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Study of endometrial thickness and pregnancy outcome following induction of ovulation and intrauterine insemination in primary infertility

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ABSTRACT

Objective: Infertility affects approximately 10–15% of couples. Assessment of the endometrium with ultrasound has become a standard procedure during the diagnostic workup and treatment of infertility. Our study was designed to investigate whether endometrial thickness on the day of human chorionic gonadotropin administration is a predictor of intrauterine insemination (IUI) success as the primary outcome.

Materials and Methods: In the prospective observational study, a serial transvaginal ultrasound scan was performed to measure endometrial thickness following ovulation induction with clomiphene citrate and IUI. One hundred and nine IUI cycles were chosen and the outcome was measured in terms of whether pregnancy occurred or not.

Results: There was a statistically significant difference ($P = 0.001$) between the two groups with respect to mean endometrial thickness (mm). It was also seen significantly higher numbers of pregnancy in Group A (endometrial thickness ≥ 7 mm).

Conclusion: The present study identified a statistically significant difference in mean endometrial thickness between cycles that resulted in pregnancy and those did not. Consequently, clinicians providing IUI for infertile couples must pay close attention to endometrial development.

Keywords: Intrauterine insemination, Endometrial thickness, Infertility, Ovulation induction

INTRODUCTION

Infertility is generally defined as 1 year of unprotected intercourse without conception.[1] Approximately 85–90% of healthy young couples conceive within 1 year, most within 6 months.[2] Infertility, therefore, affects approximately 10–15% of couples. The major causes of infertility include ovulatory dysfunction (20–40%), tubal and peritoneal pathology (30–40%), male factors (30–40%), and uterine pathology (relatively uncommon). The remainder is largely unexplained, a diagnosis of exclusion ranging from 10% to as high as 30% among infertile populations.[3] Combined treatment with clomiphene and intrauterine insemination (IUI) is commonly recommended for couples with unexplained infertility, but evidence for its effectiveness is quite limited. In a review of eight studies involving 932 treatment cycles, the estimated cycle fecundity was 5.6% with clomiphene and 8.3% with clomiphene and IUI.[4] A

2002 systematic review of trials comparing outcomes of treatment with clomiphene/IUI and gonadotropins/IUI concluded that evidence is insufficient to suggest that either treatment is superior.[5]

Assessment of the endometrium with ultrasound has become a standard procedure during the diagnostic workup and treatment of infertility. Despite the widespread use of high-resolution ultrasound equipment, the clinical significance of differences in endometrial thickness and appearance has remained controversial.[6] Some studies demonstrated low pregnancy rates (PRs) in the presence of thin endometrial layers,[7] but others could not confirm this association.[8,9] The present study was designed to investigate whether endometrial thickness on the day of human chorionic gonadotropin (hCG) administration is a predictor of intrauterine insemination (IUI) success as the primary outcome. It was hypothesized that a thicker endometrium is predictive of better PR when all other parameters are comparable.

MATERIALS AND METHODS

The prospective observational study was done after obtaining approval from the Institutional Ethics Committee in medical college and hospital from February 2015 to March 2016 among women attending our outpatient department seeking treatment of infertility. Anovulatory or oligo-ovulatory women without any other causes for infertility (with normal semen analysis, tubal patency determined by HSG, and normal uterine factors) were selected for our study. A semen specimen was obtained by masturbation and collected in a clean container followed by processing by washing. In the swim-up procedure, semen samples were mixed with 1 mL of Ham's F10 media containing human serum albumin and centrifuged at 1800 rpm for 5 min. Ovulation induction was started on the 3rd day of cycle for 5 days, with 50 or 100 mg of clomiphene citrate administered, depending on antral follicles. In subsequent cycles, CC doses were increased in 25–50 mg increments to a maximum of 150 mg. For most patients, vaginal ultrasound was initiated on day 10–12 of the cycle and then repeated every alternate day until one of the follicles was more than or equal to 18 mm, at which time 5000 IU hCG was administered. A serial transvaginal ultrasound scan was performed to measure the endometrial thickness. Measurements were made from the outer edge of the endometrial-myometrial interface to the outer edge in the widest part of the endometrium. If two or three layers of endometrium were visible, it was defined as a triple-line pattern, and a single round structure was considered to be a non-triple-line structure. A single IUI was performed with fresh sperm within 36 h after hCG administration. A fresh sperm pellet was resuspended in 0.4 mL of sperm wash medium, drawn into an insemination catheter, and then deposited high in the uterus. The patient was instructed to be in the same position for ½ h. Then, she was reviewed after the first missed menstruation or if she attains menstruation. Patients who missed menstruation underwent a urine pregnancy test (UPT). Patients with positive UPT were subjected to ultrasonography to confirm intrauterine pregnancy and number of gestational sac. Only pregnancies with a confirmed gestational sac are reported. Patients who experienced menstruation were subjected to the next ovulation induction cycle. A maximum of six cycles were done. Thus, the number of IUI cycles was more than number of patients. During statistical analysis, the number of IUI cycles was considered. One hundred and nine IUI cycles were chosen by purposive sampling technique for our study. The outcome was measured in terms of whether pregnancy occurred or not. Only pregnancies with a confirmed gestational sac were reported. Observations were tabulated in Excel sheet and analyzed. Continuous data were expressed as mean ± standard error of the mean (SEM). Discrete categorical data were presented as number of IUI cycles (*n* [%]) and median value. Comparisons of continuous data with a normal distribution were performed using the independent Student's *t*-test. Categorical data were analyzed with contingency tables using the Pearson Chi-square test. A statistical test was considered significant when $P < 0.05$. All analyses were conducted using GraphPad InStat for Windows.

RESULTS

Initially, 52 patients were assessed for eligibility. However, 10 patients of them did not meet the inclusion criteria and six patients opted out. Finally, 36 patients were taken up for study. A total of 36 patients completed 109 cycles of IUI. Data from all these IUI cycles were collected and divided into two groups on the basis of endometrial thickness on the day of hCG administration. Hence, data from patients were available for analysis;

Group A = Cycles with endometrial thickness ≥7 mm ($n = 73$)

Group B = Cycles with endometrial thickness ≤ 7 mm ($n = 36$)

Table 1 shows the mean age, height, weight, BMI with SEM, and duration of infertility in years. It was evident that there was no statistically significant difference between the two groups. Table 2 shows the mean and standard error of the mean of both groups in terms of husband age, total sperm count, normal sperm morphology, and progressive motility of sperms. G`roup A had a mean husband's age of 30.46 ± 0.39 years and Group B had 30.38 ± 0.44 years. The independent Student's *t*-test shows that there was no statistically significant difference between the two groups. Total sperm count was 77.72 ± 4.51 million for Group A and 82.51 ± 5.56 million for Group B. They were statistically

Table 1: Distribution of patients undergoing IUI cycles according to age (years), weight (kg), height (m) and BMI (Kg/m^2) and duration of infertility of Group A and Group B.

Parameters		Group A (*n*=73)	Group B (*n*=36)	*P* value
Age (years)	Mean	27	26.3	0.369(NS)
	SEM	±0.440	±0.468	
Weight (kg)	Mean	59.99	59.31	0.47(NS)
	SEM	±0.48	±0.92	
Height (m)	Mean	1.50	1.51	0.13
	SD	±0.002	±0.002	
BMI(Kg/m^2)	Mean	26.47	25.95	0.209(NS)
	SEM	±0.223	± 0.374	
Duration of infertility	Mean	6.51	5.77	0.18(NS)
	SEM	±0.33	±0.38	

Table 2: Distribution of patients undergoing IUI cycles according to husband age(years), total sperm count (millions), normal morphology of sperm (%), progressive motility of sperms (%).

Parameters		Group A (*n*=73)	Group B (*n*=36)	*P* value
Husband's Age (years)	Mean	30.46	30.38	0.90(NS)
	SEM	±0.39	±0.44	
Total sperm count (millions)	Mean	6.51	5.77	0.52(NS)
	SEM	±4.51	±5.56	
Normal sperm morphology (%)	Mean	64.39	67.80	0.45(NS)
	SEM	±2.4	± 4.3	
Progressive motility (%)	Mean	78.23	74.72	0.39(NS)
	SEM	±2.17	±3.85	

matched (P = 0.52). The normal sperm morphology was recorded and it was found to be 64.39 ± 2.4% for Group A and 67.80 ± 4.3% for Group B. Thus, the results showed that both groups were comparable (P = 0.45). Progressive motility was 78.23 ± 2.17% for Group A and 74.72 ± 3.85% for Group B. P = 0.39 shows that there was no statistically significant difference between the two groups. Table 3 expresses the mean and standard error of mean of luteinizing hormone (LH) level (IU/L) and follicle-stimulating hormone (FSH) level (IU/L) in Group A and Group B. Mean LH level of Group A was 6.17 ± 0.17 IU/L and 5.63 ± 0.25 for Group B (P = 0.08). For Group A, FSH level was 7.94 ± 0.25 IU/L and 8.13 ± 0.49 IU/L for Group B (P = 0.70). Thus, the LH and FSH levels were statistically not significantly different between the two groups. In Group A, the mean serum prolactin level was 16.95 ± 0.56, and in Group B, it was 15.68 ± 0.93. In Group A, the mean thyroid-stimulating hormone level was 2.04 ± 0.11 mIU/L, and in Group B, it was 1.79 ± 0.17 mIU/L (P = 0.20). The results of independent Student's t-test suggested that both groups had no statistically significant difference (P = 0.21). In Table 4, the mean number of follicles growth in Group A

Table 3: Different gonadotrophins, serum prolactin and TSH levels of Group A and Group B and their statistical analysis.

Parameter		Group A (*n*=73)	Group B (*n*=36)	*P* value
LH level (IU/L)	Mean	6.17	5.63	0.08
	SEM	±0.17	±0.25	
FSH Level (IU/L)	Mean	7.94	8.13	0.70
	SEM	±0.25	±0.49	
Serum Prolactin level (ng/ml)	Mean	16.95	15.68	0.21(NS)
	SEM	±0.56	±0.93	
TSH level (mIU/L)	Mean	2.04	1.79	0.20(NS)
	SEM	±0.11	±0.17	

Table 4: Number and Duration of follicles growth, Diameter of dominant follicle (mm), endometrial thickness (mm) and result of pregnancy tests in two groups and their statistical analysis.

Parameters		Group A (*n*=73)	Group B (*n*=36)	*P* value
Number of follicles growth	Mean	2.36	2.27	0.45(NS)
	SEM	± 0.07	± 0.09	
Duration of follicles growth (Days)	Mean	9.19	9.27	0.54(NS)
	SEM	± 0.07	± 0.12	
Diameter of dominant follicle (mm)	Mean	21.02	20.72	0.34(NS)
	SEM	± 0.18	± 0.26	
Endometrial thickness (mm)	Mean	9.79	6.52	0.0001(S)
	SEM	± 0.17	± 0.06	
No of Positive pregnancy test		11	0	0.0149 (S)
No of Negative pregnancy test		62	36	

and Group B was 2.36 ± 0.07 days 2.27 ± 0.09 days in Group B (P = 0.45). The mean duration of follicles growth (days) in Group A and Group B was 9.19 ± 0.07 days and 9.27 ± 0.12 days, respectively (P = 0.54). There was no statistically significant difference (P = 0.20) between the two groups. The mean diameter of the dominant follicle (mm) in Group A was 21.02 ± 0.18 in Group A and 20.72 ± 0.26 in Group B. There was no statistically significant difference (P = 0.34) between the two groups. In Group A, the mean endometrial thickness was 9.79 ± 0.17 mm, and in Group B, it was 6.52 ± 0.06 mm. The value of independent Student's t-test indicated that there was a statistically significant difference (P = 0.001) between the two groups with respect to mean endometrial thickness (mm). In Group A, the total number of pregnancy was 11, and in Group B, there was no pregnancy. The value of Fisher's exact test indicated that there was a statistically significant difference (P = 0.0149) between the two groups with respect to number of pregnancy. Thus, there were significantly higher numbers of pregnancy in Group A (endometrial thickness ≥ 7 mm).

DISCUSSION

Primary infertility is one of the common problems faced by every gynecologist. IUI with ovulation induction is generally considered the first line of management for these patients. Endometrial thickness can be regarded as a reflection of the degree of endometrial proliferation in the absence of intrauterine pathology. These data showed that endometrial thickness can be considered as the main predictor of PR in CC-IUI cycles.[10] Despite the widespread use of high-resolution ultrasound equipment, the clinical significance of differences in endometrial thickness and appearance has remained controversial.[6] Some studies demonstrated low PRs in the presence of thin endometrial layers,[7] but others could not confirm this association.[8,9]

Gonen *et al*. suggested that transvaginal sonographic evaluation of endometrial texture and thickness may be an indicator of the likelihood of achieving pregnancy.[11] Noyes *et al*. concluded that endometrial thickness >9 mm as well as ring and intermediate endometrial patterns denoted a more favorable prognosis for pregnancy in *in vitro* fertilization.[12] Isaacs *et al*. concluded that endometrial thickness is a valid screening test for conception outcome in cycles stimulated with hMG.[13] In their study, no pregnancy occurred when the endometrium measured <7 mm. In the present study, the mean duration of infertility for Group A was 6.51 ± 0.33, while for Group B, it was 5.77 ± 0.38. Thus, both groups were comparable with respect to the duration of infertility ($P = 0.18$).

In our study, husband's age and semen parameters (count, motility, and morphology) were comparable in both groups ($P > 0.05$). Branigan *et al*. reported that none of the basic semen parameters of concentration, motility, and morphology were related to IUI success. The numbers of motile sperm available for insemination, and especially their 24-h survival, were highly predictive of IUI success. Esmailzadeh *et al*. found that although sperm quality (count, motility, and morphology) was associated with PR, only the motility of the sperm was a significant factor in the multiple regression model.[10] This study used only one type of sperm preparation, insemination technique, and follicular monitoring for insemination timing. Other programs will be needed to confirm these findings because different sperm preparations may yield different results.

Duration of follicles growth, number of follicles, and size of dominant follicle were comparable in both groups. Ghosh *et al*. reported that women with follicular diameters ≥20 mm were more likely to become pregnant than women with diameters between 15.00 and 19.99 mm.[14] In this study, we evaluated endometrial thickness in two divided groups >7 mm and <7 mm. All other parameters were comparable in both groups. Thus, endometrial thickness is independent of these factors. In all age ranges, PR was lower with endometrial thickness ≤7 mm. There was no pregnancy when endometrial thickness was ≤7 mm. There were 11 pregnancies in group with ET thickness ≥7 mm. In Esmailzadeh study, endometrial thickness on the day of Human chorionic gonadotrophin (HCC) administration was significantly greater in cycles where the pregnancy was achieved (10.1 ± 3 vs. 7.7 ± 3.5). The woman's age was negatively associated with pregnancy outcome, while ET and the total motile sperm count were positively associated with pregnancy outcome.[10]

CONCLUSION

Intrauterine insemination with ovulation induction is generally considered first line of management for the infertile women. Endometrial thickness can be regarded as a reflection of the degree of endometrial proliferation in the absence of intrauterine pathology. Our data showed that endometrial thickness can be considered as a main predictor of pregnancy rate. Present study identified a statistically significant difference in mean endometrial thickness between cycles that resulted in pregnancy and those that did not. Consequently, clinicians providing IUI for infertile couples must pay close attention to endometrial development.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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