Pilot Study to Assess Endometrial Compaction as a Tool to Predict Successful Pregnancy Outcomes in IVF and ICSI Cycles

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Abstract

Background : Accurately predicting the possibility of pregnancy during an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle has long been challenging.

Aim of the Work : to determine whether the clinical pregnancy rate in IVF and ICSI cycles is affected by the alteration in endometrial thickness, volume, and perfusion between the end of the estrogen phase and the day of embryo transfer.

Patients and Methods: The present study was a prospective observational study conducted in the obstetrics and gynecology department of Mansoura University Hospitals, Mansoura, Egypt. The present study was conducted on 25 subfertile women undergoing IVF and ICSI cycles. Endometrial preparation with the use of progesterone was done for all patients. In these 25 women candidates for ICSI, endometrial thickness and sub-endometrial perfusion were measured with a trans-vaginal 2-dimensional ultrasound (2D U/S) and 3-dimensional power Doppler ultrasound (3D PD U/S), respectively, on the day of human chorionic gonadotrophin (hCG) trigger and embryo transfer (ET).

Results: When comparing instances with positive pregnancy tests to those with negative pregnancy tests, there is a notable increase in endometrial volume and sub-endometrial vascularization flow index (VFI), corresponding to the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer. The average uterine resistance index (RI) on the day of embryo transfer in positive pregnancy cases is considerably higher than in negative pregnancy instances, and it is also significantly higher on the day of embryo transfer compared to the day of HCG trigger in positive pregnancy cases. By contrasting cases in which pregnancies were positive with those in which they were negative, there is a significant increase in the average uterine pulsatility index (PI) on the days of embryo transfer and HCG trigger as well as on the day of embryo transfer when compared to the day of HCG trigger in positive pregnancy cases.

Conclusion: Endometrial volume, sub-endometrial VFI, uterine RI, and uterine PI had an impact on the pregnancy outcome and clinical pregnancy rate in IVF and ICSI cycles.

Keywords: Compaction, endometrial, IVF and ICSI cycles, pregnancy.

Introduction

Endometrial receptivity is the term used to characterize the complex process by which the uterine lining gets ready for an embryo's implantation. The success of embryo apposition, adhesion, invasion, and ongoing pregnancy depends on the synchronization of endometrial preparation and embryo growth, which are independent but contemporaneous processes. [1].

Endometrial compaction can be defined as an increase in endometrial vascular density associated with the progressive coiling of the spiral arteries during the luteal phase. This feature is a characteristic of the late luteal phase, in which endometrial thickness is different from that at the end of the estrogen phase [2].

The term "assisted reproductive technology" (ART) describes techniques that manipulate oocytes outside of the body; the most popular kind of these techniques is in vitro fertilization (IVF). The phrase "in vitro" refers to fertilizing oocytes outside of a living creature in a petri dish, whereas embryos grow into pregnancy in the uterus and oocytes mature in vivo in the ovary. [3].

Advances in in vitro fertilization (IVF) and embryo transfer (ET) have come about as a consequence of examining every stage of the procedure, comparing the effects of various approaches, and assessing the outcomes to determine which approach is best. This includes patient preparation, stimulation protocol selection, culture technique, embryo selection, transfer mechanics, and post-transfer management. [4].

Age, the quality of the embryo, and endometrial receptivity are the primary factors that determine whether an assisted reproductive technology cycle is successful. An essential condition for embryonic implantation is the synchronization of endometrial and embryonic development. Most couples can now acquire high-quality embryos owing to advancements in laboratory technology. As a result, determining the patient's anticipated course of treatment depends greatly on the endometrial receptivity.

While endometrial receptivity has a significant guiding role in therapy that can significantly increase the success rate of in vitro fertilization (IVF), one of the primary issues is the dearth of real clinical trials to assess endometrial receptivity. [5].

Endometrial compaction, which is the change in endometrial thickness between the end of the estrogen-only phase and the day of embryo transfer, has been the subject of recent research evaluating its predictive power for success after frozen embryo transfer (FET). The endometrium's compaction upon progesterone initiation suggests that it is receptive to the hormone, suggesting that it may serve as a surrogate for endometrial receptivity. There have been inconsistent findings from three cohort studies on the connection between endometrial compaction and clinical outcomes after ET. [2, 6].

However, when Bu et al. evaluated 1334 natural cycle blastocyst FETs as well as 1757 medicated FETs, they discovered that cycles in which the endometrial lining expanded following the onset of progesterone had a higher clinical pregnancy rate (CPR) than cycles in which the lining either compacted or remained unchanged in both medicated and natural cycle FET. In this investigation, every embryo was a high-quality, untested blastocyst. [7].

The current study set out to determine if the clinical pregnancy rate and pregnancy outcome in IVF and ICSI cycles were affected by changes in endometrial thickness, vol-

ume, and perfusion between the end of the estrogen phase and the day of embryo transfer.

Patients and Methods

The current study was a prospective observational study conducted at the obstetrics and gynecology department of Mansoura University Hospitals in Mansoura, Egypt.

Before their involvement in the study, all women who were chosen for participation provided written informed consent. The Mansoura Faculty of Medicine Institutional Research Board (MFM-IRB) granted approval.

Twenty-five subfertile women having IVF/ICSI cycles participated in the current study. We excluded from our study any patient who was less than 20 years old or more than 40 years old, had a body mass index (BMI) of less than 18.5 kg/m2 or more than 30 kg/m2, had lesions in the uterus, had poor quality embryos, and had chronic hypertension, lung disease, diabetes mellitus, renal disease, liver disease, endocrine disorder, or autoimmune disease.

If the endometrial thickness is not sufficient, estrogen treatment is continued, and ultrasound evaluation is done repeatedly until the endometrium becomes apparent to be sufficient. Following ovulation induction and oocyte retrieval, in every patient, progesterone was utilized to prepare the endometrium. Patients whose endometrial thickness at the end of the estrogen phase was less than 7 mm had their cycles cancelled and were not included in the analysis. Any naturally occurring or artificially created cycles were not included in this research.

On the day of the hCG trigger and embryo transfer (ET), endometrial thickness and sub-endometrial perfusion were examined in these 25 women who were eligible for ICSI using a transvaginal 2-D ultrasound and a 3-D power Doppler ultrasound, respectively. The endometrial volume (EV), thickness, and other angiographic power Doppler indexes (vascularization index (VI), flow index (FI), and vascularization flow index (VFI), which stand for the number of vessels, blood flow, and endometrial perfusion, respectively, plus uterine resistance index (RI) and pulsatility index (PI), were measured by utilizing the Samsung UGEO H60 device.

Endometrial compaction is assessed by ultrasound measurements of endometrial thickness, endometrial volume, and sub-endometrial perfusion using a trans-vaginal 2-D ultrasound and 3-D power Doppler on the day of triggering and the day of embryo transfer.

The main outcome measure is modifications to endometrial thickness, volume, perfusion, and ongoing pregnancy rate.

Results

Pregnancy rates were 40% (table 1).

Between instances with positive and negative pregnancy tests, there was not a significant difference in endometrial thickness based on the incidence of pregnancy on the day of the hCG trigger and the day of embryo transfer ($p > 0.05$). (table 2).

The endometrial volume significantly increases in cases of positive pregnancy tests compared to negative pregnancy tests on the day of embryo transfer and the day of the hCG trigger occurs. However, in both the positive and negative pregnancy groups, there is no discernible difference in endometrial volume between both the day of the embryo transfer and the HCG trigger. (table 3).

Regarding sub-endometrial VI, there was no discernible difference between instances with positive and negative pregnancy tests based on the occurrence of pregnancy on the day of the embryo transfer and the hCG trigger ($p > 0.05$). Between cases with positive pregnancy tests and negative pregnancy tests, there was no discernible change in sub-en-

dometrial FI according to the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer ($p > 0.05$). When compared to negative pregnancy tests, there is a notable increase in sub-endometrial VFI in cases of positive pregnancy tests based on the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer. In contrast, there is no discernible variation in sub-endometrial VFI in the groups of women who did not become pregnant between the day of the embryo transfer and the HCG trigger. Comparing the day of embryo transfer to the current HCG trigger in the group of women who became pregnant, there is a significant rise in sub-endometrial VFI (table 4).

Regarding the average uterine RI, there was no discernible difference between instances with positive and negative pregnancy tests based on the incidence of pregnancy on the day of the hCG trigger ($p > 0.05$). The average uterine RI on the day of embryo transfer in positive pregnancy instances is significantly higher than in negative pregnancy instances, and it is also significantly higher on the day of embryo transfer compared to the day of HCG trigger in positive pregnancy cases. By comparing instances with positive pregnancies to those with negative pregnancies, there is a significant increase in the average uterine PI on the days of embryo transfer and HCG trigger and on the day of embryo transfer when compared to the day of HCG trigger in positive pregnancy cases (table 5).

Discussion

Since the first IVF was created in 1978, the processes used in assisted reproductive technologies (ART) have undergone significant change. [8]. There are currently methods for determining high-quality embryos and evaluating endometrial health. Additionally, ART procedures are always being improved to boost the number of successful pregnancies, reduce the number of multiple births, and produce healthier offspring from genetically modified progenitors. [9]. The birth rate has not increased significantly over the past ten years, despite these improvements. This suggests that the low implantation rates in stimulated cycles will persist [10].

a variety of female reproductive processes, including implantation, endometrial expansion, the formation of the corpus luteum, and the development of a dominant follicle, are undoubtedly influenced by angiogenesis. Therefore, in attempts to forecast the success of IVF treatment, a lot of research has concentrated on ovarian and endometrial vascularization. Given that embryonic implantation occurs in the endometrium, endometrial blood flow provides a realistic representation of uterine receptivity. [11]. Nonetheless, the pregnancy rate increases when vessels are visible, reaching the endometrium and the sub-endometrial halo. [12].

This research project sought to ascertain if changes in the thickness of the endometrium, volume, and perfusion the day of embryo transfer and the completion of the estrogen phase possess an effect on the clinical pregnancy rate and pregnancy outcome in IVF/ICSI cycles.

This study, which included 25 subfertile women having IVF/ICSI cycles, was a prospective observational study performed in the obstetrics and gynecology department at Mansoura University Hospitals, Mansoura, Egypt. Progesterone was utilized in every case to prepare the endometrium.

Most of the cases under investigation are urban dwellers, with an average age of 29.2 ± 3.38 and a mean BMI of 25.69 ± 2.22. These findings were compared to those of Hashad et al., who found that women in the research cohort had a mean age of 26, whereas women in the control group had a mean age of 27. [14]. El-Shourbagy et al. concluded that there was no discernible age difference between the groups that were fertile and infertile [15]. The mean age of the study group was 26.9 ± 3.8 years, and the mean age of the

control group was 28.5 ± 4.9 years, neither group's differences were statistically different. (P = 0.194) as regards age [16].

Pregnancy rates were 40%, according to the current study. This was comparable to other research, as live births occur in about one-third of IVF and ICSI cycles [17, 18]. 44.8% was calculated to be the overall 1-year continuing pregnancy rate [19].

In terms of endometrial thickness, the current study observed not a noticeable statistical difference between instances with positive and negative pregnancy tests based on the occurrence of pregnancy on the day of embryo transfer and the day the hCG trigger occurs ($p > 0.05$).

Comparable to our results, other research revealed no association between endometrial thickness on the day of the hCG application and pregnancy rates [20–23] or a distinction that is statistically significant in mean endometrial thickness between groups who were pregnant and those who were not pregnant [24–26].

On the other hand, prior research by Kehila and colleagues revealed a statistically significant correlation between the total pregnancy rate (PR) and endometrial thickness, which is evaluated before triggering ovulation. They contend that if the endometrium measures more than 12 mm in width, the likelihood of a successful pregnancy increases by around three times. [27]. Roughly the same conclusion is drawn from the Bozdag et al. study, which discovered a considerably higher clinical PR in individuals whose endometrial thickness was greater than 14 mm on the day that hCG was administered [28].

The current study found that, in cases with positive pregnancy tests compared to negative pregnancy tests, there is a considerable increase in endometrial volume in accordance with the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer. However, in both the positive and negative pregnancy groups, there is no discernible alteration in endometrial volume between the day of the embryo transfer and the HCG trigger.

Comparable to this, Kovachev et al. looked at the endometrial volume as determined by 3-D ultrasound on the day of ET and discovered that an endometrial volume of less than 2 ml was associated with significantly lower implantation rates, while an endometrial volume of more than 2 ml was positively correlated with a successful outcome of ART. [29].

Additionally, a study found that women who were successful in becoming pregnant had a considerable increase in endometrial volume following hCG treatment, but not those who were unsuccessful. Nevertheless, they disagreed with our findings since they demonstrated that no variation was observed in endometrial volume between conception and non-conception cycles on the day of oocyte aspiration. [30].

Additionally, Mercé et al. discovered that patients who became pregnant had a noticeably larger endometrial volume. [26].

According to our research, there was no discernible change in sub-endometrial FI or VI between instances with positive and negative pregnancy tests on the day of the embryo transfer and the hCG trigger ($p > 0.05$).

In keeping with what we discovered, on the day of embryo transfer, Kim et al. conducted a prospective observational study on 234 women (n = 113 pregnant group and n = 121 nonpregnant group) having their first IVF-ET utilizing a GnRH-long protocol with stimulation by recombinant follicular stimulating hormone (rFSH). The women had color Doppler ultrasonography and 3D power Doppler-US scans. While sub-endometrial region VI and FI did not vary throughout the groups, the group of pregnant women showed increased endometrial VI, FI, and VFI values than the nonpregnant group ($p = 0.001$, $p = 0.000$, and $p = 0.021$, respectively) [31].

These findings contrast with a study by Kupesic et al. that included 89 patients and revealed that, on the day of embryo transfer, pregnant patients had considerably higher sub-endometrial FI compared to non-pregnant patients, whereas sub-endometrial VI and VFI were equivalent in both groups [32]. In addition, Vohra et al. demonstrated that endometrial VI was substantially higher in the pregnant group than in the non-pregnant group. [33].

The current study demonstrated that, in cases with positive pregnancy tests compared to negative pregnancy tests, there is a considerable rise in sub-endometrial VFI in accordance with the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer. In contrast, there is no discernible variation in sub-endometrial VFI in the negative pregnancy groups between the day of embryo transfer and the HCG trigger. There is a discernible increase in sub-endometrial VFI when the day of embryo transfer is compared to the day of HCG trigger in the pregnant positive group.

Consistent with our results, Mishra et al. proved that there was a substantial difference in endometrial VI, FI, and VFI between the pregnant and non-pregnant groups. While sub-endometrial FI was identical between the two groups, there was a substantial difference in sub-endometrial VI and VFI [34].

More than half of pregnancies that are successfully achieved in the absence of endometrial and sub-endometrial flow on the day of embryo transfer end in spontaneous miscarriage, indicating that the development of the endometrial vascular tree is crucial for supporting the early stages of gestation [35].

According to Ng et al., the pregnant group had considerably higher levels of uterine RI, endometrial VI, and VFI than the non-pregnant group. [36].

According to our research, the average uterine RI did not show any significant difference between the cases of positive and negative pregnancy tests on the day of the hCG trigger ($p > 0.05$). The mean uterine RI on the day of embryo transfer in cases of positive pregnancy is considerably higher than in cases of negative pregnancy; additionally, in cases of positive pregnancy, it is significantly higher on the day of embryo transfer in comparison to the day of HCG trigger.

These results might be related to the impact of elevated serum estradiol and the hormonal state during ovarian-controlled stimulation. When using recombinant HCG (rhCG) as a trigger, all parameters for both groups significantly decreased; flowmetry parameters then recovered on the day of embryo transfer. Due to its up-regulation effect on vascular endothelial growth factors, the rhCG effect on vascularization may be linked to a decrease in both resistance and pulsatility flow. [37].

Consistent with our findings, Ragheb et al. show that sub-endometrial RI does not differ statistically between pregnant and non-pregnant groups [38].

However, in contrast, a study conducted in Turkey by Adkan et al. used transvaginal color Doppler ultrasonography on the day of the hCG injection to compare uterine and arcuate blood flow parameters in 46 women having IVF therapy with and without a good outcome. They showed that women who had successful IVF had considerably lower mean uterine artery PI and RI as well as arcuate artery RI than those who had unsuccessful operations. [39].

The outcomes of the current investigation exhibited that there was a significantly higher increase in the average uterine PI on the days of embryo transfer and HCG trigger in positive pregnancy instances than in negative pregnancy instances. Additionally, in cases of positive pregnancy tests, the average uterine PI on the day of embryo transfer is greater than the day of the HCG trigger.

Conversely, Zollner et al. showed that in cryo cycles, no distinction was made. in the uterine artery blood flow parameters (PI [3.2 vs.

3.0], RI [0.9 vs. 0.9], and peak systolic velocity (PSV) (53.2 vs. 51.2) between patients who were pregnant and those who were not. [13].

Furthermore, Ng and colleagues examined the impact of smoking, female age, different forms of infertility and parity, reasons for infertility, and estradiol (E2) serum levels on Doppler ultrasound during IVF treatment. All the previously described parameters were discovered to have no effect on the endometrial and sub-endometrial Doppler flow indices. assessed on the day of the hCG injection during ICSI treatment. [40].

A study performed in 2011 demonstrated that in cases of recurrent miscarriage, there is a requirement for both healthy blood flow to the uterus and endometrium, as evidenced by decreased endometrial blood flow and increased uterine artery blood flow resistance. Additionally, women who experience unexplained recurrent pregnancy loss may exhibit abnormalities in both uterine and endometrial blood flow. [41]. However, Alcázar and Ruiz Perez found no statistically significant variations in Doppler parameters between patients who had a threatened first-trimester abortion and those who did not. [42].

Conclusion

Endometrial volume, sub-endometrial VFI, uterine RI, and uterine PI all impact the clinical pregnancy rate and pregnancy outcome in IVF/ICSI cycles.

Table (1): Pregnancy rate in the study cases.

Variables	Study cases. n= 25	
	Number	Percent
Pregnancy		
Negative pregnancy	15	60
Positive pregnancy	10	40

Categorical data expressed as number (%)

Table (2): Analysis of endometrial thickness according to the occurrence of pregnancy

Variables	Negative pregnancy (n= 15)	Positive pregnancy (n= 10)	Test of significance
On the day of the hCG trigger	10.27 ± 1.51	10.32 ± 2.05	t = - 0.075 P= 0.957
On the day of embryo transfer	10.31 ± 1.51	10.44 ± 2.04	t = - 0.186 P= 0.854
P1	0.638	0.116	

t: Paired samples t-test

*: Statistically significant (p< 0.05)

P1: Comparison between the value on the day of embryo transfer and the hCG trigger

Table (3): Analysis of Endometrial Volume according to the occurrence of pregnancy

Endometrial Volume	Negative pregnancy (n= 15)	Positive pregnancy (n= 10)	Test of significance
On the day of the hCG trigger	3.14 ± 0.85	4.29 ± 1.25	t = - 2.746 P= 0.012*
On the day of embryo transfer	2.96 ± 0.84	4.16 ± 1.26	t = -2.862 P= 0.009*
P1	0.308	0.426	

t: Paired samples t-test
*: Statistically significant (p< 0.05)
P1: Comparison between the value on the day of the hCG trigger and the day of embryo transfer

Table (4): Analysis of sub-endometrial VI, FI and VFI according to the occurrence of pregnancy

		Negative pregnancy (n= 15)	Positive pregnancy (n= 10)	Test of significance
Sub-endometrial VI	On the day of the hCG trigger	1.39 ± 0.63	1.74 ± 0.92	t = - 1.128 P= 0.271
	On the day of embryo transfer	1.65 ± 0.63	2 ± 0.92	t = -1.119 P= 0.275
	P1	0.284	0.280	
Sub-endometrial FI	On the day of the hCG trigger	28 ± 4.84	30.42 ± 2.57	t = - 1.444 P= 0.162
	On the day of embryo transfer	28.60 ± 4.83	30.84 ± 2.56	t = -1.340 P= 0.193
	P1	0.457	0.695	
Sub-endometrial VFI	On the day of the hCG trigger	0.35 ± 0.18	0.71 ± 0.29	t = - 3.745 P= 0.001*
	On the day of embryo transfer	0.52 ± 0.18	0.99 ± 0.29	t = - 4.961 P < 0.001*
	P1	0.106	0.045*	

t: Paired samples t-test
*: Statistically significant (p< 0.05)
P1: Comparison between the value on the day of the hCG trigger and the day of embryo transfer

Table (5): Analysis of average uterine RI and PI according to the occurrence of pregnancy

		Negative pregnancy (n= 15)	Positive pregnancy (n= 10)	Test of significance
average uterine RI	On the day of the hCG trigger	0.81 ± 0.03	0.80 ± 0.06	t = 0.221 P= 0.827
	On the day of embryo transfer	0.82 ± 0.03	0.88 ± 0.06	t = -3.829 P= 0.003*
	P1	0.642	0.001*	
average uterine PI	On the day of the hCG trigger	1.86 ± 0.36	2.27 ± 0.51	t = - 2.369 P= 0.027*
	On the day of embryo transfer	2.01 ± 0.35	2.50 ± 0.51	t = -2.864 P= 0.009*
	P1	0.124	0.041*	

t: Paired samples t-test
*: Statistically significant (p< 0.05)
P1: Comparison between the value on the day of the hCG trigger and the day of embryo transfer

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