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Original Research Article

The relationship between endometrial thickness and pregnancy rates in subfertile women underwent intrauterine insemination following ovulation induction

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Abstract

Objective: The aim of this study is the comparison of effects of Clomiphene Citrate (CC) & human menopausal Gonadotrophin (hMG) stimulated cycles on the Endometrial Thickness (ET) in intrauterine insemination (IUI) in one cycle & to establish any relation between ET on the day of IUI and achieving clinical pregnancy in these stimulated cycle.
Study design: A prospective observational study was undertaken for assessing effects of clomiphene citrate (CC) and human menopausal gonadotrophin hMG stimulated cycle on the ET and clinical pregnancy in single IUI cycle.
Subfertility cases were studied in two groups; Group A [ovulation induction (OI) with CC and IUI, n = 150] and Group B (OI with hMG and IUI, n = 150).
Results: Comparable data obtained in mean, age, duration of subfertility female, male (only oligo sperm a) in both group range of ET of clinical pregnancy in group A (n = 21) were 8.0 – 12.9 mm and 9.0 – 12.9 mm in group B (n = 40). (p value < 0.001) ongoing pregnancy beyond 1st trimester was higher in group B (n= 42) than group A (n = 19).
Conclusion: Mean ET and clinical pregnancy rate both were higher in hMG group compared to CC.
Keywords: Infertility, intrauterine inseminations, endometrial thickness, pregnancy rate.

1. Introduction

Subfertility in defined as inability to conceive after at least one year of unprotected Intercourse.[1]

Primary infertility is defined when pregnancy has never occurred.

Secondary infertility is defined when the couple had conceived previously (irrespective of results of that pregnancy), but they are unable to conceive again after a year of trying.[2]

During ovulatory cycle, pattern & thickness of endometrium is variable, after menstruation, endometrium thin & become thicker gradually.[3,4]

During the menstrual cycle the endometrium undergoes cyclic changes in preparation for implantation. In the follicular phase, the growing follicles produce increasing amounts of E_2 that induce proliferative endometrial changes. After ovulation, the corpus Luteun produces progesterone, which leads to secretory changes.[3]

The thickend endometrium provides a site for attachment, and is the source of nourishment for an implanting embryo during its first few weeks unhile placenta develops.

While there is little doubts that physiologically thickend endometrium is critical to a successful Implantation and pregnancy, controversy exist regarding the clinical significance of variation in endometrial thickness observed among patients undergoing assisted reproduction previous observation studies had conflicting results with regard to the association of endometrial thickness and pregnancy rate (PR) after IVF & ET.[5,6]

Many studies have been conducted in the past to find out the factors affecting the endometrium in women but the results are still unclear.

The anatomic and physiological changes in the functional endometrium under the influence of endogenous gonadotrophins (proliferative to secretory phase & how it behaves for the implantation of the embryo during post-ovulation period is important for resulting in pregnancy.[7]

1.1 The aim of the study

The aim of this study is the comparison of effects of CC & hMG stimulated cycles on the ET in IUI in one cycle & to establish any relation between ET on the day of IUI and achieving clinical pregnancy in these stimulated cycles.

2. Material & Method

2.1. Study design

A prospective observational study was carried out at fertility center of Al Sader Teaching Hospital in Al-Najaf from September 2014- November 2016. Study protocol was approved by the Institutional Ethical committee. From 350 subfertile women, 300 patients Intrauterine Insemination cases were enrolled into this study successively.

2.2. Inclusion criteria were

Female age ≤ 36yrs or younger, Patient with primary infertility including (Unexplained inferlility, Ovulatory dysfunction, PCOs), documented patent tube by either hystrosalpingogram or laproscopy, documented ovulatory cycles with regular mens either normally or with CC.

2.3. Exclusion criteria

Abnormal HSG/Laproscopy, Pelvic adhesion proved by laproscopy, Congenital anomalies of uterus, Major mullerian mal formations, Tubal blockage, Cases - with uro-genital infection including, tuberculosis, bacterial vaginosis, Failed cases of ovulation induction, Primary amenorrhea, Premature ovarian failure, Sever male factor contributing to infertility. (azospermia, aspermia, teratozoospermia etc)

2.4. Study procedure

Ovarian stimulation was done after performing baseline transvaginal sonography.(TVs) on day 2 of menstrual cycle. CC 100mg daily from day 2 to day 6 of the cycle or injection hMG 75IU (step up protocol), From Day 2 to day 8 of the cycle was given respectively in Group A & B. The response was monitored with serial Tvs ultrasound starting from day 9 of the cycle and repeated at 1-3day interval for measurement the number and diameter of follicles and ET (endometrial thickness measurement were made from the outer edge of the endometrial interface to the outer edge in the widest part of the endometrium. The ovulation trigger with injection hCG 10.000IU was administrated intramuscularly on appropriate day considering leading follicular side of 18-20mm.

At the time of hCG administrations, monitoring of the follicular response and ET were done with B-mode imaging using wide band micro convex endocavity probe, specially used for obstetrics and gynecological purpose, semen preparation was done by the swim up procedure& Insemination was done36-hrs after hCG trigger. All patients were advised for intercourse for next 3 days and vaginal micronized progesterone support was provided for 21 days following IUI. Follow- up were done when next menstruation was missed with b-hCG & sonography as per standard international infertility management protocol.[8,9]

Primary out comes measured were ET on day of IUI in both group, number of no pregnancy numbers of biochemical pregnancies (β -hCG positive >2 without Gestational sac on sonography & number of serological, clinical pregnancies diagnosed by appearance of Gestational sac.

2.5: Statistical analysis

Data entry and statistical analysis were done using SPSS version 21 statistical package was used.

3. Results

The present study was involved 300 female, 150 allocated as group A (OI with CC followed by IUI) and 150 as group B (OI with hMG followed by IUI) Table 1 summarized the demographic parameters of study participants including age, duration of infertility, female and male factors. No significant differences (p>0.05) were observed in respect to these

Table 1: Demographic and other parameters (n=300)

Parameters	Subgroups	Group (A) N (%)	Group (B) n (%)	Total	t value	P value
Age groups	21-25	9(6.00)	11(7.33)	21	0.266NS	0.966
	26-30	82(54.67)	78(52.00)	155		
	31-35	51(34.00)	52(34.67)	103		
	>36	8(5.33)	9(6.00)	21		
	Total	150	150	300		
Mean age±SD	28.37±4.01	28.92±4.23				
Duration (years)	<3	59(39.33)	60(40.00)	119	0.136NS	0.934
	4 to 6	63(42.00)	64(42.67)	127		
	>7	28(18.67)	26(17.33)	54		
	Total	150	150	300		
Females factors	Normal	56(37.33)	58(38.67)	114	0.104NS	0.991
	Ovulatory dysfunction	59(39.33)	55(36.67)	114		
	Endocrine causes	22(14.67)	23(15.33)	45		
	Combined	13(8.67)	14(9.33)	27		
	Total	150	150	300		
Male factors	Normal	129(86.00)	126(84.00)	255	0.157NS	0.843
	Oligospermia	21(14.00)	24(16.00)	45		
	Total	150	150			

NS not significant, chi-squared (*2) test.

Table 2 shows the change in mean endometrial thickness on day of IUI in relation to total conception rate and clinical rate in both studied groups.

Significant changes (p<0.001) were observed in mean ET in respect of total conception in group (A), whereas no significant changes were observed in group (B). Same results were observed in respect of clinical conception, change in mean ET was significant (<0.001) in group A, while no significant differences (0.965) were observed in group B.

Table 2: Change in mean endometrial thickness on day of IUI in relation to total conception rate and clinical rate in both groups (n=300)

Type of conception	Groups	Conception	n	Change(mm)	P value
total conception	Group A	Yes	32	7.75±1.68)**	<0.001
		No	118	5.24±1.83	
	Group B	Yes	48	8.43±2.01ns	0.862
		No	102	8.52±2.12	
Clinical conception	Group A	Yes	21	11.97±1.52**	<0.001
		No	129	8.15±1.03	
	Group B	Yes	43	10.98±1.64ns	0.965
		No	107	11.23±1.22	
	Both groups	Yes	64	11.01±1.32**	<0.001
		No	236	9.46±1.98	

**significant (p<0.01), ns not significant, student t-test

A total of 7 biochemical pregnancies were in group A, and group A clinical pregnancies were 14 and 21 in groups A and B respectively. Out of those continued beyond 1 trimester, 19 cases were in group A and 42 cases were in group B (p value<0.001in both group).(Table 3).

Table 3: types of pregnancy wise distribution of endometrial thickness on day of IUI (n=300)

Type of pregnancy	Group	Pregnancy (yes/no)	<6.9	7.0-8.9	9.0-10.9	11.0-12.9	13.0-14.9	>15	Total	P value
Biochemical pregnancy	A	YES	O	4	1	1	1	0	7	<0.001
		NO	41	68	18	10	6	0	143	
	B	YES	0	6	1	3	3	1	14	<0.001
		NO	21	18	58	23	16	0	136	
Clinical pregnancy	A	YES	0	4	13	4	0	0	21	<0.001
		NO	41	68	6	7	7	0	129	
	B	YES	0	0	21	19	0	0	40	<0.001
		NO	21	24	38	7	19	1	110	
Ongoing pregnancy	A	YES	0	4	11	4	0	0	19	<0.001
		NO	41	68	8	7	7	0	131	
	B	YES	0	0	23	19	0	0	42	<0.001
		NO	21	24	36	7	19	1	108	

2.5. Statistical Analysis

For the data analysis SPSS version 21 statistical package was used. Significant differences of variables were assessed by

a- Chi-squared test()for data of table1
b- Student t-test for data of table2 and3
c- A p-value <0.001wereconsidered as statistically significant at 1% (**), were as p value more than 0.05 considered as non- significant (NS).

4. Discussion

Adequate proliferative & secretary changes are necessary for successful implantation to occur. 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 a main predictor of pregnancy rate in controlled ovarian stimulation – IUI cycle. The reported pregnancy rates per cycle ranges from 8 to 22% in different studies. [10-11-12] The results in literatures concerning the impact of ET on successful pregnancy rate are very disparate. Many studies identify a threshold thickness needed to obtain a successful pregnancy. According to different studies the optional thickness in between 8-15mm. [13-14- 15] In this study, threshold ET for CC was 8.2-13 mm and 9.5-13.mm for hMG. Significant higher mean ET with use of hMG was observed compared to that with cc in this study (p value<0.001). The fact of having a smaller mean ET using CC can be explained by antiestrogenic effect of CC on the endometrium. Dickey, RP *et al* [16] found No pregnancy resulted when ET was <6mm 6.9% pregnancies were observed when ET between 6-8mm and 12.8% when ET was ≥ 9mm. In this study found no pregnancy resulted when ET< 6mm, 18% when ET was. 7-

8.9mm. 36% and 39% of total pregnancy cumulatively observed when ET was 9.0-10.9mm and 11-12.9mm ranges respectively in this study. Only 5% and 1% cases got pregnant in 13-14.9mm and >15mm range respectively and no conception noted when ET<6mm on day of IUI. This study showed significant differences in a total conception rate with different a gents used for ovulation induction (n=28, 19.75% with CC and n=34, 34% with hMG). Difference in mean ET on day of IUI was significant in group A but not group B in cases with clinical pregnancy.

Thus, increased ET is not related to increased clinical pregnancy rates statistically, but definitely a threshold ET for clinical pregnancy can be inferred. That is 8.0 – 12.9 mm in Group A and 9.0 – 12.9 mm in Group B. In this study, there was no significant differences in demographic parameters in both groups [table 1].

- Kasius *et al* [16] Found a thin endometrium (less than or equal to 7 mm) was reported in only 2.4% of cases where pregnancy occurred. The probability of clinical pregnancy for an ET less than or equal to 7mm was significantly lower Compared with Cases with ET greater than 7mm *(23.3% versus 48.1%).
- Kovacs *et al* [17] Reported that an increased endometrial thickness of at least 10mm was associated with higher pregnancy rate.
- Weissman *et al* [18] reported lower implantation and pregnancy rates among the women with and endometrial thickness $\geq 14\ mm$ on the day of HCG administration.
- Victoria Habib Zadeh *et al*[19] They, did not found any correlation between age, number of follicles and gonadotrophine ampoules with endometrial thickness but in all ranges, there is a possibility of higher chance of pregnancy in endometrial thickness $6 < ET \leq 10mm$.
- In Esmailzadeh study [20], endometrial thickness on the day of HCG administration was significantly greater in cycles where pregnancy was achieved$(10.1 \pm 3\ us\ 7.7 \pm 3.5$. The women's age was negatively associated with pregnancy outcome, while ET and the total motile sperm counts were positively associated with pregnancy outcome.
- Dickey *et al* [21] Studied on relationship of ET and pattern to fecundibility in ovulation induction cycles and concluded that no pregnancy occurred when thickness was < 6mm, the continuing pregnancy rate was 12.6% when thickness was$\geq 9mm$.

5. Conclusions

Adequate and optimum endometrial development is required for a successful pregnancy to occur thought it was not concluded statistically that increased ET on day of IUI was related to increased clinical pregnancy, but ET of 8 – 12.8mm was required for successful pregnancies in both type of OI agents followed by IUI in single cycle.

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