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Original Research Article

A Hospital Based Retrospective Study Assessing Endometrial Thickness and Pregnancy Outcome in Intrauterine Insemination Cycles

Niharika[1], Shubhanti Kumari[2], Bhawana Tiwary[3]

[1]Senior Resident, Department of Reproductive Medicine, IGIMS, Patna, Bihar, India
[2]Assistant Professor, Department of Reproductive Medicine, IGIMS, Patna, Bihar, India
[3]Assistant Professor, Department of Reproductive Medicine, IGIMS, Patna, Bihar, India

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Corresponding Author: Dr. Niharika
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Abstract

Aim: The aim of the present study was to assess endometrial thickness and pregnancy outcome in intrauterine insemination cycles.

Methods: This study retrospectively considered 250 ovarian stimulation cycles undertaken in 120 candidates for IUI. These patients were candidates for IUI because of either male factor infertility or unexplained infertility.

Results: In the cycles that resulted in pregnancy, the patients were generally younger, had a shorter duration of infertility, and had a higher number of previous IUI cycles. Mean (SD) endometrial thickness on the day of HCG administration was significantly greater in cycles where pregnancy was achieved. The mean (SD) number of follicles and the diameter of the dominant follicle were significantly greater in cycles where pregnancy was achieved. The duration of follicle growth in women with a positive clinical pregnancy was significantly less than that in women with a negative clinical pregnancy. The quality of sperm (count, motility, and morphology) in the women with a positive clinical pregnancy was significantly better than for the women with negative clinical pregnancy. Baseline demographic stimulation parameters and sperm quality were similar between ongoing and abnormal pregnancies. Endometrial thickness did not differ between ongoing and abnormal pregnancies.

Conclusion: The results of the 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 infer- tile couples must pay close attention to endometrial development as well as to follicle growth and sperm motility.

Keywords: Intrauterine Insemination, Endometrial Thickness, Pregnancy Rate, Transvaginal Sonography.

Introduction

During ovulatory cycles, pattern and thickness of endometrial is variable. After menstruation, endometrium is thin and becomes thicker gradually. Although many studies were done about affecting factors on endometrial thickness in infertile women, over the years, but the results is still unclear. [1,2] Researchers suggest effect of age, etiology of infertility and factors such as dominant follicle number on endometrial thickness and some of studies suggest strong effect of endometrial thickness on the pregnancy rate. [3-5] Some factors such as women age, infertility etiology, drug protocol, estradiol levels, previous injuries to endometrium, were supposed as important affecting factors with endometrial growth. [6-8]

Intrauterine insemination (IUI) is the first-line treatment for couples with unexplained or mild male factor infertility. During an IUI cycle, adjunctive stimulation can be achieved via clomiphene citrate (CC), aromatase inhibitors, or injectable gonadotropins to promote the growth of ovarian follicles. Estrogen produced by growing follicles induces endometrial proliferation, leading to increased thickness of the endometrial stripe as measured by transvaginal ultrasound. Peak endometrial stripe thickness (EST) has been studied as a predictive factor of pregnancy outcome in IUI, but most studies have focused on letrozole. In postmenopausal women, letrozole achieves significantly greater plasma estrogen suppression of estrogens and greater inhibition of in vivo aromatization than anastrozole. [9] Another study conducted in 54 postmenopausal women with invasive breast cancer showed that more complete inhibition of aromatase was achieved with 2.5 mg of letrozole than 1 mg of anastrozole, resulting in

significantly greater suppression of estradiol ($P < 0.0001$), the most bioactive estrogen. [10] A recent meta-analysis by Weiss et al. examining EST in IUI cycles found no evidence that EST was associated with chances of clinical pregnancy. [11] However, this study encompassed a heterogeneous mixture of ovarian stimulation methods including letrozole, and injectable gonadotropins. In addition, data comparing EST between cycles that were pregnant vs negative were only available for a subset of the studies included for analysis. 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. [12] Some studies demonstrated low pregnancy rates (PRs) in the presence of thin endometrial layers, [13] but others could not confirm this association. [14,15]

The aim of the present study was to assess endometrial thickness and pregnancy outcome in intrauterine insemination cycles.

Materials and Methods

This study retrospectively considered 250 ovarian stimulation cycles undertaken in 120 candidates for IUI in Department of Reproductive Medicine, IGIMS, Patna, Bihar, India from Feb 2022 to January 2023. These patients were candidates for IUI because of either male factor infertility or unexplained infertility.

Inclusion criteria included the following:

1. Female age 22-35 years.
2. Documented patent tubes by either hysterosal-pingogram or laparoscopy.
3. Documented ovulatory cycles with regular menses and for the men.
4. A minimum of $1X10^6$ processed total motile sperm. No therapeutic intervention was per-formed on patients.

A semen specimen was obtained by masturbation and collected in a clean container. Sperm specimens were processed by washing. [16] In the swim-up procedure, semen samples were mixed with 1 mL of Ham's F10 media containing human serum albumin and centrifuged at 569 g (1,800 rpm) for 5 minutes. Normal values suggested by the World Health Organization were used to interpret semen quality. [17]

Ovulation induction began on a 3-day cycle for 5 days, with 2.5-5 mg of letrozole and injection gonadotropin on day 8 and day 9administered, depending on antral follicles. For most patients, vaginal ultrasound (FukuDa ESAOTE-AU 350, 5 MHZ transducer) was initiated on day 10–12 of the cycle and then re- peated every 1–2 days until two to three follicles were about R18 mm^1, at which time 5000 IU hCG was administered.

On the day of HCG administration, a transvaginal ultra- sound scan was performed to measure endometrial thickness. Measurements were made from the outer edge of the endo- metrial-myometrial interface to the outer edge in the widest part of the endometrium. If two or three layers of endometrium were visible, it would be 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 hours after hCG administration. A fresh sperm pellet was re- suspended in 0.4 mL of sperm wash medium, drawn into an insemination catheter, and then deposited high in the uterus. Serum hCG levels were drawn on day 14 after injection to confirm pregnancies. The presence of an intrauterine pregnancy and the number of gestational sacs were confirmed by ultrasound at 5 weeks' gestational age. Only pregnancies with a confirmed gestational sac are reported in the present analysis. Pregnant patients were followed with ultrasound for 12 weeks.

Statistical analysis of the data was performed with SPSS software for windows, version 10.0 (SPSS, Chicago). In the univariate analysis, the woman's age, the man's age, the number of IUI cycles, the length of infertility, the duration of follicle growth, the number of follicles, the diameter of the dominant follicle, sperm count, the percent of sperm motility, the percent of normal sperm morphology, and endometrial thickness were compared using means, standard deviations, and a t-test between pregnant and nonpregnant women. Also, a t-test was used to compare these variables in women having normal pregnancies versus abnormal pregnancies.

Any pregnancy (singleton, twins, etc.) where a heartbeat was identified on ultrasound before was considered to be an ongoing pregnancy. Any pregnancy that resulted in a loss (spontaneous abortion, missed abortion, etc.) was considered to be an abnormal pregnancy. To achieve the multiple primary regression endpoints of this study, including endometrial thickness as a predictor of IUI outcome, the analysis was carried out in a backward stepwise manner. All of the variables used in univariate analysis (11 variables) were entered into a multiple regression model to answer the question of which one had the main effect on ongoing pregnancy. The significance level for all analyses was $P<0.05$.

Results

Parameter	Clinical pregnancy				F	P
	Yes (n =100) Mean ±SD		No (n=400) Mean ±SD			
Woman's age (years)	26.4	5.4	28.2	5.8	0.68	0.01
Man's age (years)	34.6	5.8	35.5	5.7	0.7	0.96
Length of infertility (years)	4.8	2.8	5.2	3.2	4.7	0.03
No. of IUI cycles	1.8	1.4	1.7	0.8	4.9	0.002
Ovarian response:						
Duration of follicle growth, days	9.1	2.5	10.4	3.2	1.66	0.01
No. of follicles	2.8	2.6	2.5	2.1	4.36	0.01
Diameter of the dominant follicle	17.7	1.7	15.7	1.1	0.24	<0.0001
Sperm quality:						
Sperm count ($\times 10^6$)	39.3	46	32.8	38.2	3.33	0.01
Total motile sperm, %	36.4	16	34.6	17.7	4.96	0.004
Normal morphology,%	39.7	21.6	38.7	15.3	1.36	0.02
Uterine response: endometrial thickness	10.1	3.0	7.7	3.5	4.56	0.001

In the cycles that resulted in pregnancy, the patients were generally younger, had a shorter duration of infertility, and had a higher number of previous IUI cycles. Mean (SD) endometrial thickness on the day of HCG administration was significantly greater in cycles where pregnancy was achieved. The mean (SD) number of follicles and the diameter of the dominant follicle were significantly greater in cycles where pregnancy was achieved. The duration of follicle growth in women with a positive clinical pregnancy was significantly less than that in women with a negative clinical pregnancy. The quality of sperm (count, motility, and morphology) in the women with a positive clinical pregnancy was significantly better than for the women with negative clinical pregnancy.

Table 2: Baseline demographic and stimulation parameters in women with positive or negative ultrasound triple-line in IUI cycles

Variables	Ultrasound triple line				F	P
	Yes (n=420) Mean ±SD		No (n=80) Mean ±SD			
Stimulation parameters						
Duration of follicle growth (days)	9.4	2.3	10.2	2.3	1.25	0.01
No. of follicles	2.8	2.4	2.2	1.0	1.36	0.04
Diameter of the dominant follicle	18.0	1.6	16.6	1.4	0.16	0.01
Demographics						
Woman's age, years	27.3	6.5	29.7	4.0	2.08	0.02
Length of infertility, years	4.7	3.6	7	4.6	4.26	0.007
No. of IUI cycles	1.9	1.3	1.8	0.8	0.34	0.08
Uterine response: endometrial thickness	9.4	2.5	6.9	3.5	3.47	0.008

Among the cycles that resulted in a triple-line ultrasound pattern, the younger patients had a shorter duration of infertility and follicle growth showed greater dominant follicle size and a thicker endometrial lining.

Table 3: Baseline demographics, stimulation parameters, and sperm quality in IUI cycles leading to normal (singleton, twins, etc.) and abnormal (missed abortion, spontaneous abortion, etc.) pregnancies

Parameters	Normal Pregnancy	Abnormal Pregnancy
Woman's age (years)Man's age (years)	27.3±3.6	27.3 ±4.6
Length of infertility (years)	34.6± 5.4	34.6±5.6
No. of IUI cycles	4.6±2.7	5.4±3.6
Ovarian response:	1.8±1.2	1.9±0.6
Duration of follicle growth, days	9.1 ±2.8	9.2 ±3.4
No. of follicles	2.8 ±3.6	2.7 ±1.8
Dominant follicle size	17.9 ±1.5	17.7 ±2.2

Baseline demographic stimulation parameters and sperm quality were similar between ongoing and abnormal pregnancies. Endometrial thickness did not differ between ongoing and abnormal pregnancies.

Discussion

During the menstrual cycle, the endometrium undergoes cyclic changes in preparation for implantation. In the follicular phase, the growing follicles produce increasing amounts of E2 that

induce proliferative endometrial changes. After ovulation, the corpus luteum produces P, which leads to secretory changes. Since serum hormonal E2 and P levels cannot always accurately predict the development of the endometrium and other methods such as histological studies are too invasive, ultrasound has been used as a noninvasive technique to monitor infertile women for over two decades. The measurements are easy to perform, easily reproducible, and have been shown to have a good interobserver correlation. The advent of transvaginal ultrasound greatly increased the visualization of the endometrium, providing more accurate and detailed evaluation. [1,18,19] Endometrial thickness and pattern have been implicated in the successful outcome of assisted reproductive technologies (ART). Although the assessment of the endometrium with ultrasound has become a standard procedure during the diagnostic workup and treatment of infertile women, the clinical significance of the difference in endometrial thickness and appearance has remained controversial. [20]

In the cycles that resulted in pregnancy, the patients were generally younger, had a shorter duration of infertility, and had a higher number of previous IUI cycles. Mean (SD) endometrial thickness on the day of HCG administration was significantly greater in cycles where pregnancy was achieved. The mean (SD) number of follicles and the diameter of the dominant follicle were significantly greater in cycles where pregnancy was achieved. The duration of follicle growth in women with a positive clinical pregnancy was significantly less than that in women with a negative clinical pregnancy. The quality of sperm (count, motility, and morphology) in the women with a positive clinical pregnancy was significantly better than for the women with negative clinical pregnancy. Yaman et al. concluded that three-dimensional ultrasound measurement of endometrial volume can be a predictor of pregnancy in ART cycles. [21] Tsai et al. found that women who had an ultrasound triple-line pattern conceived by IUI more frequently than women without this pattern. [22] Kovacs et al. reported that an increased endometrial thickness of at least 10 mm was associated with a higher pregnancy rate. [23]

Among the cycles that resulted in a triple-line ultrasound pattern, the patients had a shorter duration of infertility and follicle growth showed greater dominant follicle size and a thicker endometrial lining. Baseline demographic stimulation parameters and sperm quality were similar between ongoing and abnormal pregnancies. Endometrial thickness did not differ between ongoing and abnormal pregnancies. However, non-pregnant women who had endometrial thicknesses <6 mm were candidates for an hMG protocol in future cycles. These findings indicate that the woman's age was negatively associated with pregnancy outcome. In the study by Ghosh et al., women >30 years of age were half as likely as women <30 years to become pregnant. [24] On the contrary, Iberico et al. concluded in a study with 1010 IUI cycles that female age was not a significant predictor of pregnancy [25], which was confirmed by de Geyter et al.'s study. [26] Aging is associated with progressive follicular depletion and diminished oocyte quality, which is accompanied by a reduction in the size or activity of the cohort of follicles available to respond to letrozole stimulation. This negative impact on treatment outcome may be due to the higher rate of aneuploidy found in dysmorphic oocytes. In this study, the ongoing success of pregnancy once it was achieved showed no difference between the age groups, but pregnancy rates were related to the woman's age, suggesting that aging effects may begin after 30 years.

Conclusion

In conclusion, the results of the 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 as well as to follicle growth and sperm motility. Further studies are needed to compare endometrial thickness on the day of hCG administration in IUI cycles over various methods of ovulation induction such as hMG or CC. The current findings need replication in randomized studies to determine the effects of different protocols of induction ovulation on endometrial thickness and various doses of hCG administration on IUI success.

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