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# THE EFFECT OF ENDOMETRIAL PATTERN AND THICKNESS ON PREGNANCY RATE IN CONTROLLED OVARIAN HYPERSTIMULATION - INTRAUTERINE INSEMINATION

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### ABSTRACT

**Objective:** In order to evaluate the endometrium by ultrasound in patients undergoing controlled ovarian hyperstimulation (COH) with clomiphene citrate (CC) and human menopausal gonadotropin (HMG) with intrauterine insemination (IUI) to determine the relationship between endometrial pattern and thickness on pregnancy rate (PR).

**Methods:** In this prospective study, 108 infertile couples underwent COH with CC and HMG. The patients were categorized in 4 groups according to etiology. Overall 261 COH-IUI cycles with CC-HMG were evaluated. Thickness of the endometrium was measured and its pattern was classified according to its echogenicity.

**Results:** In the homogenous group the pregnancy rate (PR)/cycle was 16.7%, and in the trilaminar group it was 15.5%. This difference was not statistically significant ( $p>0.05$ ). The mean endometrial thickness in trilaminar and homogenous groups was  $8.92\pm 1.18$  mm, and  $8.72\pm 1.56$  mm respectively. In cycles in which conception occurred, the mean endometrial thickness was significantly higher in trilaminar and homogenous groups ( $p<0.001$ ).

In patients with a trilaminar pattern, the pregnancy was equal with those who had a homogenous pattern. The endometrial thickness was a major factor in determining PRs. There was no significant difference between PRs in cycles with trilaminar and homogenous patterns according to the etiology of infertility.

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**Keywords:** Transvaginal sonography, Endometrial pattern, Endometrial thickness, pregnancy rate.

### INTRODUCTION

Measurement of endometrial thickness during the treatment cycle is used routinely to assess uterine re-

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ceptivity and predict implantation.<sup>1</sup> Throughout the menstrual cycle, the endometrium progresses through several stages of maturation. In the proliferative phase, the endometrium thickens and is homogenous; by the late proliferative phase, it converts to a trilaminar pattern,<sup>2</sup> which probably arises from the central opposing surfaces of the endometrium and the outer echogenic basal layers of the endometrium.<sup>3</sup>

Sonography has been used as a non-invasive technique to monitor infertile women for over two decades. The advent of transvaginal sonography greatly increased the visualization of the endometrium, allowing for more accurate and detailed evaluation.<sup>4</sup>

Despite the widespread use of high resolution ultrasound equipment, the clinical significance of differences in endometrial thickness and appearance has remained controversial.<sup>5</sup> Some studies<sup>6,9</sup> have shown that a trilaminar endometrial pattern adds prognostic value on pregnancy rate. Few studies<sup>10,12</sup> have suggested that the sort of endometrial pattern is more effective than endometrial thickness for achieving a pregnancy. Some studies demonstrated low pregnancy rate in the presence of thin endometrial layers,<sup>13,14</sup> but one could not confirm this association.<sup>15</sup>

Patients with a thin endometrium present the clinician with the dilemma of whether to continue the cycle despite a possibility of reduced chance of pregnancy or to cancel the cycle and cryopreserve the embryos.<sup>16</sup>

Some investigators<sup>17</sup> have suggested that both endometrial pattern and thickness influence the outcome of a treatment cycle, but others argue that one characteristic plays a more important role than the other.<sup>13,8</sup> So this leads to a question as to which one of them, endometrial pattern, thickness or both can predict the outcome of an induction cycle.

In this study we tried to find out whether there was a correlation between endometrial thickness and pattern on pregnancy rate following IUI cycles and also study the same correlation in different causes of infertility separately.

These hypotheses were tested: 1- there is no difference in PRs among patients having a trilaminar pattern and those having a homogenous pattern and 2- endometrial thickness is not related to the chance of achieving a pregnancy.

### MATERIAL AND METHODS

The study was carried out from February 2000 to March 2002, on 108 infertile couples with 261 cycles undergoing COH-IUI, who referred to our tertiary infertility center. The protocol and consent forms were approved by Shiraz University of Medical Sciences insti-

tutional review board.

All couples enrolled in the study had an infertility workup that included: semen analysis (SA), post-coital test (PCT), endometrial biopsy, hormonal assay, hysterosalpingography (HSG) and diagnostic laparoscopy with or without hysteroscopy. After all other major pathologies were excluded (such as mullerian anomaly); the patients were classified into four groups according to their diagnosis as follows: male factors, cervical factors, mechanical factors and unexplained infertility.

The definition of the four classifications according to cause is as follows:

Male infertility was diagnosed on the basis of abnormal findings in semen analysis according to the World Health Organization (WHO) criteria.<sup>18</sup> In summary we considered a volume of less than 2cc, count less than 20 million/mL; motility less than 50% and normal shape less than 30% as abnormal. Semen analysis was performed at least two times with an interval of three months. If abnormality in the semen analysis was detected, a comprehensive urologic evaluation by a specialist was done to exclude any medical or surgical correctable problem. We performed IUI for patients with male factor infertility, if total motile sperm count is equal or more than 5 million. If sperm quality was too poor, other therapeutic options such as in vitro fertilization or intracytoplasmic sperm injection were used. If the semen analysis was normal and repeat of PCT showed no sperm, dead sperm or shaking movement despite the presence of good mucus, the patients were classified as cervical factor.

Mechanical factor consists of patients with the following characteristics: uterine and cervical myoma, peritubal adhesions caused by infection, and other adhesions caused by previous pelvic operation or endometriosis. In the patients with mechanical factor after laparoscopic adhesionolysis, myomectomy and fulguration of endometriosis foci, the following treatment protocol was prescribed.

A couple were considered as unexplained infertility when the result of semen analysis, post-coital test, hormonal assay, endometrial biopsy, hysterosalpingogram and laparoscopy were normal and the patients were having ovulatory cycles, or had normal ovulation after medical or surgical treatment.

All of the patients were asked to undergo three cycles of COH-IUI unless pregnancy occurred. The patients underwent 261 controlled ovarian hyperstimulation cycles with CC and HMG for IUI. Clomiphene (Iran hormone, Tehran, Iran) was administered orally for 5 days, 100 mg/day starting on day 5 of the cycle and HMG (Organon, Oss, Netherlands) was injected intramuscularly 150 IU/day from day 8 of the cycle. Sonographic assessment was performed transvaginally with a 6.5 MHz

endovaginal probe using Medison SA 600 (Medison Inc, Seoul, South Korea) by the same physician on day 10 or 11 of the cycle and according to the size and number of stimulated follicles, HMG was continued until at least 2 dominant follicles with size of  $\geq 18$ mm were present. The endometrium was imaged in a longitudinal antero-posterior dimension. The echogenicity of the endometrium was compared with that of the surrounding myometrium and two patterns were noted. A homogeneous pattern was described. A single hyperechoic or isoechoic layer and a trilaminar pattern was identified as a hypoechoic layer with a central hyperechoic line. Then 5000–10000 IU HCG (Organon, Oss, Netherlands) was injected. Sperm preparation and insemination procedure was performed by standard technique as previously described 34 hours after HCG injection.<sup>19</sup>

If the patients missed a period of 16 – 18 days after the insemination, a quantitative  $\beta$ HCG assay was performed. When the  $\beta$ HCG was positive, it was repeated 2 to 4 days later and after an appropriate rise, a transvaginal ultrasound was performed three weeks after the positive pregnancy test.

Only clinical pregnancies, which were diagnosed by transvaginal ultrasound, were considered in the analysis.

#### Statistical analysis

The data were analyzed using the Chi-square and Fisher's exact tests. A  $p$  value  $<0.05$  was considered statistically significant.

## RESULTS

During the study, 261 COH-IUI cycles were analyzed in 108 infertile couples. The mean duration of infertility was  $5.31 \pm 4.2$  years in all. The mean duration of infertility

in trilaminar and homogenous groups were  $4.83 \pm 3.54$  and  $7.66 \pm 6.22$  years respectively. Among the patients studied the following percentages were detected: 80.55% primary infertility, 16.66% secondary infertility and 2.77% primary and secondary infertilities. In 42 (16.1%) of the cycles, a homogenous pattern was noted, whereas 219 (83.9%) of them revealed a trilaminar pattern. The PRs / couples in the homogeneous group was 38.9% compared with 37.8% for the trilaminar group ( $p$  value  $>0.05$ ). The PR / cycle in the homogeneous and trilaminar groups were 16.7%, and 15.5% respectively ( $p$  value  $>0.05$ ).

Among forty-one pregnant women, ten cases were aborted (eight of them with trilaminar pattern and two others with homogeneous pattern); one ectopic pregnancy and two twin pregnancies were seen. There was no significant difference in age, parity, diagnosis and number of total follicles between them (Table I).

The mean endometrial thickness in trilaminar and homogeneous groups was  $8.42 \pm 1.18$  mm and  $8.72 \pm 1.56$  mm respectively ( $p$  value  $>0.05$ ) (Table I).

The mean endometrial thickness was  $8.46 \pm 1.67$  mm in conception cycles and  $6.64 \pm 0.35$  mm in nonconception cycles in the group with trilaminar echogenicity ( $p < 0.001$ ). Meanwhile this thickness in the group of patients with homogenous echogenicity was different in conception cycles ( $8.43 \pm 1.83$ ) and in non-conception cycles ( $6.94 \pm 0.51$ ) ( $p < 0.001$ ).

There was no significant difference between PRs in cycles with trilaminar and homogeneous echopatterns according to the etiology of infertility ( $p$  value  $>0.05$ ) (Table II).

## DISCUSSION

Although the receptivity of endometria to implantation is possible with a homogeneous pattern, despite

**Table I:** The patients' characteristics.

Demographics	Trilaminar pattern	Homogeneous pattern
No. of patients	90 (83.3%)	18 (16.7%)
No. of cycles	219 (83.9%)	42 (16.1%)
Age	$25.74 \pm 5.99$	$27.28 \pm 6.92$
Endometrial thickness	$8.92 \pm 1.18$	$8.72 \pm 1.56$
Total no. of follicles	$6.23 \pm 5.8$	$4.27 \pm 2.47$
Diagnosis		
Male factor	23 (25.6%)	4 (22.2%)
Cervical factor	26 (28.9%)	4 (22.2%)
Mechanical factor	21 (23.3%)	5 (27.8%)
Unexplained infertility	20 (22.3%)	5 (27.8%)

## Effect of Endometrial Status on Pregnancy Rate in COH-IUI

**Table II:** Pregnancy rate/cycles in trilaminar and homogeneous endometrium regarding different etiologies using Chi-square test.

Etiology	Trilaminar pattern	Homogeneous pattern	P value
Male factor	10.90%	9.10%	NS
Cervical factor	11.50%	11.40%	NS
Mechanical factor	13.61%	12.50%	NS
Unexplained infertility	19.00%	18.90%	NS

NS: Not significant.

thickness of the endometrium, conversion of the homogeneous pattern seen in the early proliferative phase to the trilaminar pattern visualized later in the proliferative phase must occur to produce optimal receptivity. The biological changes that occur to produce this sonographic conversion are still unknown.<sup>20</sup>

During our study the mean endometrial thickness in cycles with pregnancy was significantly higher than non-conception cycles ( $p$  value < 0.001). According to the etiology of infertility there was no significant difference between pregnancy rates in cycles with trilaminar and homogeneous echogenicities ( $p$  value > 0.05).

Our study showed that there was no difference in PRs between the two groups of trilaminar and homogeneous patterns of endometrial echogenicity. So this study could not reject the first hypotheses. This result is comparable with the study performed by Oliveria et al. He evaluated 139 cycles stimulated with CC/HMG for IVF. The incidence of clinical pregnancy did not differ between the groups with trilaminar endometrium and homogeneous, hyperechogenic patterns.<sup>21</sup> Check et al.<sup>8</sup> reported that no correlation was found between endometrial echopattern and PR in donor oocyte recipients immediately before transfer. Dickey et al.<sup>22</sup> showed that endometrial pattern was unrelated to pregnancy in patients who received CC with HMG for IUI. In some other previous studies the results were different. Hock et al.<sup>20</sup> showed that in patients receiving sequential CC/HMG for COH, a homogeneous endometrial pattern on the day of HCG administration predicts a significantly decreased PR compared with a trilaminar pattern. Check et al.<sup>23</sup> and Serafini et al.<sup>24</sup> confirmed the negative influence of homogeneous hyperechoic endometrial echopattern on PRs following the luteal phase Leuprolide acetate-HMG ovarian stimulation regimen. Bohrer et al.<sup>15</sup> demonstrated that in patients receiving menotropins, a homogeneous pattern is a bad prognostic sign for pregnancy regardless of endometrial thickness. But in this study patients with homogenous pattern were somewhat older and had on average a thinner endometrium.

In our study mean endometrial thickness in two groups of trilaminar and homogeneous patterns were similar. There was a significant difference in the trilaminar and homogeneous group on the basis of endometrial thickness between conception and non-conception cycles. Thus this study rejected the second hypotheses. This result is in contrast with the studies performed by others in patients undergoing ART.<sup>21, 25, 26</sup> Some investigators have shown that higher thickness of the endometrium has a positive effect on PRs. Dickey et al.,<sup>22</sup> Reuter et al.<sup>17</sup> and Isaacs et al.<sup>27</sup> concluded that endometrial thickness is a valid screening test for conception outcome in cycles stimulated with HMG or CC. Check et al.<sup>8</sup> reported that endometrial thickness alone was associated with a higher PR in patients undergoing IVF, but they evaluated only 70 cycles.

Our study showed that there was no significant difference between PRs in cycles with trilaminar and homogeneous echopatterns on the basis of etiology of infertility. This subject has not been studied in the literature till now.

Finally we concluded that endometrial echopattern had no effects on the pregnancy rates in patients undergoing COH-IUI. Thus ultrasonographic analysis of endometrial echogenicity on the day of HCG administration had no predictive value for conception. There was no difference between PRs in cycles with trilaminar and homogeneous pattern according to the etiology of infertility.

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