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ASSISTED REPRODUCTION TECHNOLOGIES

In vitro fertilization and embryo transfer outcomes in relation to myometrial thickness

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Abstract
Purpose To evaluate the effects of myometrial thickening on the outcomes of in vitro fertilization and embryo transfer (IVF-ET).
Methods Four hundred thirteen patients, a total of 551 IVF-ET cycles, were divided into group A (<2.00 cm), group B (2.00–2.49 cm), and group C (≥2.50 cm) based on myometrial thickness.
Results The implantation, clinical pregnancy, and live birth rates were significantly lower in group C. The abortion rates were significantly higher in group C. Among patients in group B, cases with other sonographic findings suggestive of adenomyosis, such as myometrial striations, heterogeneous myometrium, myometrial cysts, and poor definition of the endometrial–myometrial junction showed lower implantation, clinical pregnancy, live birth rates, and higher abortion rates.
Conclusions Myometrial thickening of more than 2.50 cm on TVUS exerts overall adverse effects on IVF-ET outcomes. Even with mild thickening (2.00–2.49 cm), the presence of sonographic findings suggestive of adenomyosis is associated with adverse outcomes of IVF-ET.

Capsule Myometrial thickening on TVUS examination exerts adverse effects on IVF-ET outcomes, and even with mild thickening, the presence of sonographic findings suggestive of adenomyosis is associated with adverse outcomes.

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Keywords Myometrial thickness · Adenomyosis · IVF-ET outcome · TVUS

Introduction

A baseline imaging study of the uterus, endometrium, ovary, and fallopian tube by transvaginal ultrasonography (TVUS) is an important step for predicting pregnancy outcomes in infertile patients undergoing in vitro fertilization and embryo transfer (IVF-ET). A diffusely enlarged uterus, in the absence of a well circumscribed mass as in uterine myomas, can be considered as adenomyosis, the influence of hormones, and secondary enlargement due to vascular lesions [1]. Among these, adenomyosis is generally the first consideration. Such findings are frequently observed in patients undergoing IVF-ET. Therefore, the impact of such findings on the outcomes of IVF-ET must be considered when counseling patients.

Adenomyosis is caused by invasion of the endometrial gland and stroma into the myometrium, and is associated with myometrial hypertrophy and hyperplasia [2, 3]. Definite histopathologic diagnosis of adenomyosis through hysterectomy is not possible in patients who want to conceive. Therefore, an alternative diagnostic method is correlation of clinical symptoms and imaging modalities, such as TVUS, computed tomography (CT), and magnetic resonance imaging (MRI).

Although there is no current consensus for diagnostic criteria of adenomyosis based on imaging studies, diagnostic criteria for adenomyosis through TVUS can be based on characteristic findings of two components. One is the 'myosis'-component, which includes myometrial thickening with globular uterine configuration and/or myometrial anteroposterior asymmetry, and myometrial striations. The

other is the presence of ectopic endometrial implants, the 'adeno'-component, which includes heterogeneous myometrium, myometrial cysts, and poor definition of the endometrial–myometrial junction. These findings other than myometrial thickening still require definitive histopathologic confirmation. The evaluation of such findings is very subjective and may differ greatly depending on the examiner [4–11].

In the current study, the degree of uterine enlargement was classified according to myometrial thickness on TVUS to evaluate effects of myometrial thickening on IVF-ET outcomes. Additionally, other sonographic findings suggestive of adenomyosis were examined and analyzed its effects on IVF-ET outcomes.

Materials and methods

This investigation was designed as retrospective case-controlled analysis. From January 2000 to December 2009, 413 patients (551 cycles) out of 763 patients (1067 cycles) undergoing IVF-ET at our infertility clinic were included. The study group excluded cases aged older than 40 years, cases demonstrating a well circumscribed mass suggestive of a uterine myoma by TVUS, cases in which male factor is the cause of infertility, and cases demonstrating poor response to controlled ovarian hyperstimulation (COH).

All patients received TVUS examination prior to induction of COH, during COH, and on the day of triggering of ovulation for evaluation of follicles, endometrium and myometrium with the Aloka SSD-5000 or the Aloka SSD-α10 device. Myometrial thickness was measured retrospectively from longitudinal view image of the uterus taken on the day of triggering of ovulation with human chorionic gonadotrophin (hCG). Myometrial thickness of the anterior, posterior, and fundal myometrium was measured using the borderline of endometrium and uterine serosa as end points. The largest of the three values was defined as the maximum myometrial thickness.

Infertility work-up, COH, oocyte retrieval, embryo transfer (ET) and TVUS examination of all patients included in our study was performed at our infertility clinic by a single infertility specialist. The TVUS images and records were reviewed and reevaluated with another specialist.

Patients were divided into three groups according to maximum myometrial thickness: group A (<2.00 cm: 302 patients, 397 cycles), group B (2.00–2.49 cm: 63 patients, 81 cycles), and group C (≥2.50 cm: 48 patients, 73 cycles). The sonographic findings suggestive of adenomyosis such as myometrial striations, heterogeneous myometrium, myometrial cysts, and poor definition of the endometrial-myometrial junction, were examined.

Gonadotropin-releasing hormone agonist (GnRH-a, Superfact, Sanofi-Aventis, Paris, France) and recombinant human follicle stimulating hormone (rhFSH, Gonal F, Merck Serno, Geneva, Switzerland) were used for COH. hCG (Pregnyl, Schering-Plough, Kenilworth, NJ, USA) 10,000 IU was injected intramuscularly or recombinant hCG (rhCG, Ovidrel, Merck Serno, Geneva, Switzerland) 250 μg was injected subcutaneously when one or more follicles reached a mean diameter of 18 mm. Thirty-five hours after injection of hCG, the oocyte-cumulus complex was retrieved by ultrasonography-guided aspiration and fertilization was performed 4–6 h after retrieval. The fertilized embryos were transferred 3 days after oocyte retrieval. The luteal phase was supported with progesterone in oil 50–100 mg daily, initially for 14 days starting on the day of oocyte retrieval and continued for another 2–4 weeks in cases where a pregnancy was achieved. A clinical pregnancy was defined by the presence of an intrauterine gestational sac with pulsating fetal heart beats 3–4 weeks after oocyte retrieval [12].

The power of the study was calculated through a PS sample size calculator. With the level of significance put at 0.05, the power can be calculated as 52.7%. Statistical analysis was performed using the SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The results were compared among three groups and statistically analyzed using chi-square test and ANOVA. Differences were considered statistically significant at $P<0.05$.

This study was approved by Institutional Ethics Committee of Yonsei University Wonju College of Medicine.

Results

For all 413 patients, the myometrial thickness (mean ± SD) for each area was as follows: anterior, 1.66±0.48 cm; posterior, 1.70±0.50 cm; fundal, 1.37±0.35 cm. There were significant differences in myometrial thickness according to area. The posterior myometrium was thickest ($P<0.05$). In group A (302 patients), myometrial thickness at each area was as follows: anterior, 1.51±0.21 cm; posterior, 1.56±0.21 cm; fundal, 1.30±0.19 cm. Myometrial thickness was statistically significantly different between areas; the posterior myometrium was thickest ($P<0.05$). In group A, B-1 and C-1 (353 patients; cases without other sonographic findings suggestive of adenomyosis), myometrial thickness at each area was as follows: anterior, 1.58±0.27 cm; posterior, 1.63±0.27 cm; fundal, 1.32±0.21 cm. Myometrial thickness was statistically significantly different between areas; the posterior myometrium was thickest ($P<0.05$).

Clinical characteristics including patient age, duration of infertility, number of previous IVF-ET cycles, and causes of infertility were not different among the three groups (Table 1). Serum E_2 levels on day of hCG administration, number of oocytes retrieved, number of fertilized oocytes, fertilization rates, and number of embryos transferred were not different among the three groups. The endometrial thickness on the day of hCG administration for group C was significantly thinner than that of group A and B ($P<0.05$). The implantation, clinical pregnancy, and live birth rates of group C (12.3%, 31.5%, 15.1%, respectively) were significantly lower than those of group A (22.8%, 56.4%, 46.9%, respectively) and B (21.9%, 53.1%, 40.7%, respectively). The abortion rates of group C (52.2%) were significantly higher than those of group A (12.9%) and B (20.9%). The ectopic pregnancy rates were not significantly different among three groups (Table 2).

Cases with other sonographic findings suggestive of adenomyosis, such as myometrial striation, heterogeneous myometrium, myometrial cysts, and poor definition of the endometrial–myometrial junction were 29 cycles (35.8%) in group B and 52 cycles (71.2%) in group C. In group B, cases with other sonographic findings suggestive of adenomyosis showed significantly lower implantation, clinical pregnancy, and live birth rates and higher abortion rates compared to cases without these findings (12.4%, 34.5%, 17.2%, 50.0% *vs*. 27.2%, 63.5%, 53.8%, 12.1%, respectively; $P<0.05$). In group C, there were no significant differences in implantation, clinical pregnancy, live birth, and abortion rates between cases with or without these findings (11.6%, 26.9%, 11.5%, 57.1% *vs*. 14.0%, 42.9%, 23.8%, 44.4%, respectively) (Table 3).

Discussion

Mean myometrial thickness varies in literature. In 'Berek & Novak's gynecology', myometrial thickness ranges from 1.50 to 2.50 cm [13]. Although there is no study on the precise measurement of mean myometrial thickness in reproductive age women by TVUS, according to 'Ultrasonography in obstetrics and gynecology', the anteriorposterior (AP) diameter is 2.00–5.00 cm in reproductive women (2.00–4.00 cm in nulliparas, 3.00–5.00 cm in multiparas) [14]. From which normal range of myometrial thickness is estimated to be roughly 1.00–2.50 cm. Diffuse uterine myohypertrophy (DUMH) is a condition clinically diagnosed by the presence of uterine bleeding, homogeneous and diffuse uterine enlargement, and absence of any myoendometrial cause of bleeding. One of the diagnostic criteria of DUMH is myometrial thickness of at least 2.00 cm [15]. In our study, mean myometrial thickness of patients without other sonographic findings suggestive of adenomyosis (group A, B-1 and C-1; 353 patients) was as follows: anterior, 1.58±0.27 cm; posterior, 1.63±0.27 cm; fundal, 1.32±0.21 cm. About 75% (73%; 302 patients) of all patients (413 patients) had myometrial thickness of less than 2.00 cm, and about 90% (88%; 365 patients) had myometrial thickness less than 2.50 cm. Based on these findings, the authors considered thickened myometrium as 2.50 cm or more, mild thickness or upper normal as 2.00–2.49 cm, and normal thickness as less than 2.00 cm.

The outcomes of IVF-ET according to myometrial thickness were compared. Significant reductions in implantation, clinical pregnancy, and live birth rates and increases in the abortion rates were observed in group C. Group B demonstrated mild myometrial thickening and, in comparison to group A, a reduction in implantation, clinical pregnancy, and live birth rates and an increase in the abortion rate were observed, though these were not significant.

The current study demonstrates that as myometrial thickness increases, it exerts overall adverse effects on IVF-ET outcomes. This differs from a study by Camargo et al., which found no effects of adenomyosis on IVF-ET outcomes [16]. However, they did not consider myometrial thickening but used the presence of myometrial cysts as a diagnostic criteria for adenomyosis, which may be attribut-

Table 1 Clinical data of patients

	Group A (397 cycles)	Group B (81 cycles)	Group C (73 cycles)	*P*-value
Age (years)[a]	33.0±3.7	33.7±3.7	33.6±3.7	NS
Duration of infertility (years)[a]	3.2±1.2	3.3±1.4	3.3±1.5	NS
No. of previous IVF-ET cycles[a]	0.5±0.7	0.5±0.8	0.5±0.7	NS
No. of causes of infertility				
Tubal factor (%)	160 (40.3)	32 (39.5)	26 (35.6)	NS
Endometriosis (%)	39 (9.8)	7 (8.6)	11 (15.1)	NS
Anovulatory (%)	55 (13.9)	10 (12.3)	9 (12.3)	NS
Unexplained (%)	143 (36.0)	32 (39.5)	27 (37.0)	NS

NS not significant.

[a]Data are mean ± SD.

Table 2 Response to ovarian stimulation and clinical outcomes

	Group A (397 cycles)	Group B (81 cycles)	Group C (73 cycles)	*P*-value
E_2 level, hCG day (pg/mL)[a]	1930.2±1319.1	1725.3±1314.0	2017.0±1306.7	NS
Endometrial thickness, hCG day (cm)[a]	1.1±0.2	1.1±0.2	0.9±0.2[b]	0.001
No. of oocytes retrieved[a]	11.4±7.2	11.8±8.2	10.2±5.0	NS
No. of fertilized oocytes[a]	8.2±5.6	8.3±6.4	7.5±3.9	NS
Fertilization rate per retrieved oocyte (%)[a]	82.2±18.7	81.7±17.0	82.1±19.6	NS
No. of embryos transferred[a]	3.1±0.8	3.2±0.8	3.1±0.8	NS
Implantation rate (%)	264/1158 (22.8)	55/251 (21.9)	28/228 (12.3)[b]	0.002
2000–2004 (290 cycles)	133/627 (21.2)	25/123 (20.3)	11/102 (10.8)[b]	0.04
2005–2009 (261 cycles)	131/531 (24.7)	30/128 (23.4)	17/126 (13.5)[b]	0.03
Clinical pregnancy/cycle (%)	224/397 (56.4)	43/81 (53.1)	23/73 (31.5)[b]	0.02
2000–2004 (290 cycles)	122/219 (55.7)	24/43 (55.8)	8/28 (28.6)[b]	0.02
2005–2009 (261 cycles)	102/178 (57.3)	19/38 (50.0)	15/45 (33.3)[b]	0.02
Abortion/clinical pregnancy (%)	29/224 (12.9)	9/43 (20.9)	12/23 (52.2)[b]	<0.001
2000–2004 (290 cycles)	16/122 (13.1)	5/24 (20.8)	5/10 (50.0)[b]	0.009
2005–2009 (261 cycles)	13/102 (12.7)	4/19 (21.1)	7/13 (53.8)[b]	0.001
Ectopic pregnancy/clinical pregnancy (%)	9/224 (4.0)	1/43 (2.3)	0/23 (0.0)	NS
2000–2004 (290 cycles)	5/122 (4.1)	1/24 (4.2)	0/10 (0.0)	NS
2005–2009 (261 cycles)	4/102 (3.9)	0/19 (0.0)	0/13 (0.0)	NS
Live birth/cycle (%)	186/397 (46.9)	33/81 (40.7)	11/73 (15.1)[b]	<0.001
2000–2004 (290 cycles)	101/219 (46.1)	18/43 (41.9)	5/28 (17.9)[b]	0.017
2005–2009 (261 cycles)	85/178 (47.8)	15/38 (39.5)	6/45 (13.3)[b]	<0.001

NS not significant.

[a] Data are mean ± SD.

[b] Significantly different to corresponding values in group A and B ($P<0.05$).

ed to the conflicting results. The results of the current study are also different from a study by Chiang et al. They evaluated IVF-ET outcomes in 19 infertile patients with a sonographical pattern of diffusely enlarged uterus without distinct uterine masses defined by the criteria such as the presence of a diffusely enlarged uterus and one or more heterogeneous myometrial areas not encapsulated and within round anechoic areas 1–3 mm in diameter and reported that pregnancy outcomes, excluding abortion rates, were not different from age-controlled group of 144

Table 3 Clinical outcomes in cases with and without sonographic findings suggestive of adenomyosis in group B and C

	Group B (81 cycles)		*P*-value	Group C (73 cycles)		*P*-value
	B-1 (52 cycles)	B-2 (29 cycles)		C-1 (21 cycles)	C-2 (52 cycles)	
Implantation rate (%)	44/162 (27.2)	11/89 (12.4)[a]	0.007	9/64 (14.0)	19/164 (11.6)	NS
Clinical pregnancy/cycle (%)	33/52 (63.5)	10/29 (34.5)[a]	0.012	9/21 (42.9)	14/52 (26.9)	NS
Abortion/clinical pregnancy (%)	4/33 (12.1)	5/10 (50.0)[a]	0.01	4/9 (44.4)	8/14 (57.1)	NS
Live birth/cycle (%)	28/52 (53.8)	5/29 (17.2)[a]	0.001	5/21 (23.8)	6/52 (11.5)	NS

B-1: Group B without myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial–myometrial junction

B-2: Group B with myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial–myometrial junction

C-1: Group C without myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial–myometrial junction

C-2: Group C with myometrial striation, heterogeneous myometrium, myometrial cysts, or poor definition of the endometrial–myometrial junction

NS not significant.

[a] Significantly different to corresponding values in group B-1 ($P<0.05$).

infertile patients [17]. This is thought to be secondary to the fact that this study did not classify the degree of myometrial thickening.

In group C, cases with myometrial thickness exceeding 2.50 cm in the anterior, posterior, and fundal myometrium were 37.5%, 64.6%, and 14.6% of the total, respectively. The most frequently observed area where the myometrial thickness was greater than 2.50 cm was the posterior myometrium. Forty-one patients (85.4%) had a myometrial thickness exceeding 2.50 cm in one area. Seven patients (14.6%) had a myometrial thickness exceeding 2.50 cm in more than two areas. Clinical pregnancy was achieved in cases with a myometrial thickness exceeding 2.50 cm in only one area (36.5%). In cases with thickening in more than two areas of the myometrium, pregnancy could not be achieved (data not shown).

Cases with other sonographic findings suggestive of adenomyosis, such as myometrial striations, heterogeneous myometrium, myometrial cysts, and poor definition of the endometrial–myometrial junction, occurred in 35.8% of group B and 71.2% of group C. It was observed that as the myometrium becomes thicker, it was more likely that additional imaging findings were present. In group B, significant differences in the clinical outcomes between the patients with additional sonographic findings and those without were observed. This demonstrates that even with mild myometrial thickening, if other imaging findings characteristic of adenomyosis are associated, these may exert adverse effects on IVF-ET outcomes.

The causes of adverse effects of adenomyosis on pregnancy outcomes may include mechanical traction and distortion of the myometrium, uterotubal spasm due to prostaglandin released by ectopic endometrial implants, and immunological factors [18–21]. The current study found that endometrial thickness on the day of hCG administration in group C was significantly thinner than in group A and B. This suggests that the endometrium may exert effects on pregnancy rates. It may be speculated that the reduction in endometrial thickness is due to a reduction of endometrial and subendometrial blood flow [22–24].

In the current study, myometrial thickness was measured by TVUS and divided by degree and the outcomes of IVF-ET were compared in relation to the degree of myometrial thickness. As a result, the authors found that myometrial thickening exerts overall adverse effects on IVF-ET outcomes. To our knowledge there have been no previous studies on this subject. A limitation to our study is that patients undergoing multiple IVF-ET cycles were also included in the analysis. Although this may have no effect on the study outcome because number of previous IVF-ET cycles is very similar among group A, B and C (0.5±0.7, 0.5±0.8, 0.5±0.7, respectively), a large prospective studies of only one cycle per patient are needed for a more accurate analysis.

In conclusion, it was observed that myometrial thickening, particularly myometrial thickening of more than 2.50 cm, exerts overall adverse effects on IVF-ET outcomes. Even with mild myometrial thickening (2.00–2.49 cm), in light of the fact that adenomyosis is a progressive disease, immediate and appropriate treatment plans are recommended.

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