In vitro fertilization outcomes In infertile women with adenomyosis

Tran Ngoc Ha Giang[1], Le Minh Tam[1*]
(1) Hue University of Medicine and Pharmacy, Hue University

Abstract

Objectives: This study aimed to investigate the efficacy of in vitro fertilization (IVF) in infertile patients with adenomyosis and to identify relevant factors. **Subjects and methods:** Retrospective descriptive study of infertile cases with adenomyosis who received IVF therapy and embryo transfer from November 2013 to October 2022 at the Center for Reproductive Endocrinology and Infertility, Hue University of Medicine and Pharmacy Hospital, excluding cases of oocyte donation or surrogacy. The β-hCG test was examined two weeks following embryo transfer. Then, women with hCG positive test were followed the pregnancy at 6 weeks, 8 weeks, and 12 weeks, and examined some factors that influence the clinical outcome of pregnancy. **Results:** Among 61 cycles of IVF treatment for infertile patients with adenomyosis, the average number of retrieved oocytes was 10.9±6.6 oocytes. The percentage of mature oocytes was 82.7%, the fertilization rate was 79.5%, the implantation rate was 16.7%, the clinical pregnancy rate was 19.7%, the miscarriage rate was 6.6%, and the ongoing pregnancy rate was 13.1%. In the group with GnRH agonist administration before embryo transfer, the pregnancy rate was greater than in the group without therapy (29.2% vs. 13.5%), and th e pregnancy rate in the group with > 10 oocytes was higher than in the group with ≤ 10 oocytes (28.0% vs 13.5%). However, these differences were not statistically significant (with $p > 0.05$). The cut-off point of endometrial thickness on the day of hCG injection, 10.25 mm, had a sensitivity of 58.3%, a specificity of 81.6%, an area under the curve (AUC) of 75.6%, and a p-value of 0.006; the cut-off point of endometrial thickness on the day of embryo transfer, 9.75 mm, had an accuracy of 9.75 mm. sensitivity 75%, specificity 71.4%, AUC 78.50%, $p = 0.002$ for clinical pregnancy prognosis. **Conclusion:** The IVF treatment of infertile patients with adenomyosis remains challenging, and additional research is required to explain the influence of this disorder on IVF outcomes.

Keywords: *in vitro fertilization (IVF), adenomyosis, β-hCG.*

1. INTRODUCTION

Endometriosis is a benign condition characterized by the development of endometrial glands and stroma outside the uterine cavity [1]. This disease affects 6-10% of women, with symptoms ranging from no symptoms to severe symptoms, and can be accompanied by a variety of symptoms, including dysmenorrhea, dyspareunia, infertility, and urinary troubles, with the most prevalent symptoms being dysmenorrhea, pelvic discomfort, and infertility. Up to 25 - 50% of infertile women have endometriosis, while 30 - 50% of endometriosis-affected women are infertile [2]. These findings indicate that endometriosis is strongly associated with female infertility.

Adenomyosis is a form of endometriosis characterized by the development of localized or diffuse glandular tissue inside the myometrium [1]. Despite the benign nature of this invasion, ectopic glandular tissue can result in dysmenorrhea, hypogastric retention, and abnormal uterine bleeding. Excessive growth of adenomyosis can result in uterine deformities, constriction of the uterine cavity, and decreased fertility by impeding embryo implantation and increasing the risk of miscarriage, significantly impacting the quality of life of women [1-2].

In vitro fertilization (IVF) is one of the best options for treating infertility and is a fairly common method for infertility caused by endometriosis. Up to now, studies on the impact of adenomyosis on IVF outcomes have not been consistent. Some reports suggest that IVF reduces the ability of embryo implantation and pregnancy development, so the clinical pregnancy rate, the live birth rate after IVF in these patients is lower than in the control group [3-4]. Meanwhile, another study reported that IVF did not affect pregnancy outcomes after IVF [5-6].

Although assisted reproduction techniques are growing day by day, IVF treatment in infertile patients with adenomyosis is still a challenge. This study aimed to evaluate the results of IVF and to find out some factors affecting the treatment outcomes in infertile patients with adenomyosis.

Corresponding author: Le Minh Tam, email: leminhtam@hueuni.edu.vn
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2. METHODS

Infertility cases with adenomyosis who got IVF treatment and embryo transfer from November 2013 to October 2022 at the Center for Reproductive Endocrinology and Infertility, Hue University of Medicine and Pharmacy Hospital, were recruited. Donor oocyte and surrogacy instances were omitted from the research group. The study sample included 61 cycles of IVF-embryo transfer that matched the inclusion criteria.

The patient underwent a general examination, baseline hormone testing (LH, FSH, Estradiol, Prolactin), AMH at the beginning of the menstrual cycle and the CA-125 test, a gynecologic ultrasound. Uterine saline infusion sonography and hysterosalpingography (HSG) were indicated within the first three to five days after menstruation. The patient received ovarian stimulation in accordance with the GnRH antagonist protocol, with a starting dose of FSH between 150 - 300 UI. Embryos were cultured and transferred using the same methods. The β-hCG test was conducted two weeks following embryo transfer. Then, in the sixth week of pregnancy, a clinical pregnancy will be reported if an ultrasound reveals the presence of a gestational sac in the uterus. Follow-up will continue for another eight weeks, and the on-going pregnancy will be recorded at 12 weeks.

The primary outcomes were the clinical pregnancy outcomes, and the secondary outcome included maternal age, obstetric history (type of infertility, mean duration of infertility), history of long-term GnRH agonist therapy, diameter anterior-posterior of the uterus (DAP) and adenomyosis pattern, mean CA-125, number of oocytes obtained (> 10 oocytes and ≤ 10 oocytes), and endometrial thickness on the day of embryo transfer. All embryos were evaluated according to the Istanbul consensus [7]. At the blastocyst stage (day 5), 1 - 2 embryos per transfer were conducted. In the absence of embryos of grade A, grade B embryos were selected for transfer.

SPSS 20.0 was used for statistical analysis, data were cleaned and examined. The quantitative variable findings is reported as the mean±standard deviation. Examine the association between variables using the Chi-Square test and the Fisher's Exact test. Using the Mann-Whitney test, compare the mean of a quantitative, non-normally distributed variable with a qualitative variable. The ROC curve was produced to determine the cut-off point with the best sensitivity and specificity for predicting clinical pregnancy outcomes based on endometrial thickness on the day of hCG injection and the day of embryo transfer. A p-value less than or equal to 0.05 was considered statistically significant.

3. RESULTS

Table 1. Demographic and baseline characteristics of study population

	Factors	Number	Percentage (%)
Age	≤ 35	34	55.7
	> 35	27	44.3
	Mean ± SD	35.2 ± 4.8	
BMI (kg/m2)	< 18.5	14	23.0
	18.5 - 22.9	42	68.9
	23 - 24.9	4	6.6
	≥ 25	1	1.5
	Mean ± SD	19.9 ± 2.0	
Infertility type	Primary	36	59.0
	Secondary	25	41.0
Infertility duration	< 5 years	28	45.9
	5 - 10 years	28	45.9
	> 10 years	5	8.2
	Mean ± SD	5.3 ± 3.3	

Other causes	Abnormal semen parameters	58	95.1
	Endometrioma	34	55.7
	Low ovarian reserve	28	45.9
	PCOS	9	14.8
	Tubal disorders	11	18.0
	Fibroids	6	9.8
	Endometrial polyp	8	13.1

The mean age of the study group was 35.2 ± 4.8 years, in which, the group ≤ 35 years accounted for 55.7%. The mean BMI was 19.9 ± 2.0 kg/m2, of which, 68.9% had mean BMI of 18.5 - 22.9, and 8.1% were overweight or obese. 59.0% of cases are primary infertility. The mean duration of infertility was 5.3 ± 3.3 years, of which, infertility ≥ 5 years accounted for 54.1%. Other causes of infertility accompanied by abnormal semen analysis 95.1%, endometrioma was 55.7%, low ovarian reserve was 45.9%.

Table 2. Hormone testing and characteristics of the cycles with ovarian stimulation

Characteristics	Results
Baseline FSH (mIU/ml)	7.0 ± 2.5
Baseline LH (mIU/ml)	5.7 ± 2.2
Baseline Estradiol (pg/ml)	44.8 ± 21.8
Prolactin (µUI/ml)	415.4 ± 200.1
AMH (ng/ml)	3.6 ± 3.2
CA-125 (UI/ml)	54.9 ± 47.5
AFC (follicles)	9.2 ± 6.0
Days of stimulation (days)	8.9 ± 1.4
Total dose of Gonadotropin (UI)	2324.2 ± 576.7
Endometrial thickness on the day of hCG (mm)	9.3 ± 1.7
Retrieved oocytes	10.9 ± 6.6

The basal hormone and AMH levels were within normal limits. The mean CA-125 was 54.9 ± 47.5 UI/ml. The basic parameters of the ovarian stimulation cycle are recorded in Table 2. Accordingly, the mean number of oocytes obtained was 10.9 ± 6.6 oocytes.

Table 3. The in-vitro fertiliazation outcomes

Characteristics	Percentage (%)
Mature oocyte rate	82.7
Fertilization rate	79.6
Embryo quality	
Grade A	45.9
Grade B	28.9
Grade C	25.2
Implantation rate	16.7
Clinical pregnancy rate	19.7
Miscarriage rate	6.6
On-going pregnancy rate	13.1

In this study, the rate of mature oocytes was 82.7%, fertilization rate was 79.6%, in which, embryos of type A, B, and C were 45.9%, 28.9% and 25.2%, respectively. Implantation rate was 16.7%, clinical pregnancy rate was 19.7%, miscarriage rate was 6.6% and on-going pregnancy rate was 13.1%.

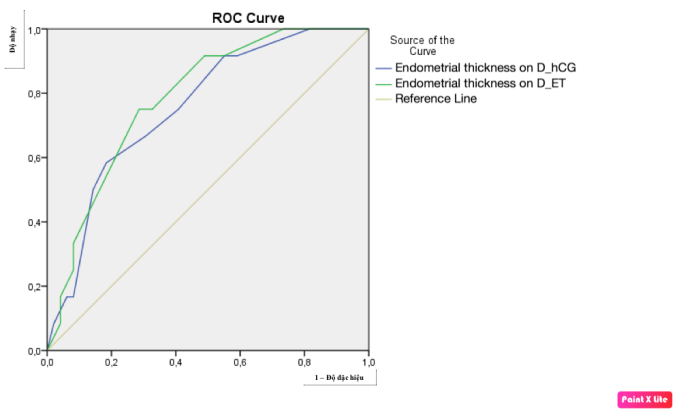
Table 4. Some related factors affecting clinical pregnancy outcome

Characteristics	Pregnancy		p
	Yes	No	
Maternal age (years)			p = 0.134
≤ 35	9 (26.5%)	25 (73.5%)	
> 35	3 (11.1%)	24 (88.9%)	
Infertility type			p = 1.0
Primary	7 (19.4%)	29 (80.6%)	
Secondary	5 (20.0%)	20 (80.0%)	
Infertility duration	5.3 ± 3.2	5.3 ± 3.3	p = 0.729
GnRHa administration			
Yes	7 (29.2%)	17 (70.8%)	p = 0.189
No	5 (13.5%)	32 (86.5%)	
CA-125 (mean±SD)	64.7 ± 74.6	52.6 ± 38.9	p = 0.849
Retrieved oocytes			p = 0.203
> 10	7 (28.0%)	18 (72.0%)	
≤ 10	5 (13.9%)	31 (86.1%)	
DAP (mm)			
< 40			
40 – 50	2 (15.4%)	11 (84.6%)	p = 0.655
> 50	7 (18.4%)	31 (81.6%)	
	3 (30.0%)	7 (70.0%)	
Adenomyosis pattern			
Local	4 (16.7%)	20 (83.3%)	p = 0.749
Diffuse	8 (21.6%)	29 (78.4%)	

CA-125: cancer antigen 125; DAP: anterior-posterior diameter of the uterus.

The pregnancy rate in the group ≤ 35 years old was higher than that in the group > 35 years old (26.5% vs 11.1%), the group with GnRH agonist treatment had a higher pregnancy rate than the group without treatment 29.2% vs. 13.5%) and the pregnancy rate in the group obtained > 10 oocytes was higher than in the group obtained ≤ 10 oocytes (28.0% vs 13.9%). However, these differences were not statistically significant with p > 0.05. Other factors such as infertility type, mean duration of infertility, mean CA-125, anterior-posterior diameter of the uterus or type of adenomyosis were not associated with clinical pregnancy outcome with p > 0.05.

Figure 1. Relationship of endometrial thickness on the day of hCG injection and date of embryo transfer with clinical pregnancy outcome



	AUC (%)	Endometrial thickness	Se	Sp	p
Day of hCG	75.6	10.25	58.3	81.6	0.006
Day of embryo transfer	78.5	9.75	75.0	71.4	0.002

The area under the ROC curve on the relationship between endometrial thickness on the day of hCG injection and the day of embryo transfer with clinical pregnancy outcome is 75.6% and 78.5%, respectively, so it has a predictive value for clinical pregnancy, at the moderate level, with $p < 0.05$. The cut-off point of endometrial thickness on the day of hCG injection (10.25 mm) had a sensitivity of 58.3% and a specificity of 81.6%. The cut-off point of endometrial thickness on the day of embryo transfer of 9.75 mm had a sensitivity of 75.0% and a specificity of 71.4%.

4. DISCUSSION

4.1. Results of IVF in infertile patients with adenomyosis

The percentage of mature oocytes, fertilization rate in this study were similar to those in Chan Woo Park's study (2016) [8], Sunita Sharma (2019) and Chloe's study [3, 8,9]. Regarding the quality of embryos obtained, the percentage of embryos grade A, B, and C were 45.9%, 28.9% and 25.2%, respectively. The percentage of embryo A was higher than that of Chloe Higgins (2021). 29.2% may be due to differences in improved embryo culture techniques [9].

The implantation rate in the study group was 16.7%, lower than that in the study of Jiaxin Zhang (2021) at 31.91% [10]. However, other reports by Martínez-Conejero (2011), Tasuku Harada (2016) demonstrated that adenomyosis does not affect implantation rates, especially in those who received long-term GnRH agonist therapy before embryo transfer. Based on its ability to inhibit proliferation of ectopic endometrial cells, reduce negative effects of cytotoxic cytokines and oxidative stress, and clearly improve pregnancy outcomes of patients with adenomyosis [5-6, 11-12]. The clinical pregnancy rate in this study was 19.7%, lower than the results of Chan Woo Park (2016) with a clinical pregnancy rate of 25.2 - 39.5% and Sunita Sharma (2019) with a clinical pregnancy rate of 25.2 - 39.5%.

The miscarriage rate as reported by Sunita Sharma (2019) in the 2 groups of adenomyosis and endometrioma was 9.38% and 7.95%, respectively [3], even up to 15.69% [10], higher than those in our study.

4.2. Some related factors affecting the outcome of IVF in infertile patients with adenomyosis

Pregnancy rates in this study were associated with maternal age, GnRH agonist treatment group and number of oocytes obtained. The study of some other authors also noted the difference in the pregnancy rate when the mother's age gets older [14-15]. The study of Houwen (2014) and Chan Woo Park (2016) also reported the benefit of GnRH agonist treatment before embryo transfer compared with no treatment and similar to the results of the meta-analysis by Loendersloot (2010). There was a positive correlation between the number of oocytes obtained and the pregnancy rate following IVF, with OR = 1.04 (95% CI: 1.02 - 1.07) [7,16,17]. However, these differences are not statistically significant with $p > 0.05$, possibly because our sample size is still limited. Other factors such as infertility classification, mean duration of infertility were not associated with clinical pregnancy outcome. This result is similar to the studies of Matalliotakis (2008), Liao (2019), and Loendersloot (2010) [17-19].

CA-125 is an important marker in suggesting the diagnosis of endometriosis. In this study, the mean CA-125 concentration in the pregnant group and the non-pregnant group did not differ, with $p > 0.05$. According to a study by Ling Huang (2021) conducted on 84 infertile patients with adenomyosis, there was no association between CA-125 levels and pregnancy outcomes [20]. Similarly, KE Fish (2004) also found that CA-125 levels had no value in predicting pregnancy outcomes (AUC = 0.63) [21].

Hong Gao (2019) and colleagues concluded that patients with uterine anteroposterior diameter < 30mm have a higher live birth rate than the group with DAP ≥ 50 mm (RR = 1.636) and Yaoqiu Wu's study (2019) performed on patients with adenomyosis after frozen embryo transfer showed that the mean DAP in the live-birth group (4.97 ± 0.86 cm) was lower than that in the non-live-pregnant group (5.34 ± 1.17 cm), with $p < 0.05$ [15,22]. Our study did not record this difference, possibly due to the treatment of GnRH agonists 3 months before embryo transfer, which improved the size of the uterus and improved the pregnancy rate [11,15]. Regarding the type of adenomyosis, in

our study the number of cases of diffuse was more than that of focal pattern, however, there was no difference in the clinical pregnancy rate between these two groups, with p > 0.05 . This result is similar to the studies of Chan Woo Park (2016) and Laura Benaglia (2014), and Yaoqiu Wu (2022) [7,15,23].

Vaginal ultrasound assessment of endometrial thickness on the day of hCG injection and the day of embryo transfer is an indispensable step in IVF treatment. Many authors believe that the ideal endometrial thickness at embryo transfer from 8-14mm helps to increase the clinical pregnancy rate, live birth rate and reduce the miscarriage rate [27-28]. In this study, the endometrial thickness on the day of embryo transfer ranged from 7-13mm and we investigated that the cut-off point of endometrial thickness of 9.75 mm had 75% sensitivity and 71.4% specificity in predicting the probability of miscarriage and clinical pregnancy. Research by Georg Griesinger (2018) also recorded a cut-off point of ≥ 9 mm, or by Neal Mahutte (2022) if endometriosis 10 - 12 mm the live birth rate is better [29-30]. More studies with a larger sample and other confounding factors such as embryo transfer quality, embryo transfer technique, are needed to be able to agree on the optimal cut-off points.

5. CONCLUSION

This study evaluated the results of in vitro fertilization (IVF) in infertile patients with adenomyosis and noted several factors related to the success rate such as maternal age, the number of oocytes obtained. IVF treatment in infertile patients with adenomyosis remains a challenge and further studies are needed to clarify the impact of this pathology on IVF outcomes.

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