women without adenomyosis (25 subjects per group). Study groups were compared for the primary outcomes of the gravida/para/abortus (GPA) system.
Results: Distribution of the different age, BMI, and residency area categories were similar in the case and control groups (P>0.05). The frequency of the secondary or primary infertility does not differ between adenomyotic or non-adenomyotic women with a history of infertility (P=0.039). The frequency of various gravida, parity, live or dead children, and abortion did not significantly differ among the study groups (P>0.05). Infertility-related symptoms and coexisting diseases were not significantly different among the study groups (P>0.05).
Conclusion: The results of the present study revealed similar frequencies of secondary infertility, abortion, and pregnancy outcomes in adenomyotic and non-adenomyotic women with a history of infertility.

GRAPHICAL ABSTRACT



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Introduction

Adenomyosis is defined as an endometrial invasion of the uterine myometrium resulting in uterine enlargement, the formation of adenomyotic tumors, heavy menstrual and intermenstrual bleeding, and recurrent pain. It is a benign disease of the uterus in which the stroma and ectopic networks of the endometrial glands are present inside the myometrium. This invasion induces hypertrophy (enlargement) and hyperplasia (increased) of the uterine muscle and enlarges the uterus diffusely [1]. Adenomyosis is increasingly diagnosed in young women, affecting 20-35% of women of reproductive age [2]. It is associated with uterine enlargement, pelvic pain, excessive vaginal bleeding, and decreased quality of life [3]. However, adenomyosis cannot be easily diagnosed among asymptomatic young women. However, adenomyosis is recently diagnosed with better imaging techniques with the increasing frequency of women at an older age referring to infertility clinic. The prevalence of pregnancy-related adenomyosis complications is rising in older pregnant women and pregnancies resulting from assisted reproductive technologies [4]. Adenomyosis can vary considerably regarding the extent and location of the invasion in the uterus; therefore, there are no independent pathological features for the definitive diagnosis of adenomyosis through non-invasive imaging. However, non-invasive imaging modalities, such as transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) can be used to strictly diagnose adenomyosis to guide treatment options and monitor response to treatment [5-6]. During pregnancy, trophoblast invasion of the endometrium, and myometrial junction causes significant decidualization and marked vascular changes [7]. The junction thickening and disruption in women with adenomyosis may be associated with placental insufficiency and pregnancy outcome complications. Additionally, the type of adenomyosis is considered an important factor in deciding on the shape and function of the endometrium and placenta. Adenomyosis can be divided into two categories. 1) Focal adenomyosis is sometimes considered isolated in which the endometrial area is hypertrophic and deformed and is surrounded by the myometrium (usually located within the myometrium), 2) Diffuse adenomyosis is the most prevalent and widespread form of the disease characterized by endometrial mucosal foci (glands and stroma) which are dispersed throughout the uterine muscle [8]. The recent reports indicate that pregnant women with adenomyosis are at risk for abortion, preterm delivery, early rupture of membranes, spontaneous uterine rupture during labor, and postpartum hemorrhage [9]. Nevertheless, the mechanism by which adenomyosis affects fertility remains controversial. Adenomyosis can affect uterine contractions, sperm transport in the uterine cavity, and embryo implantation, ultimately reducing fertility [10-11]; it also reduces sperm function due to high levels of nitric oxide in the uterine cavity [12]. However, the potential influence of adenomyosis on pregnancy outcomes is still unclear, because these cases have been addressed in few studies. This study aimed to determine the relationship between the type of uterine adenomyosis and pregnancy outcomes, abortion, and infertility in women with adenomyosis.

Materials and Methods

In this case-control study, all women with history of infertility in reproductive age (18-40 years) in Jahrom, who referred to the women's clinic in 2020-2021 to receive medical services, were included in the study. Women with and without of adenomyosis were selected as the case and control groups (n = 25 per group). Research approval (with the code of ethics IR.JUMS.REC.2020.148) was received from the Vice-Chancellor for Research at Jahrom University of Medical Sciences.

Inclusion criteria were age between 18 and 40 years, history of infertility, normal primary pregnancy (without using assisted reproductive technique such as IVF), women diagnosed with adenomyosis (case group), women without adenomyosis (control group), no history of radiotherapy, various cancers, autoimmune and chronic diseases (such as hypertension, diabetes mellitus, polycystic ovary syndrome, etc.), no

long-term drug use, medical and surgical abortions, and no abortion with any chromosomal abnormality. Exclusion criteria were incomplete information, anatomical abnormalities in the female reproductive system, lack of cooperation, patients with known causes of abortion (such as chromosomal aberrations and lupus), and patients with known causes of infertility (such as polycystic ovaries and endometriosis). Next, all patients underwent transvaginal ultrasound. Those patients who were diagnosed with and without adenomyosis on ultrasound were assigned to the case and control groups, respectively. The writte consent forms were obtained from the participants who were sampled by observing all ethical issues and assuring the confidentiality of their information. First, a history was obtained from the patients. Then, questionnaires for demographic information(age, BMI, and location) and clinical data (pregnancy status and type of contraception, history of infertility, oligomenorrhea, hair loss, acne, hypertrichosis, obesity, diabetes, thyroid disease, hypertension, sterility, parity, number of deliveries, number of live births, number of stillbirths, number of abortions, history of depression, cramping pain, heavy bleeding, bloating and swelling, behavior change, breast resizing, history of headache, PMS problems, painful intercourse, bleeding during intercourse, decreased libido, itching and inflammation, discharge, and history of ovarian laziness) were completed by the researchers. All women in both groups were matched in terms of age, week of pregnancy, abortion week, history of infertility, and multiple pregnancies in both groups. The patients' information was collected and recorded to examine the relationships between abortion, infertility, and fertility results from adenomyosis. Data were analyzed by descriptive (mean, percentage, and standard deviation) and inferential (Fisher's and Chi-square) statistical tests using SPSS software (version 21) at a significant level of $P < 0.05$ in all tests.

Results and Discussions

Fifty women referred to Jahrom Women's Clinic were participated in the study and assigned to the groups of women without adenomyosis (25 subjects) and those with adenomyosis (25 subjects). The results of statistical analyses revealed that the distribution of the different age, BMI, and residency area categories were similar in the case and control groups ($P>0.05$) (Table 1).

Table 1: Frequency of demographic variables in groups of women without adenomyosis infertility and women with adenomyosis and infertility

		With adenomyosis		Without adenomyosis		P-value*
		Frequency	Percentage	Frequency	Percentage	
Age	15-20	1	4.0	2	8.0	0.6092
	21-25	2	8.0	5	20.0	0.4174
	26-30	9	36.0	10	40.0	1
	31-35	8	32.0	2	8.0	0.0738
	36-40	5	20.0	6	24.0	1
BMI	Normal	11	44.0	18	72.0	0.0845
	Overweight	11	44.0	7	28.0	0.3772
	Obesity	3	12.0	0	0.0	0.2347
Residency area	City	18	72.0	14	56.0	0.5427
	Rural	7	28.0	11	44.0	0.3772

**Fisher exact test*

The frequency of infertility-related symptoms and co-existing diseases were not significantly different incidences among the study groups ($P>0.05$).

Frequency of different gravidities, parities, number of the live children of the mother, dead children, and abortion did not differ among the groups ($P>0.05$)(Table 3).

Table 2: Frequency of infertility related symptoms and co-existing diseases in study groups

		With adenomyosis		Without adenomyosis		P-value
		Frequency	Percentage	Frequency	Percentage	
Oligomenorrhea		2	8.0	7	28.0	0.14
Hair loss		15	60.0	13	52.0	0.57
Acne		6	24.0	4	16.0	0.48
Hypertrichosis		10	40.0	6	24.0	0.22
Obesity		2	8.0	0	0.0	0.49
Diabetes		1	4.0	0	0.0	0.39
Thyroid disease		3	12.0	7	29.2	0.99
Blood Pressure		1	4.0	1	4.0	0.17
Infertility	Primary	9	36.0	12	48.0	0.39
	Secondary	16	64.0	13	52.0	

Table 3: Frequency of pregnancy status and type of contraception in groups in women without adenomyosis infertility and women with adenomyosis and infertility

		With adenomyosis		Without adenomyosis		P-value
		Frequency	Percentage	Frequency	Percentage	
Gravida	0	9	36.0	12	48.0	0.5672
	1	6	24.0	8	32.0	0.7536
	2	5	20.0	2	8.0	0.4174
	3	3	12.0	3	12.0	0.99
	5	2	8.0	0	0.0	0.4898
Para	0	11	44.0	15	60.0	0.3961
	1	12	48.0	9	36.0	0.5672
	2	2	8.0	1	4.0	0.99
Live	0	11	44.0	15	60.0	0.3961
	1	12	48.0	9	36.0	0.5672
	2	2	8.0	1	4.0	0.99
Dead Children	0	24	96.0	25	100.0	0.99
	1	1	4.0	0	0.0	0.99
Abortions	0	14	56.0	18	72.0	0.3772
	1	8	32.0	4	16.0	0.3209
	2	1	4.0	3	12.0	0.487
	3	1	4.0	0	0.0	0.99
	4	1	4.0	0	0.0	0.99

As depicted in Table 4, none of the symptoms studied in our study were statistically significantly distributed among the study groups (P>0.05) (Table 4).

Table 4: Frequency of symptoms in groups of women without adenomyosis and women with adenomyosis

	With adenomyosis		Without adenomyosis		P-value
	Frequency	Percentage	Frequency	Percentage	
Depression	2	8.0	1	4.0	0.99
Crampy pains	7	28.0	11	44.0	0.24
Severe bleeding	1	4.0	5	20.0	0.19
Breast change	14	56.0	10	40.0	0.26
Headache	9	36.0	11	44.0	0.56
Acne	4	16.0	1	4.0	0.16
PMS problems	1	4.0	5	20.0	0.19
Painful intercourse	4	16.0	8	32.0	0.18
Bleeding when approaching	1	4.0	2	8.0	0.99
Decreased libido	0	0.0	2	8.0	0.49
Itching and inflammation	6	24.0	7	28.0	0.75
Secretion	1	4.0	3	12.0	0.61
History of PCOS	5	20.0	3	12.0	0.71

In recent years, the frequency of adenomyosis in pregnancy has been on the rise with the increased number of pregnancies in older women and the increasing rates of pregnancies using assisted reproductive techniques [13]. Recent studies have indicated that adenomyosis can adversely affect in vitro fertilization, pregnancy, and live birth rates, and has been reported to increase the risk of abortion. Additionally, adenomyosis increases the risk of pregnancy complications, including preterm delivery and premature rupture of the amniotic membranes [14-15]. However, the potential effect of adenomyosis on pregnancy outcomes is still unclear, as the association between adenomyosis and pregnancy outcomes has been examined in few studies. Therefore, this study focused on the relationship between uterine adenomyosis and pregnancy outcomes, abortion, and infertility in women with adenomyosis. The results of the present study showed that the frequency of secondary or primary infertility does not differ between infertile women with adenomyosis or none-adenomyotic ones. Association of infertility with adenomyosis was reported in several studies [16]. Likewise, adenomyosis might affect the outcome of the IVF [17]. In adenomyotic patients, fertility can be disrupted by various mechanisms, including gamete and fetal transfer in an abnormal fallopian tube and endometrial dysfunction and acceptance [18]. An enlarged uterus, anatomical deformity, and adenoma within the wall can all affect the shape of the uterine cavity, and may also adversely influence sperm migration, embryo transfer, and implantation potential [18, 19]. The results of this study showed that abortion did not occur more frequently in women with adenomyosis than in those without adenomyosis. Furthermore, Tamura *et al*. (2017) observed a higher rate of abortion in pregnant women with adenomyosis (24%), particularly after 12 weeks of gestation (9.9%) [20]. In another study, a high rate of abortion was reported in pregnant women with adenomyosis (31.8%) versus a control group (12.5%) [21]. Our results are also similar to a study where a high rate of abortion was observed in adenomyotic pregnant women (32.8%) compared to the control group (16.3%) [22]. In a systematic and meta-analysis study, Huang *et al*. (2020) investigated the relationship between endometriosis and adenomyosis with abortion in pregnancies using assisted reproductive techniques. They found that these diseases were associated with abortion and particularly cause premature abortion (under 12 weeks); the rate of abortion caused by these diseases was lower in the second trimester. Moreover, the abortion rate was higher in pregnant women with adenomyosis and endometriosis who used assisted reproductive techniques than in those who became pregnant spontaneously. Their study revealed that the risk of abortion increased in women with superficial (SUP) and deep infiltrating endometriosis (DIE), respectively, while no marked association was found between endometrioma (OMI) and abortion. However, the risk of abortion is not significantly different from the staging of endometriosis, and the differences seem to be related to epidemiological areas, but the relationship of adenomyosis subtypes with abortion was not studied in their research [23]. Hashimoto *et al*. (2018) reported that the incidence of abortion increased in pregnancies complicated by adenomyosis in the second trimester [24]. Martinez *et al*. (2011) examined the effect of adenomyosis on patients receiving egg donation and reported an increase in abortion in adenomyosis patients who were fertilized using embryos obtained from young egg donors [22]. In a meta-analysis study, Younes and Tulandi (2017) investigated the effects of adenomyosis on in vitro fertilization results and found an increase in the rate of abortion in women with adenomyosis [25].

Patients with adenomyosis possess high levels of inflammatory substances, including prostaglandins, which can potentially cause uterine contractions [9]. Uterine contractions caused by chronic inflammation and high intrauterine pressure due to myometrial stiffness may be the factors causing adenomyosis-associated abortion and cervical disability. Takeuchi *et al*. (2006) reported the prevalence rates of diffuse and focal adenomyosis to be 81.7% and 18.3%, respectively [26]. In another

study, diffuse adenomyosis was observed in 58.2% of pregnant women [20]. Diffuse adenomyosis seems to be worse than focal or localized adenomyosis. Moreover, focal adenomyosis can be easily removed to increase the pregnancy rate [27, 28]. Diffuse adenomyosis is associated with multiple findings, including an enlarged uterus, which involves the entire myometrium in the anterior or posterior wall. In diffuse adenomyosis, such cases as decidualization disorder may also be more severe than the focal type.

Conclusion

The results of the present study demonstrated no differences in pregnancy history status among the adenomyotic and non-adenomyotic women with a history of infertility. Therefore, studies with a higher number of participants are needed to investigate the hypothesis more accurately.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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