

The Effect of Endometrial Compaction During the Luteal Phase on Pregnancy Outcomes in Patients Undergoing Intrauterine Insemination

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ABSTRACT

OBJECTIVE: Compression/thinning of the endometrial thickness with the effect of progesterone during the luteal phase of the menstrual cycle is defined as endometrial compaction. This study aimed to show the effect of changes in endometrial thickness in the luteal phase of intrauterine insemination cycles on pregnancy outcomes.

STUDY DESIGN: Fifty-eight patients who were planned for intrauterine insemination were included in this prospective cohort study. The effect of the change between the patients' endometrial measurements on the day of trigger and the 7th day after intrauterine insemination on pregnancy outcomes were compared. Patients were divided into 3 groups according to endometrial thickness change. Those with an endometrial thickness change of less than 5% were called the no change group (n=18). The groups with endometrial thickness decreasing more than 5% (n=9) and increasing (n=31) formed the other two groups. In addition, the effect of luteal phase support on endometrial compaction was investigated.

RESULTS: The highest pregnancy rate (55.6%) was observed in the group with more than 5% endometrial thinning. It was found to be 16.7% in the group without change and 19.4% in the group with an increased endometrial thickness ($p=0.045$). Endometrial compaction and pregnancy rates were higher in the group given oral dydrogesterone for luteal support compared to those using vaginal micronized progesterone.

CONCLUSION: Endometrial compaction increases clinical pregnancy in intrauterine insemination cycles. Further studies are necessary to confirm the results of this study.

Keywords: Endometrial compaction, Intrauterine insemination, Pregnancy

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Introduction

There are many studies evaluating prognostic factors related to pregnancy rates in the treatment of intrauterine insemination (1). Age, infertility etiology, ovarian reserve, type of ovarian stimulation, follicle count, sperm quality, and endometrial thickness (ET) are some of the prognostic factors associated with intrauterine insemination (IUI) outcomes (2). Although it is known that changes in the endometrium affect success, the contribution of ET, subendometrial blood flow changes and molecular mechanisms to this effect have not been demonstrated (3,4). Changing hormonal levels during a menstrual cycle cause molecular, cellular, structural, and vascular changes in the endometrium. This, in turn, affects the endometrial receptivity required for blastocyst placement (5). The embryo needs to reach the endometrium within the implantation window for treatment to result in pregnancy (6). This window corresponds to the middle of the luteal phase.

The most commonly used method to evaluate the endometrium is ET measurement, which is simple, inexpensive, and atraumatic. Although ET is the most studied ultrasono-

graphic parameter, the predictive value of endometrial thickness for pregnancy is controversial. Some studies reported that thicker endometrium was associated with better pregnancy rates, while others found no significant difference (7,8).

In a natural menstrual cycle, endometrial growth increases with the effect of estrogen in the follicular phase, while linear growth of endometrial glands and blood vessels increases. After ovulation, the progesterone level rises, endometrial proliferation stops, but the growth of glands and vessels continues (9). Follow-up natural cycle studies have shown that the endometrium, which reaches its peak before ovulation, plateaus or thins during the luteal phase (10). This compression/thinning of the endometrial thickness is described as endometrial compaction (EC) (11). In freeze-thawed embryo transfer cycles (FET), the pregnancy rate increased as EC increased (11).

Reducing the number of patients who will go to in vitro fertilization (IVF) in infertile patients can be achieved by increasing the success of IUI.

Our aim in this study is to reveal the relationship between EC in the luteal phase evaluated by ultrasonography and pregnancy rates in patients undergoing IUI.

Material and Method

Patients who applied to the Erciyes University Obstetrics and Gynecology outpatient clinic between 2021-2022 due to infertility and were planned for IUI after evaluation were included in this prospective cohort study. Patients who could not conceive despite regular sexual intercourse for at least one year were considered infertile. Hysterosalpingography and sperm count examinations of each patient were evaluated. Patients with uterine malformations such as the uterine septum, unicorn uterus, endometrial polyp, submucous myoma, and patients who underwent hysteroscopic surgery were excluded from the study. Patients with both open tubes, unexplained infertility, and polycystic ovary syndrome (PCOS) were included in the study. Hormone profiles, antral follicle counts, and ET in the early follicular phase of the patients were recorded. ET measurement was accepted as the maximum distance from the anterior to posterior stratum basalis-myometrial junction in the midsagittal plane. Gonadotropin was started on days 3-5 of the cycle. The dose was calculated according to the patient's diagnosis and body mass index (BMI). 250mcg recombinant human chorionic gonadotropin (HCG) (Ovitrelle®) was administered to patients whose follicles reached a diameter of 17-22mm in their follicle follow-up. Endometrial thicknesses, E2, and Progesterone values were noted on HCG day. IUI was performed 34-36 hours after HCG injection. After insemination, progesterone supplementation was started in each patient. Oral dydrogesterone (Duphaston® 20mg, Abbott Biologicals) or natural micronized progesterone (Progestan® 200mg, Koçak Farma) was administered vaginally twice a day. Progesterone

preparation selection was applied randomly. The patients were called for control one week later, and their ET and serum progesterone values were noted. Compaction was defined as >5% decrease in endometrial thickness, between HCG trigger day and 7 days after IUI. Pregnancy results were evaluated by looking at serum b-HCG values 14 days after IUI. Exogenous progesterone supplementation as luteal support was continued until the 10th week of pregnancy in patients who achieved pregnancy.

The study was reviewed and approved by the ethics committee of Erciyes University. (Ethical approval reference number: 2021/391 dated 26.05.2021) All procedures were performed according to the Declaration of Helsinki.

Statistical analysis

The categorical factors are summarised using frequencies and percentages. Normal distribution analysis was performed with the Shapiro-Wilk test. For the parameters distributed with a normal distribution, One-Way ANOVA was used. For the parameters distributed with a non-normal distribution, the Kruskal Wallis test was used. The parameters distributed with normal distribution were explained Mean±SD, and the parameters distributed with non-normally distribution were explained Median (min-max). The categorical data were compared with the aid of the Chi-square test. Pearson chi-square test was used if the proportion of groups with less than 5 numbers was <20%. Fisher's exact test was used if the ratio of groups with less than 5 numbers was >20% and the minimum expected count was less than 5. Data recording and statistical analyses were performed using SPSS (statistical package for the social sciences) software (version 17, SPSS, Inc, Chicago, IL). A p-value of <0.05 was considered to indicate statistical significance.

Results

This prospective study included 58 patients who underwent intrauterine insemination. Patients were divided into three groups according to the change between ET on the day of HCG and ET measured on the 7th day after IUI. The flow-chart and formation of the groups were classified according to the rate of change in ET between these two days (Figure 1). Those with a change of less than 5% were considered as the 'no change group'. Those that increased and decreased by more than 5% formed the other two groups. Basic demographic and cycle characteristics of all patients according to ET changes are shown in table I. Since age, BMI, Basal luteinizing hormone (LH), and Endometrial thickness (trigger day) values showed normal distribution, the difference between groups was analyzed with One-Way ANOVA. Duration of infertility, gravity, parity, basal follicle-stimulating hormone (FSH), basal estradiol, thyroid stimulating hormone (TSH), Prolactin, basal endometrium, HCG day, follicle size, estradiol (trigger day), progesterone (trigger day), endometrium IUI-post 7th day, progesterone IUI-post 7th day val-

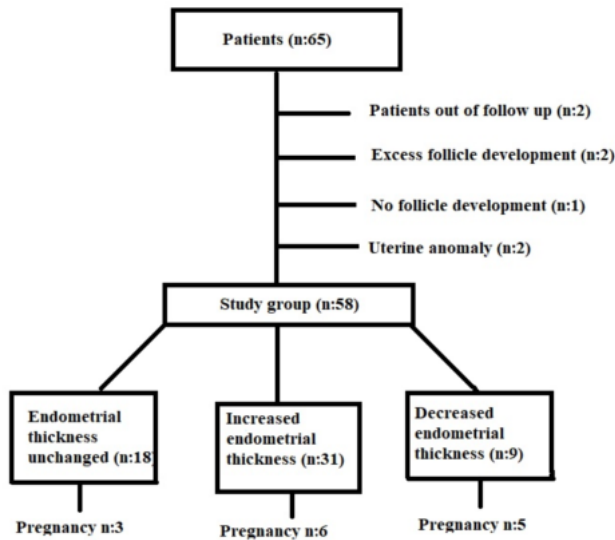


Figure 1: Distribution of patients according to endometrial thickness change

ues were evaluated with Kruskal-Wallis test as they did not show normal distribution. Basal hormone levels, maternal age and BMI, etiology of infertility treatment, duration of infertility, and the number of developing follicles were similar in the three groups.

The estradiol and progesterone values measured on the trigger day did not differ significantly between the groups. While ET decreased in 15.5% of the patients, an increase was observed in 53.4%. In 31.1%, there was less than a 5% change. Considering the pregnancy rates among the groups, the highest rate was observed in the group with EC (55.6%). This difference was statistically significant ($p=0.045$). ET on the day of the trigger (10.8 ± 2.0) was highest in the group with EC.

Of twenty-eight patients using vaginal progesterone for luteal support; while ET did not change in 28.6%, an increase in 60.7% and a decrease in 10.7% were observed. This rate was observed as 33.3%, 46.7%, and 20.0%, respectively, in patients using oral progesterone.

Table 1: Basic demographic and cycle characteristics of all patients according to ET changes

	No change n=18)	Increasing (n=31)	Decreasing (n=9)	P1	P2	P3
Agea	28.6 ± 5.5	28.4 ± 4.1	30.7 ± 3.6	0.141	0.138	0.298
BMI ^a	24.8 ± 3.7	25.9 ± 5.6	26.5 ± 4.5	0.089	0.802	0.326
Duration of Infertility ^b	5 (3-17)	4 (1-17)	4 (2-8)	0.035	0.669	0.056
Cause of infertility; n (%)				0.880	0.283	0.386
- Unexplained	13 (72.2)	23 (74.2)	5 (55.6)			
- PCOS	5 (27.8)	8 (25.8)	4 (44.4)			
G ^b	0 (0-4)	0 (0-4)	0 (0-1)	0.820	0.755	0.923
P ^b	0 (0-1)	0 (0-1)	0 (0-1)	0.476	0.901	0.707
Basal FSH ^b	5.7 (0.3-15.5)	5.6 (1.2-12.3)	6.7 (4.1-9.5)	0.641	0.437	0.247
Basal LH ^a	5.7 ± 2.9	7.0 ± 3.2	8.1 ± 2.0	0.375	0.348	0.040
Basal Estradiol ^b	34 (4-56)	40 (5-84)	46 (15-121)	0.115	0.554	0.180
TSH (day 3 measurement) ^b	2.4 (0.6-9.1)	1.8 (0.8-5.0)	2.1 (0.5-3.8)	0.378	0.373	0.877
Prolactin (day 3 measurement) ^b	16.7 (1.0-35.7)	20.9 (8.3-109.0)	10.8 (2.3-24.0)	0.110	0.007	0.269
Basal Endometrium ^b	5 (3-7)	5 (3-8.5)	5.5 (4.5-7)	0.547	0.348	0.123
HCG day ^b	13 (8-25)	12 (5-26)	12 (10-15)	0.452	0.781	0.324
Multiple Follicle; n (%)	5 (27.8)	10 (32.3)	1 (11.1)	0.502	0.211	0.326
Follicle size ^b	17.5 (16-22)	19 (16-24)	18 (16-20)	0.846	0.217	0.320
Endometrial thickness (trigger day) ^a	9.5 ± 1.7	9.4 ± 1.5	10.8 ± 2.0	0.823	0.040	0.107
Estradiol (trigger day) ^b	268 (67-1239)	333 (42-891)	288 (101-492)	0.337	0.210	0.910
Progesterone (trigger day) ^b	0.2 (0.1-11)	0.3 (0.1-11)	0.2 (0.1-8)	0.522	0.731	1.0
Endometrium IUI-post 7. day ^b	9.9 (7.5-13.3)	12 (7-17)	8.5 (6.4-13.5)	<0.001	0.004	0.330
Progesterone IUI-post 7. day ^b	20.6 (7.5-38.7)	21 (0.1-77)	20 (10-30)	0.613	0.400	0.590
Progesterone for luteal support; n (%)				0.343	0.256	0.580
- Vaginal	8 (44.4)	17 (54.8)	3 (33.3)			
- Oral	10 (55.6)	14 (45.2)	6 (66.7)			
Pregnancy; n (%)	3 (16.7)	6 (19.4)	5 (55.6)	0.815	0.032	0.037

a: Mean ± Standard Deviation, b: Median (Minimum-Maximum). BMI: Body mass index, PCOS: Polycystic ovary syndrome, G: Gravity, P: Parity, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone, HCG: Human chorionic gonadotropin, IUI: Intrauterine insemination. P1: Comparison between no change and increasing group, P2: Comparison between increasing and decreasing group, P3: Comparison between no change and decreasing group

Pregnancy was achieved in 17.9% of those using vaginal progesterone and 30.0% of those using oral progesterone ($p=0.280$).

Discussion

In this prospective study, we found that the differences in change between ET on the day of trigger and day 7 after IUI in IUI cycles were associated with pregnancy outcomes.

When we look at the literature, it is seen that all of the studies related to EC were carried out in FET cycles. However, when the studies are examined in detail, it is seen that most of the endometrial thickness is examined on different days of the cycle, and transabdominal ultrasonography is used in some studies. Therefore, its effect on EC pregnancy outcomes has not been demonstrated. Jing Ye's study of FET cycles showed that there was no significant difference in clinical pregnancy and live birth rates after progesterone administration, regardless of whether ET increased, decreased, or remained constant (12). Haas et al. in their study to determine the difference in ET change between the late estrogen phase and embryo transfer day in 274 FET cycles, found a relationship between the pregnancy outcome obtained and the change in ET (11). In this study, each level of thinning in the progesterone phase was calculated as percentages, and it was concluded that as the level of thinning increased, continued pregnancy rates increased. In another study, FET cycles were examined and their effect on EC live births was tried to be determined. In this study, EC occurred in the progesterone phase of the cycle in 89 patients, and no change was found in 194 patients. When live birth rates were compared, there was a significantly higher rate of live birth in the thinning group (23.6% vs 13.4%; $p=0.039$). Again, in the same study, it was observed that the EC in the cycles in which the endometrium was prepared with the use of artistic methods was higher than in the natural FET cycles. This is reflected in an increase in pregnancy rates (13). In our study, our pregnancy rate was significantly higher in patients in whom we saw more than a 5% decrease in ET measured on the 7th day after IUI compared to the ET measured on the trigger day. All of the studies on endometrial compaction are in IVF patients and are high-numbered studies. Therefore, in these studies, compaction was examined at certain percentages. Since our study was conducted with IUI patients and a limited number of patients, baseline thinning (5%), which was accepted in previous studies, was used. Based on our study, prospective randomized studies to be planned with large IUI patient groups can decompose this thinning as percentages and reveal which level of thinning is more effective on pregnancy outcomes.

Many studies have shown that luteal phase supplementation with vaginal progesterone increases the success of IUI (14,15). In the majority of these studies, the effects of vaginal and oral administration forms and doses applied on pregnancy

outcomes were examined. Mohamed Ahmed Maher compared pregnancy rates in 132 IUI cycles with progesterone supplementation and 126 IUI cycles without progesterone supplementation and found statistically significant pregnancy rates in cycles supplemented with progesterone (54.92% vs 35.21%; $p=0.016$) (14). Katherine A Green revealed in her meta-analysis that progesterone supplementation in gonadotropin-induced IUI cycles significantly increased the viable pregnancy rates regardless of oral or vaginal route. Again, in the same study, it was revealed that progesterone supplementation in clomiphene citrate + IUI cycles did not affect live pregnancy outcomes (15). In a study comparing oral dydrogesterone and vaginal natural progesterone for luteal phase support in IUI cycles, similar rates of clinical pregnancy and live birth were reported in both groups (16). In our study, gonadotropin induction was used in all IUI cycles. It was found that oral dydrogesterone increased the rate of endometrial thinning and pregnancy statistically significantly in patients who received randomized oral or vaginal progesterone. However, the limited number of patients limits the interpretation of the difference in progesterone administration route. Despite all these, oral administration is thought to be a method that can be easily recommended for luteal phase support, considering the ease of use and patient compliance.

Potential limitations of this study include the absence of certain data and the small group size. We concluded the patient follow-ups according to whether pregnancy occurred or not. In the study, live birth and miscarriage rates, which are the result of pregnancy, could not be evaluated because they were still in the patients who were still pregnant. Despite these limitations, the similarities in the demographic characteristics among the study population, the availability of good follow-up data, and its prospective increased the validity of our results and mitigated the weaknesses.

In conclusion; EC increases clinical pregnancy in IUI cycles. Further studies are necessary to confirm the results of this study. The effect of the progesterone route and type on EC may have been insignificant due to the insufficient number of patients in our study. Comprehensive studies are needed to show the effect of progesterone used in luteal phase support and the route of administration on endometrial thinning in more patients.

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Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

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Authors' contributions: FC: Project development, data collection, analysis, interpretation of data, manuscript writing, revising the manuscript. MD: Manuscript writing and revising the manuscript. VG, KEB: Analysis, interpretation of data SK: Data collection SK3: Idea, check, and consultancy EMA: Revising the manuscript. All authors contributed to the writing of the paper, and have read and approved the final manuscript.

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