

The effect of endometrial thickness on pregnancy outcome in patients with Asherman's syndrome post-hysteroscopic adhesiolysis

Saeed Baradwan¹
Dina Shafi¹
Amira Baradwan²
Muhammad Salman Bashir³
Dania Al-Jaroudi^{1,4}

¹Department of Obstetrics and Gynecology, Women's Specialized Hospital, King Fahad Medical City, Riyadh, ²Faculty of Medicine, King Abdulaziz University, Jeddah, ³Research Center, King Fahad Medical City, Riyadh, ⁴Department of Obstetrics and Gynecology, Reproductive Infertility and Medicine Department, King Fahad Medical City, Riyadh, Saudi Arabia

Background: Hysteroscopic adhesiolysis anatomically restores the uterine cavity in cases of Asherman's syndrome (AS); however, the extent of endometrial fibrosis could determine the pregnancy outcome.

Objectives: To determine whether endometrial thickness could influence pregnancy outcome of hysteroscopic adhesiolysis in women with a history of AS.

Subjects and methods: This was a retrospective cohort study that included 41 women who attended Women's Specialized Hospital, King Fahad Medical City from December 2008 to December 2015, presented with a history of infertility or recurrent pregnancy loss, and were diagnosed with intrauterine adhesions and treated by hysteroscopic adhesiolysis. To analyze the causative factors of AS, history of curettage, miscarriage, postpartum hemorrhage, hysteroscopy, endometritis, and any uterine surgery were recorded. Patients were followed up for 2 years to account for pregnancy. Patients were divided into two groups based on measurement of endometrial thickness in the midsagittal plane at mid-cycle of a menstrual period. Group A consisted of 26 patients with endometrial thickness ≤ 5 mm, and group B included 15 patients with endometrial thickness > 5 mm. The main outcome measures included endometrial thickness and pregnancy outcome.

Results: Group A had significantly ($P < 0.001$) lower pregnancy rates compared with group B (38.4% versus 80%, respectively). Five of 10 pregnancies (50%) from group A miscarried, compared with 1 of 12 (8.3%) pregnancies in group B. This was statistically significant ($P < 0.001$).

Conclusion: Pregnancy rates were observed to be higher when the endometrium was > 5 mm in thickness among patients with AS and miscarriage rates may be reduced in this group.

Keywords: intrauterine adhesion, operative hysteroscopy, Asherman's syndrome, endometrial thickness

Introduction

The endometrium undergoes cyclic changes during the menstrual cycle to prepare for implantation.¹ A thin endometrium that fails to respond to hormones leads to implantation failure or early miscarriages due to lack of blood supply.² Asherman's syndrome (AS) causes endometrial fibrosis. This leads to a stroma that is largely replaced with fibrous tissue and glands that are replaced by inactive cubocolumnar endometrial epithelium.³ The distinction between the functional and basal layers of the endometrium is lost. The functional layer is replaced by an epithelial monolayer unresponsive to hormonal stimulation, and the fibrotic adhesion forms across the cavity. In other cases, there may be calcification or even ossification in the stroma.

Correspondence: Saeed Baradwan
Department of Obstetrics and Gynecology, Women's Specialized Hospital, King Fahad Medical City, PO Box 59046, Riyadh 11525, Saudi Arabia
Tel +966 11 288 9999 ext 13210
Fax +966 1 288 9999 ext 3714
Email dr.saeed_bardwan@yahoo.com

The tissue is usually avascular. The intrauterine adhesions may involve different layers of the endometrium, myometrium, or connective tissue,^{4,5} thus leading to implantation failure and miscarriages.⁶ Hysteroscopy is now the gold standard of diagnosis and treatment since it provides a good view of the cavity, allowing a fairly precise description of the location and degree of adhesions and concurrent treatment of adhesions.^{7,8} However, the extent of endometrial fibrosis will determine the reproductive outcome after an anatomic restoration of the uterus. Surgical success is mainly achieved by the release of adhesions, and therefore, redevelopment of adhesions remains a limiting step to the success of the surgery.⁹ Generally, both endometrial thickness and endometrial pattern have been regarded as indicators for endometrial receptivity. Additionally, assessment of the association between these sonographic endometrial characteristics and clinical outcomes following in vitro fertilization (IVF) treatments has been the focus of interest for many years. However, no consensus was achieved on whether the endometrial ultrasound (USG) characteristics can predict the pregnancy outcome in patients with AS.

This study aimed to analyze the outcome of hysteroscopic adhesiolysis in 41 women with AS by observing the effect of endometrial thickness on pregnancy outcome.

Subjects and methods

An analytical retrospective cohort study was carried out, which included 41 women who attended Women's Specialized Hospital, King Fahad Medical City in Riyadh, Saudi Arabia, between January 2008 and December 2015 and presented with a history of infertility, recurrent pregnancy loss, or menstrual period disturbance and were diagnosed with intrauterine adhesions by hysteroscopy. King Fahad Medical City Institutional review board (IRB) approval was granted for the study (number 15-440).

All of the patients underwent preoperative evaluations, including a detailed history, age, height, weight, body mass index, types and duration of infertility, pattern of the past menstrual cycle, baseline transvaginal USG, tubal patency test, and spouse's semen analysis. Serum hormone measurements (estradiol [E2], progesterone [P] androgens, luteinizing hormone, follicle-stimulating hormone [FSH], and prolactin) were evaluated on the fifth day of the menstrual cycle or at a randomly chosen time in patients who had amenorrhea. Patients diagnosed with intrauterine adhesions and no other demonstrable causes of infertility were considered in the study.

To analyze the causative factors of AS, history of curettage, miscarriage, postpartum hemorrhage, hysteroscopy, endometritis, and any uterine surgery such as myomectomy

and cesarean section was recorded. Patients with male factor infertility, age above 40 years, ovarian failure (FSH >40 U/L), an abnormal hormonal profile that might affect the reproductive success, or any other uterine malformation such as fibroid uterus or bilateral blocked tubes were excluded from the study.

Hysteroscopic adhesiolysis was performed for all patients by four experienced surgeons in our unit using similar techniques under general anesthesia. The cervix was initially dilated to "12" using Hegar's dilators. An 8 mm, 12° rigid telescope using bipolar electrode needle or loop under direct vision was used. Normal saline was used as a distending medium through an automated hysteroscopic distension pump. Adhesiolysis began inferiorly and proceeded toward fundus until a panoramic view of the cavity was obtained and both ostia were visualized. In cases of adhesions in the cervical canal, Hegar's dilators were used to sound and dilate the cervical canal under USG guidance. The procedure was discontinued even if both ostia were not visualized when the pink myometrium was seen.

Concurrent laparoscopy was done in patients in whom tubal factor infertility was also suspected or hysteroscopy required laparoscopic guidance. In some cases, transabdominal B-mode USG was also used to guide the surgeon during the procedure. Cefazolin sodium (2 g) was administered to all patients during the operation.

All cases were diagnosed hysteroscopically and classified according to the March classification of AS (mild if filmy adhesion occupied less than one-quarter of the uterine cavity and the ostial areas and upper fundus were minimally involved; clear, moderate if one-fourth to three-fourths of the cavity was involved and the ostial areas and upper fundus were partially involved and there was no agglutination of uterine walls; or severe if more than three-fourths of the cavity was involved and there were occlusion of both ostial area and upper fundus and agglutination of uterine walls).¹⁰

Postoperatively, all patients were given cyclical hormonal therapy for 3 months, Premarin 0.625 mg for 14 days, and Primolut 5 mg three times a day added on the last 7 days.

Transvaginal USG was done to measure the endometrial thickness in the midsagittal plane at the mid-cycle of the menstrual period, and if assisted reproductive technology was planned for, then the measurement was done on the day of embryo transfer. Measurements were made from the outer edge of the endometrial-myometrial interface to the outer edge in the widest part of the endometrium. Patients were divided into two groups based on measurement of endometrial thickness in the midsagittal plane at the mid-cycle of the menstrual period. Group A consisted of 26 patients with

an endometrial thickness ≤ 5 mm, and group B included 15 patients with an endometrial thickness > 5 mm.

Patients were followed up every 3 months for a period of 6 months to 2 years. Details of spontaneous conception and reproductive outcome were recorded. Ovulation induction, intrauterine insemination, IVF, or intracytoplasmic sperm injection was done in patients who had tubal factor infertility or were unable to conceive spontaneously during 1 year.

Patients undergoing assisted reproduction technology were booked for antagonist protocol. Cetrorelix (Merck-Serono, Darmstadt, Germany) 0.25 mg was started on day 6 of ovarian stimulation by either r-FSH or human menopausal gonadotropins until the day of human chorionic gonadotropin (HCG) trigger. Monitoring was started on day 7 of ovarian stimulation by measuring estradiol level; follicle growth and endometrial response were followed using transvaginal USG. HCG (10,000 IU) was given intramuscularly when at least two follicles had reached 18 mm or three follicles were within 16 mm in diameter. Transvaginal oocyte retrieval was carried out 36 hours after the HCG injection under paravaginal block by 1% Lidocaine. The oocytes were fertilized on the day of retrieval, and cleavage-stage embryos were transferred on day 2, 3, or 5 after oocyte retrieval. One or two embryos were transferred to all patients unless they were above the age of 40 and had multiple IVF failures.

The main outcome measure was to identify the endometrial thickness and positive pregnancy test which might have ended in miscarriage, ectopic pregnancy, preterm, term, or no pregnancy and ongoing viable pregnancy which was confirmed by early USG scan.

All data were entered and analyzed through statistical package SPSS version 22. Chi-square test was applied to determine the significant relationship between pregnancy outcome and other study parameters. A *P*-value < 0.05 was considered statistically significant.

Ethical approval

King Fahad Medical City IRB approval was granted for the study (number 15-440). Due to the study being retrospective, as per our institution policy, only IRB approval is needed before conducting the study. Patient consent was waived as no patient identifiers were obtained, and the patient care was not affected or influenced in any way. This article does not contain any study performed with animals by any of the authors.

Results

The study included 41 women. Their mean age (\pm SD) was 32.24 (± 4.61) years, whereas their mean body mass index

(\pm SD) was 29.07 (± 3.60) kg/m². Mean duration of infertility (\pm SD) was 6.12 years (± 3.87). Their clinical characteristics are presented in Table 1. Hypomenorrhea was reported by 46.3% of the pregnant women, whereas amenorrhea was reported by 14.6% of the pregnant women. Also, 63.4% had dysmenorrhea. Secondary infertility was reported by most of them (70.7%), whereas primary infertility was seen among the remaining women (29.3%). Miscarriage, curettage, and postpartum hemorrhage were reported by 56.1%, 51.2%, and 31.7% of them, respectively. Open myomectomy, hysteroscopy, and endometritis were reported by 12.2%, 31.7%, and 34.1%, of the participants, respectively. About 36.6% had a previous cesarean section. Hysteroscopy alone was reported by 53.7% of cases, whereas hysteroscopy with laparoscopy

Table 1 Clinical characteristics of patients (N=41)

Characteristics	n (%)
Menstrual pattern	
Normal	16 (39)
Hypomenorrhea	19 (46.3)
Amenorrhea	6 (14.6)
Dysmenorrhea	26 (63.4)
Primary infertility	12 (29.3)
Secondary infertility	29 (70.7)
History of miscarriages	23 (56.1)
History of curettage	21 (51.2)
History of PPH	13 (31.7)
History of open myomectomy	5 (12.2)
History of hysteroscopy	13 (31.7)
History of endometritis	14 (34.1)
History of cesarean section	15 (36.6)
Operative type	
Hysteroscopy alone	22 (53.7)
Hysteroscopy + US	4 (9.8)
Hysteroscopy + laparoscopy	15 (36.6)
Endometrial thickness	
≤ 5	26 (63.4)
> 5	15 (36.6)
March classification	
Minimal	14 (34.1)
Moderate	17 (41.5)
Severe	10 (24.4)
Conception methods	
Spontaneous	15 (36.6)
IVF	16 (39)
IUI	4 (9.8)
ICSI	2 (4.9)
Induced	4 (9.8)
Pregnancy outcome	
Ectopic	2 (4.9)
Miscarriage	6 (14.6)
Preterm	5 (12.2)
Term	9 (22)
No Pregnancy	19 (46.3)

Abbreviations: ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; PPH, postpartum hemorrhage; US, ultrasound.

was reported by 36.6% of cases. Endometrial thickness was >5 mm in 12 (36.6%) patients and ≤ 5 mm in 26 (63.4%) patients. Also, 41.5% and 24.4% of cases were moderate and severe, respectively, according to March classification. The most frequent conception methods used were IVF (39%) and spontaneous (36.6%). Preterm and ectopic pregnancies were reported by 12.2% and 4.9% of cases, respectively.

From Table 2, it is evident that among the studied factors that could be associated with endometrial thickness, menstrual period pattern, previous history of cesarean section, and March classification were significantly associated with endometrial thickness. Amenorrhea was reported by 23.1% of women in group A, compared to 0% in group B ($P=0.002$).

Table 2 Association between demographic characteristics and endometrial thickness

Characteristics	Endometrial thickness		P-value
	Group A (n=26), ≤ 5 mm	Group B (n=15), >5 mm	
Age (mean \pm SD)	33.15 \pm 3.51	30.67 \pm 5.87	0.151
BMI (mean \pm SD)	6.62 \pm 4.33	5.27 \pm 2.84	0.237
Menstrual period (%)			
Normal	5 (19.2)	11 (73.3)	0.002*
Hypomenorrhea	15 (57.7)	4 (26.7)	
Amenorrhea	6 (23.1)	0 (0.0)	
Miscarriages (%)			
No	10 (38.5)	8 (53.3)	0.355
Yes	16 (61.5)	7 (46.7)	
Curettage (%)			
No	11 (42.3)	9 (60.0)	0.275
Yes	15 (57.7)	6 (40.0)	
History of PPH (%)			
No	17 (65.4)	11 (73.3)	0.598
Yes	9 (34.6)	4 (26.7%)	
Open myomectomy (%)			
No	24 (92.3)	12 (80.0)	0.246
Yes	2 (7.7)	3 (20.0)	
Endometritis (%)			
No	19 (73.1)	8 (53.3)	0.199
Yes	7 (26.9)	7 (46.7)	
History of cesarean section (%)			
No	13 (50.0)	13 (86.7)	0.019*
Yes	13 (50.0)	2 (13.3)	
March classification (%)			
Minimal	3 (11.5)	11 (73.3)	$<0.001^*$
Moderate	13 (50.0)	4 (26.7)	
Severe	10 (38.5)	0 (0.0)	
Conception methods (%)			
Spontaneous	11 (42.3)	4 (26.7)	0.325
IVF	10 (38.5)	6 (40.0)	
IUI	1 (3.8)	3 (20.0)	
ICSI	2 (7.7)	0 (0.0)	
Induced	2 (7.7)	2 (13.3)	

Note: *Statistically significant.

Abbreviations: ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; PPH, postpartum hemorrhage.

Group B had significantly ($P=0.019$) lower previous history of cesarean section rate compared with group A (13.3% versus 50%, respectively). Ten of 26 pregnancies (50%) from group A had severe form in hysteroscopic March classification, compared with 0 of 15 (0%) in group B. This was statistically significant ($P<0.001$). There was no statistical significance when the conception methods were compared to endometrial thickness ($P=0.325$).

It is evident from Table 3 that group A had significantly ($P<0.001$) lower pregnancy rates compared to group B (38.4% versus 80%, respectively). Five of 10 pregnancies (50%) from group A miscarried, compared to 1 of 12 (8.3%) pregnancies in group B. This was statistically significant ($P<0.001$).

Discussion

This study reports the pregnancy outcomes of 41 cases of hysteroscopic adhesiolysis for AS. The clinical characteristics of the patients in this study were comparable to those of other studies.^{11–14} In accordance with other reports,¹⁵ history of curettage was reported by 51.2% of AS cases. Amenorrhea was reported by 23.1% and previous cesarean section by 50% of women with AS who had thin endometrium (<5 mm).

Endometrial thickness is considered as a reflection of the degree of endometrial proliferation in the absence of intra-uterine pathology.¹⁶ It was measured in the midsagittal plane during transvaginal USG scan. In this study, lower pregnancy rates were observed with endometrial thickness <5 mm group. Overall, the association between endometrial thickness and pregnancy outcome was statistically significant. Results from the literature are conflicting. In addition to endometrial thickness, the correlation between endometrial pattern and the outcome of assisted reproductive techniques has also been the focus of interest for many years. However, their conclusions were not consistent. Dickey et al¹⁷ found that reproduction had increased when the endometrium was at least 9 mm thick and had a triple-line appearance during IVF cycles. However, biochemical pregnancies were more frequent with a thinner endometrium. On the other hand, Check et al¹ reported an improved pregnancy rate with a thicker endometrium. Noyes et al¹⁸ observed pregnancy and ongoing pregnancy rates to be higher when the endometrial thickness was >9 mm. Quite similarly, Rinaldi et al¹⁹ reported that minimum thickness of 10 mm during IVF was associated with a higher pregnancy rate.

In more recent studies,^{8,16,20–22} however, no significant association between endometrial thickness and pregnancy outcome was seen. Relatively small sample size in these

Table 3 Association between endometrial thickness and pregnancy outcome

Endometrial thickness (mm)	n	Pregnancy outcome					P-value	
		Pregnancy (%)	Ectopic (%)	Miscarriage (%)	Preterm (%)	Term (%)		No pregnancy (%)
≤5	26	10 (38.46)	0 (0.0)	5 (19.23)	2 (7.7)	3 (11.5)	16 (61.53)	0.013*
>5	15	12 (80)	2 (13.3)	1 (6.66)	3 (20)	6 (40)	3 (20)	

Note: *Statistically significant.

studies could have limited power to detect a small difference from the statistical point of view.

It is possible that, with more advanced laboratory and stimulation methods, a small effect of endometrial thickness on outcome might become obscured or overridden. The day of measurement might also influence the association between endometrial thickness and cycle outcome.¹⁶

Additionally, the influence of “increased” endometrial thickness has been evaluated in other studies. Weissman et al²³ observed lower implantation and pregnancy rates among women with an endometrial thickness >14 mm on the day of HCG administration. However, Dietterich et al²⁴ reported no adverse impact of thickened endometrium (>14 mm) on implantation, pregnancy, or abortion rates.

Kovacs et al¹⁶ observed that pregnancy rates were higher when an endometrial thickness of at least 10 mm was reached. Although the improvement was small in their study, they suggested that adequate endometrial development is one of the factors that play a significant role in IVF outcome. This study suggests the same.

Among the limitations of this study is the fact that the study sample was relatively small as it was limited to Women’s Specialized Hospital, which could affect the generalizability of results. An important limitation of our study is that it is retrospective in nature. We relied on records in this study, of which some were incomplete, particularly regarding miscarriage information (types, gestational age, and the chromosomal analysis of chorionic villi). Despite these limitations, we found a relationship between pregnancy outcome and endometrial thickness among women with AS. In the light of the study results, we recommend conducting a study with adequate sample size to increase the study power and thus provide more generalizable results.

Conclusion

The results of this study suggest that adequate endometrial thickness is required for pregnancy to occur, and the pregnancy rates were observed to be higher when the endometrium was at least 5 mm in thickness among patients with AS. This information might aid physicians in guiding their patients and taking optimal clinical decisions together.

Disclosure

The authors report no conflicts of interest in this work.

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