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The Effect Of Endometrial Scratch And Platelet Rich Plasma On Ultrasound Markers Of Endometrial Receptivity And Pregnancy Rate In Women Underwent ICSI

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ABSTRACT
Background: ICSI success relies on successful implantation, with 20-30% requiring a well-planned dialogue between high-quality embryo and receptive endometrium. Endometrial receptivity testing is crucial for ART success.
Objectives: The study investigates the impact of endometrial scratch and intrauterine autologous platelet-rich plasma infusion on endometrial receptivity and pregnancy rate.
Material and Method: This study involved 90 females randomly selected for endometrial scratch and intrauterine autologous platelet rich plasma infusion. Doppler studies were performed on ova collection and embryo transfer, assessing endometrial thickness, resistance index, pulse index, and systolic to diastolic ratio.
Result: There weresignificant difference in endometrial thickness, resistance index, pulse index and systolic to diastolic ratio between study groups at day of embryo transfer $P< 0.05$, the comparison of ultrasound characteristics between ova pickup and embryo transfer in each group: A, B, and C. In group A and B there was a significant increase in endometrial thickness, and reduction in PI, RI, and S/D ratios. No significant changes were observed in group C.
Conclusion The study suggests that endometrial scratching and platelet-rich plasma can enhance endometrial receptivity and pregnancy rate in infertile women undergoing ICS.

Keywords: Infertility, Endometrial scratch, Intracytoplasmic Sperm Injection, Ultrasound, Platelet Rich Plasma.

INTRODUCTION

Failure of a couple to conceive within a year of unprotected sexual activity is referred to as infertility [1, 2]. Infertility affects individuals globally, with severity and root causes varying based on socio-economic status and geographical location. [3,4]. IVF/ICSI treatment is crucial for infertility, with three million cycles annually. Despite advancements, success rate remains stable at 35% per embryo transfer in the past 5 years [6]. It is widely known that blastocysts cannot attach to an immature endometrium, resulting in unsuccessful implantation even when “good quality” embryos are transferred [7]. Pregnancy initiation is dependent upon the existence of a harmonized equilibrium between an infiltrating trophoblast and a responsive maternal decidua. Both the trophoblast, originating from the embryo, and the decidua, derived from the mother, necessitate continuous adjustments and mutual modifications to facilitate the occurrences of implantation, trophoblast infiltration, and placentation [8].

Endometrial receptivity is the uterine lining's preparation for embryo implantation, crucial for successful apposition, adhesion, invasion, and pregnancy, typically detected between days 20-24 of a normal menstrual cycle.[9].Many molecular pathways involve hormones, adhesion molecules, cytokines, and growth factors acting in concert to create a synchronous window of implantation. When synchrony is lost or receptivity is not achieved, the consequence is early pregnancy loss or infertility [10]. Implantation failure in assisted reproductive technologies (ART) is a prevalent issue without evidence-based therapy remedies, leading to practitioners often prescribing empirical treatments without clinical proof [11]. Research indicates that two-thirds of embryo implantation failures are due to poor endometrial reception, while the remaining one-third is

due to quality defects in embryos. Good endometrial receptivity and embryo quality are crucial for successful implantation [12].

Endometrial gene expression [13]. The disruption of progesterone and estrogen signaling leads to progesterone resistance and estrogen dominance, causing inflammation and reduced endometrial receptivity to embryo implantation. Upregulation of genes like Eps15 homology domain-containing 1 and ICAM1 is associated with reduced endometrial receptivity. Changes in endometrial morphology also result in impaired ER. [12]. Clinically, endometrial receptivity is usually evaluated from endometrial morphology, ultrasound imaging, biochemistry, and other aspects [14]. Among them, transvaginal ultrasound assessment of endometrial receptivity is non-invasive and highly repeatable and thus has been widely used in clinical practice [15]. multiple endometrial receptivity indices that can be used to predict the outcomes of IVF-ET clinical pregnancy, such as transvaginal ultrasound measurement of endometrial thickness, peak uterine systolic blood flow velocity to end-diastolic blood flow velocity ratio (systolic/diastolic S/D), pulsatility index (PI), resistance index (RI), vascularization index (VI), flow index (FI), and vascularization flow index (VFI), were assessed, with the aim of providing a diagnostic basis for clinical practice[12].

The study by Barash et al. in 2003 found that endometrial scratching before embryo transfer (ET) can increase implantation rates. They found that endometrial biopsy during the luteal phase of the menstrual cycle leads to higher pregnancy rates after IVF. They also hypothesized that scratching could enhance growth factor and cytokine secretion during wound healing[16].PRP, a plasma containing platelet-derived growth factors and cytokines, is created by centrifuging blood samples. These substances promote tissue growth, wound healing, and endometrial thickness in thin endometrium patients. PRP therapy has no negative side effects, as it is derived from the woman's blood and does not contain any adverse reactions.[17].Thus, this study aims to investigate how endometrial scratching and platelet-rich plasma affect endometrial receptivity as assessed by ultrasound and the rate of pregnancy in women undergoing ICSI.

MATERIALS AND METHODS

This prospective comparative clinical experiment was carried out by Al-Nahrain University's Higher Institute for Infertility diagnosis and Assisted Reproductive Technologies from October 2022 to April 2024. Every patient provided written informed consent, and the Local Medical Ethical Committee of the institute approved the study. Ninety infertile women were divided into three groups at random, complete medical, surgical and gynecological history obtained.

The inclusion criteria for the females should be age between 18-40 years no any history of medical or blood disease and platelet count within normal value, no any congenital uterine abnormalities, GI embryo should be obtained. All assessed at day 2-3 of menstrual cycle with 2Dimensin ultrasound and hormonal study (FSH LH, PRL, TSH, E2). BMI calculated from weight and height. Male factor infertility included in the study. Group A of thirty females endometrial scratch performed at day 21 of the preceding cycle E.S. performed by using an endometrial Pipelle, the patient in lithotomy position, the cervix was exposed by using Cusco speculum then cleaned by normal saline and usually, the endometrium is “scratched” with a small catheter, 3 mm in width, known as the Pipelle®. Usually without hooking on the cervix, the catheter is pushed forward through the cervix to the fundus, and then retracted in circular movements in order to stimulate the endometrium and PRP at day of ova pickup, group B of thirty female PRP done for them at day of ova pickup and lastly group C thirty female no interference as control group.

Tow Dimension Doppler ultrasound assessment for endometrial thickness, resistance index, pulse index and systolic to diastolic ratio was done to all patients at day of OPU and embryo transfer. All patients underwent. antagonist protocol. Autologous PRP is obtained from a samples of patients’ venous blood drawn on the day of OPU for study cases only, 30-cc venous blood draw will yield 3-5 cc of PRP, so 5-6 cc of blood is fair enough to yield 0.5-1 ml PRP, depending on the baseline platelet count of an individual, the device used, and the technique employed. The blood draw occurs with the addition of an anticoagulant, such as citrate dextrose A, to prevent platelet activation prior to its use. Since the day of OPU luteal support was started with vaginal suppositories (Cyclogest® 400mg twice:), daily till the day of pregnancy test (B-hcg), 14 days after embryo transfer, if pregnancy test is positive ultrasound examination will be performed two weeks later to confirm intrauterine pregnancy and gestational sac or (sacs) and follow-up for viability.

The study used Excel 2010 and SPSS to analyze data. Qualitative variables were expressed using number and percentage, while quantitative variables were evaluated for normality using the Kolmogorov-Smirnov test. Numerical variables were expressed as mean and standard deviation. Associations between categorical variables were assessed using the Chi-square test, the study used ANOVA, pos hoc LSD test, paired t-test, and bi-serial correlation test to analyze individual differences, treatment effects, and pregnancy outcomes, with significance at p-values below 0.05.

RESULTS

In this study there was no significance difference regarding demographic factors as shown in table 1. Table 2 showed the comparison in ultrasonic characteristics, endometrial thickness, pulse index, resistance index and systolic to diastolic ratio no testical significance seen in day of ova pickup, whereas at day of embryo transfer there was significant difference in ultrasonic characteristics $P<0.05$ table 3.

Table 1: Comparison of demographic characteristics among study groups.

Characteristic	**Group A** ***n* = 30**	**Group B** ***n* = 30**	**Group C** ***n* = 30**	***P***
Age (years)				
Mean ±SD	31.00 ±4.76	32.90 ±5.95	30.93 ±5.54	0.287 O NS
Range	23 -40	23 -40	18 -40	
BMI (kg/m^2)				
Mean ±SD	26.99 ±2.87	27.63 ±2.07	27.01 ±3.01	0.582 O NS
Range	20 -30	22.2 -30	18.6 -30	
Normal weight, *n* (%)	5 (16.7 %)	3 (10.0 %)	5 (16.7 %)	0.850 C NS
Over weight, *n* (%)	17 (56.7 %)	21 (70.0 %)	18 (60.0 %)	
Class I obesity, *n* (%)	8 (26.7 %)	6 (20.0 %)	7 (23.3 %)	

Table 2: Comparison of ultrasound characteristics at day of ova pickup (OPU) among study groups

Characteristic	**Group A** ***n* = 30**	**Group B** ***n* = 30**	**Group B** ***n* = 30**	***P***
ET at day of OPU (mm)				
Mean ±SD	9.06 ±1.33	9.67 ±1.67	9.57 ±1.28	0.316 O NS
Range	6 -11	7 -13	6 -11	
Pulsatility index (PI) at day OPU				
Mean ±SD	0.79 ±0.20	0.79 ±0.20	0.78 ±0.23	0.524 O NS
Range	0.4 -1.4	0.56 -1.5	0.5 -1.1	
Resistive index (RI) at day of OPU				
Mean ±SD	0.64 ±0.79	0.53 ±0.07	0.47 ±0.08	0.378 O NS
Range	0.32 - 0.7	0.41 -0.7	0.3 -0.65	
S/D at day of OPU				
Mean ±SD	2.05 ±0.34	2.07 ±0.31	2.06 ±0.34	0.623 O NS
Range	1.5 -2.8	1.7 -2.8	1.4 -2.8	

Table 3. Comparison of ultrasound characteristics at day of embryo transfer

Characteristic	**Group A** ***n* = 30**	**Group B** ***n* = 30**	**Group C** ***n* = 30**	***P***
ET at day of embryo transfer (mm)				
Mean ±SD	10.88 ±1.26 A	10.68 ±1.46 A	9.49 ±1.73 B	0.045 O *
Range	8 -12	7 -13	7 -13	
Pulsatility index (PI) at day of embryo transfer				
Mean ±SD	0.63 ±0.12 B	0.62 ±0.12 B	0.71 ±0.13 A	0.044 O *
Range	0.34 -0.81	0.32 -0.94	0.5 -0.95	
Resistive index (RI) at day of embryo transfer				
Mean ±SD	0.43 ±0.07 B	0.41 ±0.06 B	0.47 ±0.06 A	0.003 O ***
Range	0.26 -0.54	0.26 -0.55	0.3 -0.57	
S/D at day of embryo transfer				
Mean ±SD	1.72 ±0.19 B	1.73 ±0.22 B	1.90 ±0.27 A	0.042 O *
Range	1.4 -2.2	1.4 -2.3	1.5 -2.7	

Comparison of mean changes in ultrasound characteristics between day of ova pickup and day of embryo transfer in each individual group is shown in table 4. Regarding group, A, there was significant increase in mean endometrial thickness, and significant reductions in mean PI, RI and S/D ratios ($p< 0.001$). So as group B ($p = 0.002$), Regarding group C there was no significant changes in mean ET, PI, RI and S/D ratios ($p> 0.05$).The pregnancy rate shown in table 5 the highest rate was in group B ,followed by group A and C respectively. Although this was of no testical significance $P> 0.05$.

Table 4: Comparison of mean changes in ultrasound characteristics between day of ova pickup and day of embryo transfer in each individual group

Characteristic	**Group A** ***n* = 30**	**Group B** ***n* = 30**	**Group C** ***n* = 30**
ET (mm) (Mean ±SD)			
At day of OPU	9.06 ±1.33	9.67 ±1.67	9.57 ±1.28
At day of embryo transfer	10.88 ±1.26	10.68 ±1.46	9.49 ±1.73
Mean difference	1.82	1.01	-0.08
% change	20.1	10.4	-0.8
p-value	<0.001 Pa ***	0.002 Pa **	0.207 Pa NS
Pulsatility index (PI) (Mean ±SD)			
At day of OPU	0.79 ±0.20	0.79 ±0.20	0.78 ±0.23
At day of embryo transfer	0.63 ±0.12	0.62 ±0.12	0.71 ±0.13
Mean difference	-0.16	-0.17	-0.07
% change	-20.3	-21.5	-9.0
p-value	<0.001 Pa ***	<0.001 Pa ***	0.062 Pa NS
Resistive index (RI) (Mean ±SD)			
At day of OPU	0.64 ±0.79	0.53 ±0.07	0.47 ±0.08
At day of embryo transfer	0.43 ±0.07	0.41 ±0.06	0.47 ±0.06
Mean difference	-0.21	-0.12	0
% change	-32.8	-22.6	0.0
p-value	<0.001 Pa ***	<0.001 Pa ***	0.867 Pa NS
S/D (Mean ±SD)			
At day of OPU	2.05 ±0.34	2.07 ±0.31	2.06 ±0.34
At day of embryo transfer	1.72 ±0.19	1.73 ±0.22	1.90 ±0.27
Mean difference	-0.33	-0.34	-0.16
% change	-16.1	-16.4	-7.8
p-value	<0.001 Pa ***	<0.001 Pa ***	0.067 Pa NS

Table 5: Comparison of pregnancy rate among study groups

Characteristic	**Group A** ***n* = 30**	**Group B** ***n* = 30**	**Group C** ***n* = 30**	***P***
Pregnancy				
Positive, *n* (%)	11 (36.7 %)	14 (46.7 %)	8 (26.7 %)	0.275 C NS
Negative, *n* (%)	19 (63.3 %)	16 (53.3 %)	22 (73.3 %)	

DISCUSSION

Endometrium thickness and blastocyst quality are crucial for embryo transfer in clinical pregnancy. Proper endometrium thickness is challenging to achieve during in vitro fertilization (IVF). Despite various ART procedures, many embryos fail to implant. The endometrium secretes cytokines, growth factors, prostaglandins, and binding molecules during the receptivity period, making the right state of the endometrium essential for successful embryo implantation. [17]. The underlying reason of implant failure is obviously multifaceted and cannot be linked to any certain defect. Uterine abnormalities, alterations in the hormone, immunology and thrombophilia are diverse maternal variables that cause failure of implantation[18].

Poor endometrial receptivity has become a bottleneck issue in the ART field, and the lack of evidence-based treatments signifies the issue. Clinicians and scientists have struggled to find an effective therapeutic solution[19]. Recently, increasing evidence has shown the positive role played by autologous platelet-rich plasma (PRP) in treating endometrium [20,21].

This study found no significant differences in demographics, fertility, basal serum hormone levels, stimulation, and duration between study groups, ensuring a fair and random distribution of patients and preventing bias in the results regarding the intervention's sole effect on primary and secondary outcomes. In the other hand current study found no significant differences in oocyte and embryo characteristics among study groups due to the local nature of the intervention, which did not have systemic effects.

In present study and at day of ova pickup, no significant differences were observed in mean endometrial thickness, mean pulsatility index, mean resistive index and mean systolic velocity / diastolic velocity ratio. While, at day of embryo transfer, significant variation was reported in ultrasound parameters and that combined intervention using PRP and endometrial scratch produced the best required effect leading to the most significant decline in pulsatility index, resistive index and systolic velocity / diastolic velocity ratio and to the most significant increase in mean endometrial thickness.

Farahat and Omar conducted a study in 2019 [22], aimed at comparing the efficacy and safety of endometrial scratching performed at various points during the menstrual cycle in relation to the cumulative pregnancy rate and sub-endometrial vasculature blood flow as assessed by Doppler ultrasound. In instances of unexplained infertility, the study involved the calculation of the pulsatility index (PI) and resistance index (RI) of both endometrial and sub-endometrial arteries. The findings highlighted noteworthy reductions in these vascular indices subsequent to the endometrial scratching procedure.

In a previous Iraqi report, Al-Joran*iet al.,* in 2019 [16], performed a study which revealed that, the endometrial thickness of the scratch group was significantly higher than non-scratched group and this agreed with our finding. Therefore, the findings of the present study align with those of Farahat and Omar in 2019 and Nastri*et al.,* (2015) regarding the effectiveness of endometrial scratching in enhancing endometrial blood circulation. The process of angiogenesis triggered by endometrial injury primarily involves the mobilization of cytokines, growth factors, and natural killer cells, which subsequently facilitate sufficient blood supply to the tissue and prevent rejection of the embryo [23]

Our findings regarding alterations in average endometrial thickness subsequent to autologous PRP intra-uterine administration align closely with the results reported by Russell *et al.,* (2022) [24], who conducted a study involving 85 infertile women. Their research indicated a notable enhancement in endometrial thickness due to PRP intervention, with an average change of 1 mm. Previous research has demonstrated significant enhancements in endometrial thickness, embryo implantation, and clinical pregnancy outcomes in instances of a thin endometrium ([25], [26], [27] as well as in cases of recurrent implantation failure (RIF), [28]; [27].

The largest RCT study by Eftekhar et ala study on 83 infertile women found that patients with PRP treatment had a significantly larger endometrium thickness, while controls had a thinner one. The per-cycle clinical pregnancy rate increased from 14% to 32.5% in the PRP group, but there was no significant difference in ongoing pregnancy rates between the two groups[26],The finding ofEftekhar et al., approved with current study findings. The pregnancy rate in this study highest rate was observed in group B (46.7 %) followed by A group (36.7 %) and 26.7 in group C, however, statistical wise, these variations were not significant (p = 0.275). The study's limitation lies in its small sample size and the single center it was conducted in.

CONCLUSION

The meta-analysis indicates that Platelet Rich Plasma and Endometrial Scratch enhance the endometrium's ultrasonography properties, thereby increasing the implantation rate post-ICSI-ET.

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