Effect of endometrial thickness on pregnancy outcome in intrauterine insemination: a retrospective study

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Background: Intrauterine insemination (IUI) is a management option for infertility. We aimed to investigate the association between endometrial thickness (ET) and pregnancy outcome after IUI, and to identify factors affecting outcome in a Hong Kong population.
Methods: Medical records of women who underwent IUI at the infertility clinic of Queen Elizabeth Hospital from January 2013 to June 2019 were reviewed. Only the first cycle was included in the analysis to avoid over-representation of patients who failed treatment. Patients with or without clinical pregnancy were compared, as were patients with or without ongoing pregnancy. The predictive power of ET for pregnancy in IUI was assessed using the area under the receiver operating characteristic curve. Proportions of clinical pregnancy and ongoing pregnancy were calculated for 3 different subgroups of ET (<7 mm, 7-10 mm, and >10 mm).
Results: Of 337 IUI cycles, the clinical pregnancy rate was 12.7% (n=43); the ongoing pregnancy rate was 10.6% (n=36); and the multiple pregnancy rate was 1.4% (n=5). Shorter duration of infertility was associated with clinical pregnancy (2.67 years vs 3.51 years, p=0.003) and ongoing pregnancy (2.64 years vs 3.50 years, p=0.001). ET was not predictive of clinical pregnancy or ongoing pregnancy, with the area under the receiver operating characteristics curve being 0.473 and 0.509, respectively. Highest clinical and ongoing pregnancy rates occurred in those with ET of >10 mm. In patients with ET of >10 mm, all patients with clinical pregnancy successfully carried on to ongoing pregnancy.
Conclusion: ET is not predictive of IUI success. Longer duration of infertility adversely affects IUI outcome.

Keywords: Endometrium; Infertility; Insemination, artificial

Introduction

Intrauterine insemination (IUI) is a management option for infertility. Factors for favourable outcome include a younger age, a shorter duration of infertility, and a low body mass index (BMI).[1-3] Successful embryo implantation is related to endometrial receptiveness and thickness, which also are important factors for successful pregnancy[4]. Thin endometrium is associated with lower chance of conception, and conception is enhanced with increasing endometrial thickness (ET) in clomiphene citrate–induced IUI cycles[5]. For gonadotropin-stimulated cycles, ET of >8 mm is associated with a higher clinical pregnancy rate[6]. However, a meta-analysis of 23 studies has shown no association between ET and pregnancy rates in IUI with ovarian stimulation cycles[7]. A retrospective study investigating the effect of ET on 1065 gonadotropin-stimulated cycles also reported no significant difference between ET and reproductive outcome[8]; as did a prospective cohort study of 168 clomiphene citrate–stimulated IUI cycles[9].

In women with ovulatory disorders, ovarian stimulation with clomiphene citrate may result in lower ET than gonadotropin-stimulated cycles, but whether the lower ET causes the lower pregnancy rates is not clear[10]. The differences in ET among various ovarian stimulation agents are small and might be coincidental[7].

Most studies on the association between ET and IUI outcome are based on Caucasian populations. In this study, we aimed to investigate the association between ET and pregnancy outcome after IUI, and to identify factors affecting outcome in a Hong Kong population.

Materials and Methods

This study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference no.: KC/KE-20-0031/ER-3). Medical records of women who underwent IUI at the infertility clinic of Queen Elizabeth Hospital from January 2013 to June 2019 were

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reviewed. Women who had undergone follicular tracking or used medication without insemination were excluded, as were those who aged >40 years, which is the upper age limit eligible for IUI in our hospital. Each woman could undergo a maximum of 3 cycles.

Patients were seen by the infertility team using standard department protocols[11]. For ovarian stimulation, in the first IUI cycle, 50 mg clomiphene citrate was used on days 3 to 7, whereas in subsequent cycles, injectable gonadotropin (menotropin or follitropin alfa) were used. Oestrogen level in blood was measured at day 3 of the cycle and before IUI. Follicles were tracked by transvaginal scanning using the Philips iU22 ultrasound machine. ET was measured on the sagittal plane of the uterus at the widest part. Ovulation was triggered by injection of human chorionic gonadotropin (hCG) when a single follicle reached 18 mm in diameter. IUI was performed 24 to 48 hours later. Cycles were cancelled in case of multiple follicle development, as defined by more than two follicles on ultrasound. Utrogestan pessary was given for luteal phase support. A urine pregnancy test was performed 14 days after IUI, and if positive, an ultrasound examination was performed to confirm pregnancy.

The primary outcome measure was clinical pregnancy, defined as positive urine pregnancy test and the presence of an intrauterine sac on ultrasound. Secondary outcome measure was ongoing pregnancy, defined as viable pregnancy progressing beyond 24 weeks of gestation.

Statistical analysis was performed using SPSS (Windows version 20.0; IBM Corp, Armonk [NY], US). A p value of <0.05 was considered statistically significant. Only the first cycle was included in the analysis to avoid over-representation of patients who failed treatment. Patients with or without clinical pregnancy were compared, as were patients with or without ongoing pregnancy. Categorical variables were compared using the Chi-square test, and continuous variables were compared using the Student's t test. The predictive power of ET for pregnancy in IUI was assessed using the area under the receiver operating characteristic curve. Proportions of clinical pregnancy and ongoing pregnancy were calculated for 3 different subgroups of ET (<7 mm, 7-10 mm, and >10 mm) based on the distribution of ET in our patients and previous studies[8,12,13].

Results

Of 635 IUI cycles performed in the study period, 8 were cancelled owing to poor or excessive response and 627 were performed in 337 patients. The clinical pregnancy rate was 11.8% (n=74); the ongoing pregnancy rate was 9.2% (n=58); and the multiple pregnancy rate was 1.9% (n=12). Six cases of ectopic pregnancy were excluded. To avoid over-representation of patients who failed treatment, only the first cycles were included for analysis (n=337). The clinical pregnancy rate was 12.7% (n=43); the ongoing pregnancy rate was 10.6% (n=36); and the multiple pregnancy rate was 1.4% (n=5). Patient characteristics per cycle and per patient are presented in Table 1.

Shorter duration of infertility was associated with clinical pregnancy (2.67 years vs 3.51 years, p=0.003) and ongoing pregnancy (2.64 years vs 3.50 years, p=0.001) [Table 2]. Other factors including patient age, partner age, BMI, number of cycles, primary or secondary infertility, cause of infertility, ET, follicle size, and oestrogen level were not associated with successful pregnancy.

ET was not predictive of clinical pregnancy or ongoing pregnancy, with the area under the receiver operating characteristics curve being 0.473 and 0.509, respectively (Figure 1).

Table 1. Patient characteristics per cycle and per patient

Patient characteristic	Per cycle (n=627)[*]	Per patient (n=337)[*]
Patient age, y	34.15 (25-40)	34.07 (25-39)
Partner age, y	36.98 (26-59)	36.83 (26-59)
Duration of infertility, y	3.55 (1-13)	3.40 (1-13)
Body mass index, kg/m^2	22.34 (15.79-36.20)	22.55 (15.79-36.20)
Oestrogen, pmol/L	2460.46 (64-10091)	2342.10 (64-10055)
Follicle size, mm	17.53 (14-25)	17.76 (14-25)
Endometrial thickness, mm	8.25 (2-18)	7.34 (2-18)

[*] Data are presented as mean (range)

Table 2. Associations of patient characteristics with clinical and ongoing pregnancy

Patient characteristic	Clinical pregnancy			Ongoing pregnancy		
	Success (n=43)[*]	Failure (n=294)[*]	p Value	Success (n=36)[*]	Failure (n=301)[*]	p Value
Patient age, y	33.72±3.254	34.12±3.180	0.441	33.64±2.987	34.12±3.212	0.390
Partner age, y	36.58±4.327	36.87±5.05	0.721	36.17±3.968	36.91±5.064	0.306
Body mass index, kg/m^2	22.53±3.702	22.55±3.872	0.972	22.51±3.929	22.558±3.841	0.942
Endometrial thickness, mm	7.19±2.762	7.36±2.698	0.699	7.47±2.843	7.32±2.69	0.748
Follicle size, mm	17.58±1.592	17.78±1.753	0.475	17.61±1.573	17.78±1.752	0.592
Oestrogen, pmol/L	2545.19±1198.47	2311.56±1720.60	0.391	2647.78±1194.487	2304.54±1708.539	0.243
Duration of infertility, y	2.67±1.52	3.51±2.27	0.003	2.64±1.291	3.50±2.272	0.001
No. of cycles			0.652			0.448
1	43 (58.1)			36 (62.1)		
2	18 (24.3)			13 (22.4)		
3	13 (17.6)			9 (15.5)		
Type of infertility			0.510			0.583
Primary	28 (65.1)			25 (69.4)		
Secondary	15 (34.9)			11 (30.6)		
Cause of infertility						
Male factor			0.321			0.123
Present	26 (60.5)			23 (63.9)		
Absent	17 (39.5)			13 (36.1)		
Anovulation			0.591			0.203
Yes	7 (16.3)			7 (19.4)		
No	36 (83.7)			29 (80.6)		
Unexplained			0.215			0.152
Yes	14 (32.6)			12 (33.3)		
No	29 (67.4)			24 (66.7)		

[*] Data are presented as mean ± standard deviation or No. (%) of patients

The distribution of ET was normal, ranging from 2 mm to 18 mm, with a peak at 6 mm (Figure 2a). Patients with clinical and ongoing pregnancy had ET of 3 mm to 13 mm. Patients were classified according to ET of <7 mm, 7-10 mm, or >10 mm. Highest clinical and ongoing pregnancy rates occurred in those with ET of >10 mm. The percentage of clinical pregnancy successfully becoming ongoing pregnancy increased with ET. In patients with ET of >10 mm, all patients with clinical pregnancy successfully carried on to ongoing pregnancy (Table 2b).

Discussion

In the present study, ET was not associated with clinical pregnancy after IUI. This finding is consistent with that reported in other studies[7-9]. The distribution of ET was normal, with highest clinical and ongoing pregnancy rate achieved in patients with ET of >10 mm. This finding echoes a study reporting that the highest pregnancy rate was associated with ET of 10-11 mm[1]. In addition, pregnancy rate increases with ascending ET and is highest when ET is between 10.5 mm and 13.9 mm, after which the success rate declines[8]. In the present study, the pregnancy rate was highest in women with ET of >10 mm, and no pregnancy occurred in women with ET of ≥14 mm. Extremes of ET could hinder the endometrial receptiveness, and very thick endometrium could be related to endometrial pathology, but this association was not found in the present study probably because of small sample size.

In the present study, longer duration of infertility was associated with lower chance of clinical and ongoing pregnancy in patients undergoing IUI. This finding is

similar to that reported in other studies[2,14,15]. The pregnancy rate is compromised when the duration of infertility is >3 years, independent of age, unless multifollicular ovarian

response and a high sperm concentration are achieved[16]. Pregnancy rates are better if the duration of infertility is <6 years[2]. Thus, couples should seek medical attention for pregnancy earlier. For couples with longstanding infertility, counselling should be given about the reduced success rate.

Age is a well-known factor of infertility. Fertility decline accelerates after age 40 years[17]. The age-related decline in IUI success has been reported[3,8,18]. In the present study, age was not associated with IUI success. This may be due to exclusion of women aged >40 years and the small sample size.

Oestrogen level reflects ovarian reserve and growing of follicles and is associated with IUI outcome[8,18-20]. Peak oestrogen level is higher in successful cycles[8]. The peak oestrogen level and the number of follicles with a diameter >16 mm are significant factors for IUI success[18]. Younger women, shorter duration of infertility, and higher peak oestrogen level predict successful outcome in IUI[20]. In the present study, oestrogen level was not a significant factor for pregnancy, probably owing to the small sample size.

Peak oestrogen level and the number of follicles are also associated with multiple pregnancies[18]. Triplets
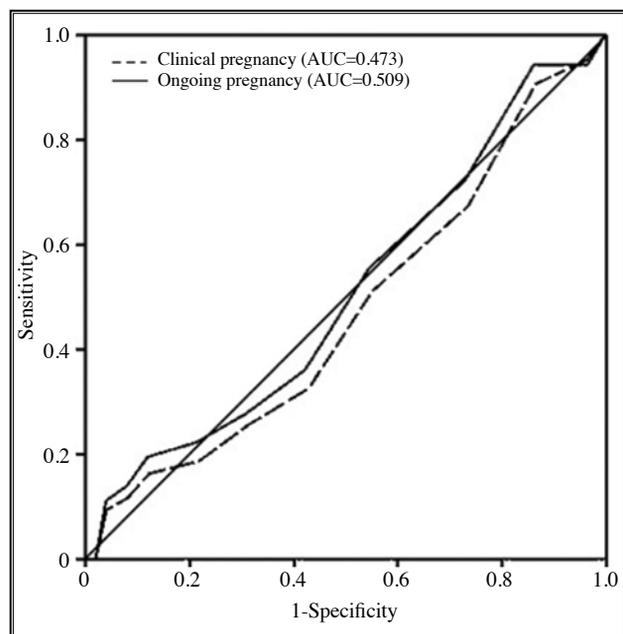

Figure 1. The area under the receiver operating characteristics curve for endometrial thickness was 0.473 for clinical pregnancy and 0.509 for ongoing pregnancy
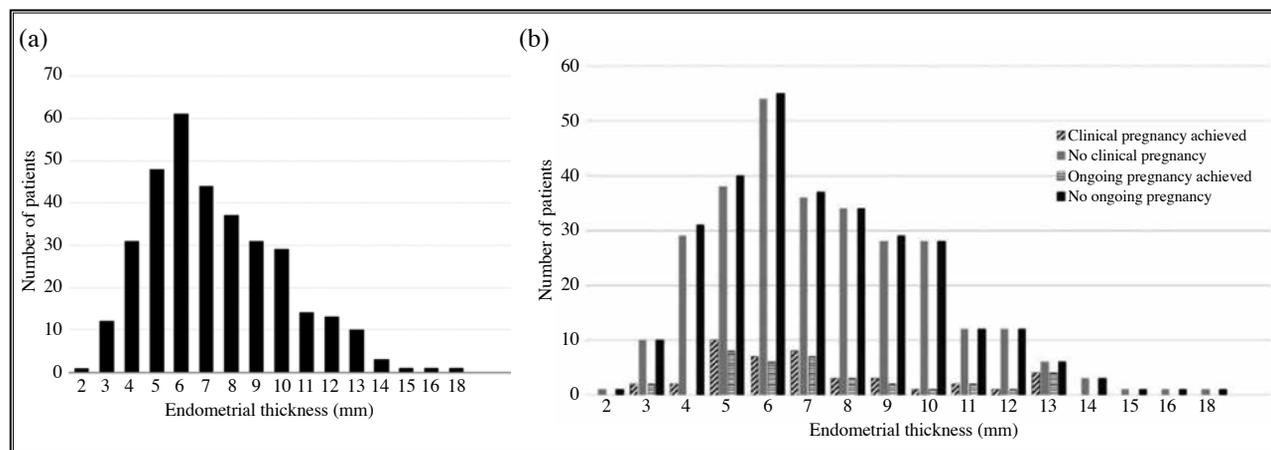

Figure 2. (a) Distribution of endometrial thickness and (b) distribution of endometrial thickness and clinical pregnancy

Table 3. Pregnancy outcome in different subgroups of endometrial thickness

Outcome	Endometrial thickness, mm		
	<7 (n=153)*	7-10 (n=141)*	>10 (n=43)*
Clinical pregnancy	21 (13.7)	15 (10.6)	7 (16.2)
Ongoing pregnancy	16 (10.4)	13 (9.2)	7 (16.2)
% of clinical pregnancy successfully becoming ongoing pregnancy	76.1	86.6	100

* Data are presented as No. (%) of patients unless otherwise stated

and higher order pregnancies are increased in higher peak oestrogen levels[21]. In the present study, there were only a few twin pregnancies, and cycles were cancelled in cases of multiple follicular development.

In the present study, primary or secondary infertility was not associated with IUI outcome. Women with secondary infertility have a higher pregnancy rate than women with primary infertility until the age 38 years[1]. The history of pregnancy is a predictor of pregnancy in IUI[22], but such an association is not found in another study[2].

Overweight or obesity is known to affect women in terms of infertility, anovulation, hormonal disturbance, and polycystic ovarian syndrome. Some studies reported that high BMI has a detrimental effect on the pregnancy rate[6,23], but other studies reported that high BMI does not affect the pregnancy rate[24,25]. In the present study, BMI was not associated with IUI success. This may be due to the fact that obese women (BMI >30 kg/m^2) only accounted for 8.9% of the sample. Obese or overweight women are advised to lose weight and maintain good health before IUI.

The study sample comprised Chinese and Southeast Asian populations. Patients were managed in the infertility clinic with standard protocol by a team of specialist doctors and nurses. Nonetheless, the present study is limited by the small sample size. Measurement of ET was performed by more than one clinician, and accuracy may be limited by the operator-dependent nature of ultrasound scans. In addition, different units in Hong Kong may have different protocols in ovarian stimulation and IUI, and the heterogeneity of protocol may hinder its generalisability and applicability.

Conclusion

Patients are advised to seek help from infertility services promptly, as longer duration of infertility adversely affects IUI outcome. In addition, ET is not predictive of IUI success; the use of medication to increase ET may not be helpful.

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