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Intrauterine Infusion of Autologous Platelet-Rich Plasma Affects the Endometrial Thickness, Epidermal Growth Factor and Pregnancy Outcome in Patients Undergoing IUI

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Abstract

Despite developments in assisted reproductive technology, there is immaterial progress in the implantation and pregnancy rates. Intrauterine infusion (IUIF) of autologous platelet-rich plasma (PRP) might renew implantation rates through its paracrine properties by progression cytokines and growth factors which favor implantation. Here we determine whether the IUIF of autologous PRP had a role in pregnancy outcome through its outcome on epidermal growth factor and endometrial thickness. An overall of 43 patients where prospectively randomly dispersed into two groups subjected to a superovulation program using Letrozole® tablet orally 2.5 mg twice daily 12 hours apart from day 2 for 5 days for one cycle. 20 women were considered as control receiving the conventional intrauterine insemination (IUI) management while 23 of them were given PRP by IUIF on the day of human chorionic gonadotrophin injection. The IUI was done for both groups 36-48 hours after confirming ovulation. The blood samples were collected from both groups on the day of IUI for the valuation of epidermal growth factor and an ultrasound was done on the day of human chorionic gonadotrophin injection and day of IUI for assessment of endometrial thickness. The mean endometrial thickness in the PRP group at the day of IUI was significantly thicker than that of the control group and the difference in percentage change of endometrial thickness between PRP group and controls significantly higher in PRP group. The mean epidermal growth factor and the pregnancy rate were significantly superior in the PRP group than that of controls. In conclusion, autologous PRP IUIF was well-tolerated and resulted in a significant expansion in endometrial thickness, epidermal growth factor Level and, subsequent pregnancy rate in an infertile woman undergoing IUI.

Keywords: Endometrial thickness, Intrauterine insemination, Platelet-rich plasma, epidermal growth factor.

1. Introduction

An actual implantation is a well-orchestrated event demanding the presence of a strong embryo, a compassionate endometrium, appropriate embryo endometrial cross-talk, and sufficient maternal immune protection (Committee Opinion [1]). Though the current advances in Assisted Reproductive Technologies (ART's), implantation degrees persist moderately truncated. Well-off implantation obliges receptive endometrium, abundant quality of embryo with perfect embryo transfer technique (Eftekhar, et al. [2]). Endometrial receptivity is well-ordered by self-motivated and precise molecular and cellular events of cytokines, homeobox transcription factors (adjust the expression of targeted genes and direct the creation of numerous body structures throughout early embryonic development and genes (Zhang, et al. [3]). Habitually, the intrauterine insemination (IUI) is considered headway of dealing for couples suffering from altered sources for infertility, comprising ovulation dysfunction, cervical Infertility with minor to moderate malefactors and for unexplained infertility (Fauque, et al. [4]). It is cost-effective, less invasive, and a transitory phase earlier to the application of stylish (ART's) like in vitro fertilization (IVF) without or with Intracytoplasmic Sperm Injection (ICSI) (Koli, et al. [5]). Letrozole is a reversible selective third-generation aromatase inhibitor that has the potential role to be employed for ovulation induction with the evidence of an endometrial sparing effect. Letrozole encourages ovulation by inhibition of the conversion of androgens to estrogens and making an estrogen-deficient situation simulant the central fall of negative feedback by which the Clomiphene Citrate (CC) acts. (Requena, et al. [6]). The PRP is well-defined as the plasma portion of autologous blood with the concentration of platelets four to five times beyond normal (Lee, et al. [7]). The PRP has been suggested as an inexpensive, safe, and easily available treatment modality for

women with obstinate endometrium and implantation failures (Tandulwadkar, et al. [8]). The platelets' solid granules comprise adenosine diphosphate, histamine, calcium ions, adenosine triphosphate, dopamine, and serotonin that describe important factors for homeostasis (Cole, et al. [9]). Among the numerous growth factors placed and unrestricted by platelets, there is the epidermal growth factor (EGF), platelet-derived growth factor, the vascular endothelial growth factor (VEGF), the insulin-like growth factor 1, the transforming growth factor b-I, the hepatocyte growth factor, and the basic fibroblast growth factor. The PRP also contains three proteins in the blood acknowledged to achieve as a cell adhesion molecule, vitronectin, fibronectin, and Fibrin (Litvinov, et al. [10]). The PRP intrauterine distillation was first described by (Chang, et al. [11]) and used for patients undergoing fertility management and have thin endometrium. Endometrial thickness is known for instance the highest expanse among echogenic interfaces for endometrium and the myometrium and was measured in a level pass the central longitudinal axis of the uterus (Yuan, et al. [12]) The endometrial thickness is reliant on several influences comprising phase of the menstrual cycle, reproductive age, the concentration of ovarian hormone estrogen and progesterone and endometrial hormone receptor density (Paulson, RJ [13]). The thickened endometrium delivers a spot for attachment and it is the source of nourishment for an implanting embryo for the period of its first few weeks until the development of placenta but, thin endometrium which fails to respond to hormones leads to early miscarriages and implantation failure due to deficiency of blood supply (Senturk and Erel [14]). The epidermal growth factor is the instituting member of the EGF-family of proteins. The members of this protein family have extremely analogous functional with structural characteristics. Also, the EGF by itself extra family member comprises

transforming growth factor-α, Amphiregulin. Epiregulin and Heparin-binding EGF-like growth factor (HB-EGF) (Dreux, et al. [15]). The EGF is expressed in endometrial epithelial cells and stromal and has been demonstrated to adjust glandular epithelial secretion, endometrial cell proliferation, and decidual transformation (Simón, et al. [16]). It is a fundamental molecule in the communications among the embryo and uterus during the attachment reaction (Cha, et al. [17]). The EGF expression is utmost in the receptive epithelium and is synchronized with pinopodes (Stavreus-Evers, et al. [18]). The existence of EGF in the proliferative phase of human endometrium and its localization to stromal cells in trophoblastic cells and secretory endometrium is expressive of its contribution to embryo implantation (Ejskjær, et al. [19]). It was found that the developing blastocysts have an implantation rate significantly superior in the attendance of EGF compared with the control blastocysts in vitro (Chia, et al. [20]). The heights of EGF protein in the glandular and luminal epithelium are elevated up during the implantation window (Chobotova, et al. [21]).

2. Materials and Methods

A randomized prospective study conducted in the Higher Institute of Infertility Diagnosis and Assisted Reproductive Techniques. Al Nahrain University in the period from (July 2018 to July 20l9). Forty-three women were included in this study and were approved by the local medical ethical committee of the High Institute for Infertility Diagnosis Assisted Reproductive Technologies. Every patient gave her written informed consent before taking part in the study. The patients had to meet the subsequent criteria, Female aged 18-40 years, normal seminal fluid analysis, negative virology screen while the exclusion criteria are Hb <11g/dl and platelet <150.000/mm^3, female on anticoagulant treatment or take non-steroidal anti-inflammatory drugs in 10 days before the procedure and any psychiatric disorder or significant

comorbidity. Forty-three women with a history of primary or secondary infertility were categorized into two groups; the PRP group were twenty-three women have received aromatase inhibiter (Letrozole® tablet, Accord, UK.) treatment orally 2.5-5 mg twice daily 12 hours apart from day 2 for 5 days for one cycle. PRP was done at the day of trigger upon revealing of a mature follicle with ≥17 mm diameter by vaginal ultrasound and ET was measured, Intrauterine insemination was done after 36-48 hours after approving ovulation and assessment of ET was done. The non-PRP group is twenty women who have received the same protocol of induction. Ultrasound was done for assessment of endometrial thickness at the day of trigger upon recognition of a mature follicle with ≥17 mm diameter and on the day of IUI. IUI was done after 36-48 hours after confirming ovulation. The blood sample was taken to measure EGF on the day of IUI for both the non-PRP group and the PRP group.

3. PRP Preparation

When the first spin to discrete red blood cells was followed by a second spin to concentrate platelets which are suspended in the lowest plasma volume (Amable, et al. [22]). The blood was collected in special sterile vacationer PRP tubes containing an anticoagulant Na citrate 3.8%, which centrifugally splits red blood cells from plasma that contains 'buffy coat' (white blood cells and platelets). The PRP tube was centrifuged at 1100 rpm for 6 min. at room temperature. The plasma was quietly aspirated from the tube into a syringe and transferred to a second tube then centrifuged again at 3000 rpm for 10 min at room temperature, thus gaining a two-part plasma: the upper part, consisting of platelet-poor plasma (POP), and the lower part, consisting of PRP. The POP was first gently aspirated to avoid its mixing up with the platelet concentrate and the lower one-third of plasma was mixed with platelet concentrate and then was infused in the endometrium by IUI catheter (Mikhael and El-Esawy [23]).

4. Statistical Analysis

The data were entered, managed, and analyzed using the statistical package for social sciences (SPSS) version 25. Descriptive statistics of the data expressed according to the types of variables as frequency (No.), percentage (%), mean, standard deviation, and range. Students t-test, independent two groups model, used to compare mean values of the studied parameters between both studied groups as continuous variables including mean age, mean body mass index BMI, duration of infertility, FSH, LH, Prolactin, TSH, No. of follicles, Day of hCG Injection, Day of IUI, ET at the day of hCG, ET at the day of IUI and EGF. Fisher's exact test used to compare the type of infertility, age groups, and BMI categories between PRP and control groups. A comparison of the percentage change in ET after treatment Z-test for two proportions was applied. The correlation between EGF from one side and ET on the other side was assessed using Pearson's correlation test, the correlation coefficient (R) value was calculated which is an indicator for the strength and direction of the correlation; statistically, R-value, ranged between zero for complete no correlation and one for perfect correlation, however, R-value closer to one indicates the stronger correlation while R-value below 0.4 indicates weak correlation regardless of the P-value. Findings and results of analyses presented in tables with explanatory paragraphs, additionally bar charts used as a graphical presentation of the comparisons of different parameters between both groups.

5. Results and Discussion

The two groups, patient characteristics are shown in Table (1, 2, 3). There were no significant differences between the two groups was observed in duration, type of infertility age, (BMI), and baseline hormonal levels. Regarding the mean EGF, it was significantly greater in the PRP group (188.2 ± 87.4) than that of controls (96.7 ± 33.6) as shown in (Figure 1). Figures (2, and 3), and Table (4),

Table (1): Distribution of the types and duration of infertility of the studied groups

Parameter		Group				P-Value
		PRP (N = 23)		Control (N = 20)		
		No.	%	No.	%	
Type of infertility	Primary	16	69.6	15	75.0	0.692 ns.
	Secondary	7	30.4	5	25.0	
Duration of infertility (years)	*mean± SD**	4.7 ± 2.2		4.5 ± 2.8		0.780 ns.
	Range	1 – 10		1 - 11		

SD: standard deviation, ns: the* difference is not significant
#Chi square test (X 2)
Student's t-test used to compare means

Table (2): Age and BMI distribution of the studied groups

Parameter		Group				P-Value
		PRP (N = 23)		Control (N = 20)		
		No.	%	No.	%	
Age (year)	≤ 20	6	26.1	5	25.0	0.488 ns
	21 - 30	14	60.9	12	60.0	
	> 30	3	13.0	3	15.0	
Mean age ± SD* (year)		25.5±4.7		26.2±5.2		0.455 ns
BMI Category	Normal	5	21.7	4	20.0	0.922 ns
	Overweight	11	47.8	10	50.0	
	Obese	7	30.4	6	30.0	
Mean BMI ± SD (kg/m^2)		27.7±4.1		27.9±3.5		0.891 ns

Table (3): Comparisons of hormonal levels between the studied groups

Parameter	Group		P-Value
	PRP (N = 23)	Control (N = 20)	
	Mean ± SD	Mean ± SD	
FSH (mIU/ml)	7.0 ± 1.6	7.2 ± 2.2	0.712 ns
LH (mIU/ml)	5.4 ± 2.3	5.2 ± 1.3	0.760 ns
Prolactin (ng/ml)	15.8±6.4	18.1 = 6.9	0.364 ns
TSH (mIU/ml)	1.9±0.80	2.0 ± 0.72	0.658 ns

SD: standard deviation, ns: the* difference is not significant
student's t-test used to compare mean age
Chi-square test (X 2) used to compare other variables

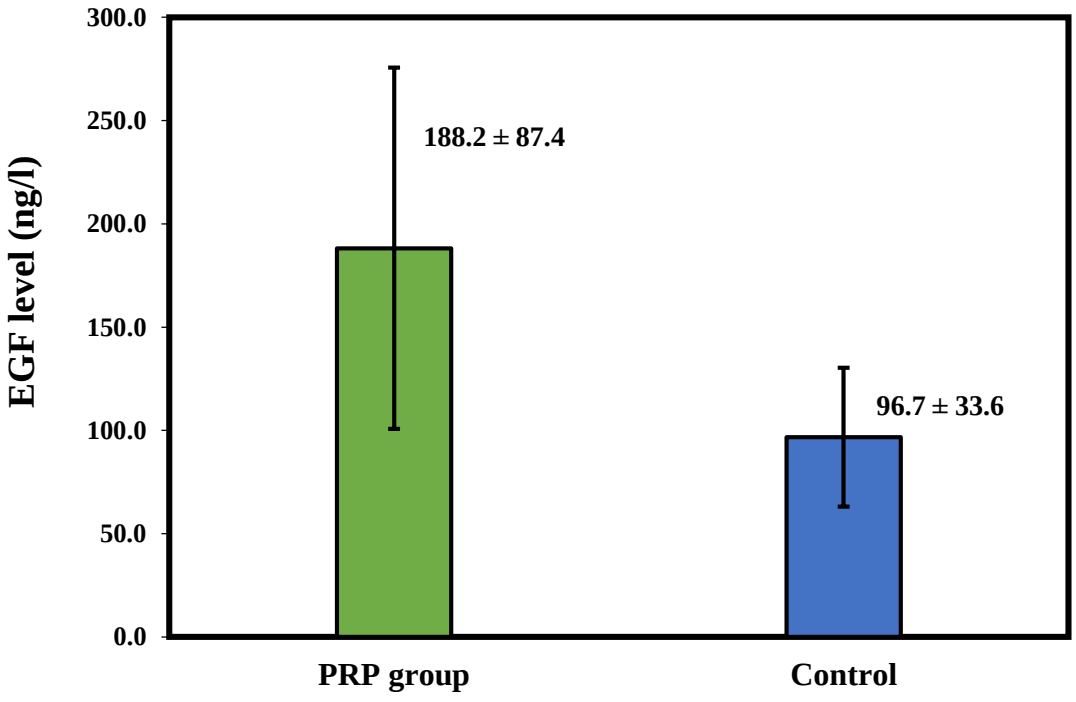

Figure (1): Comparisons of mean levels of EGF of the studied groups

summarizes the comparisons of the endometrial thickness (ET) at the day of hCG and on the day of IUI in two ways of comparisons; between groups and within each group (ET on the day of hCG against ET on the day of IUI). On the day of IUI, the mean ET in the PRP group was significantly higher than that of the control group (P-value = 0.001). The comparison within-group revealed a statistically significant difference between mean ET on the day of IUI and that on the day of hCG in both studied groups. In the PRP group the mean difference on the day of IUI with a percentage change significantly higher than its value at day of hCG, (P< 0.001). In the control group there was also a significant change of in ET with a percentage change on the day of IUI than that on the day of hCG, (P<0.001), however, the mean difference and percentage change of ET in PRP group were significantly larger than that of controls, in both comparisons (P = 0.001). The pregnancy rate in PRP group was 8/23 (34.8%) compared to 3/20 (15%) in the control group when the positive pregnancy test rates in both groups compared using the Z statistics it exposed that the 34.8% positive pregnancy test rate in PRP group was significantly greater than the 15% of controls (Z = 3.1, P = 0.001) as shown in Figure 4. Furthermore, EGF and ET were compared across the results of pregnancy tests in both studied group, the mean level of cases with a positive pregnancy test in PRP group was significantly higher than that of positive pregnancy test controls, (P = 0.015 significant), similarly the mean EGF for those with negative pregnancy test was higher in PRP group than controls, (P-value = 0.026 significant) (Figure 5). Embryo successful implantation in the decidualized endometrial stroma is necessary for early pregnancy and endometrial receptivity plays a significant role in this process (Fatemi and Popovic-Todorovic [24]). The PRP contains a platelet concentration of at minimum 1 000 000 platelets/L in 5 mL of plasma, having a 3-to-5-fold increase in growth factor concentrations (Berner, et al. [25]).

Table (4): Comparisons of mean Endometrial Thickness at the day of hCG and day of IUI within and between the studied groups

Endometrial Thickness (ET)	Groups		P-Value
	PRP (N = 23)	Control (N = 20)	
	Mean ± SD	Mean ± SD	
ET at day of hCG (mm)	6.7 ± 1.7	7.1 ± 1.2	0.395 ns
ET at day of IUI (mm)	9.9 ± 1.4	8.4 ± 0.9	0.001 s
Mean difference (mm)	3.2 ± 1.6	1.3 ± 0.5	0.001 s
Percentage change	47.8%±8.4%	18.3%±1.7%	0.001 s
P-Value within groups	**< 0.001 S**	**< 0.001 S**	
*SD: standard deviation, ns: not significant, s: significant difference; # Student's t-test used to compare means			

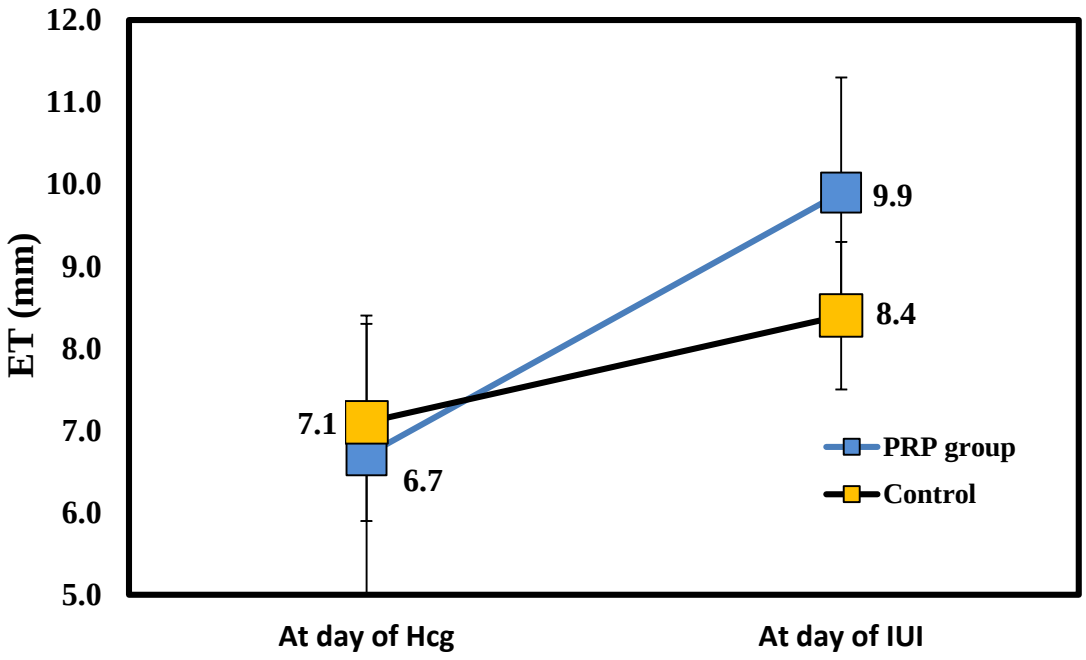

Figure (2): Change in the ET values of both studied groups

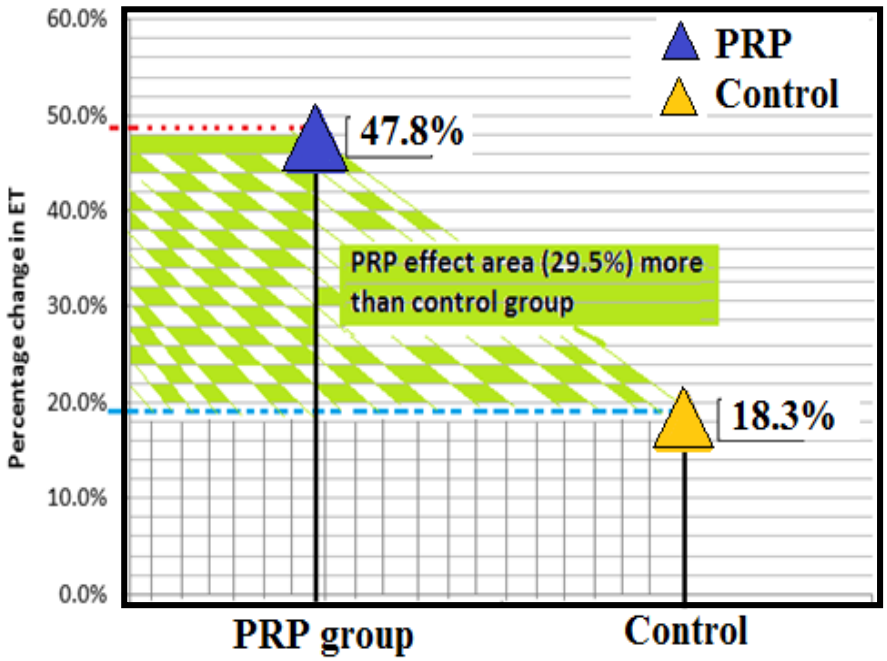

Figure (3): Comparison of the percentage change in ET after treatment with PRP Showing the area of PRP effect

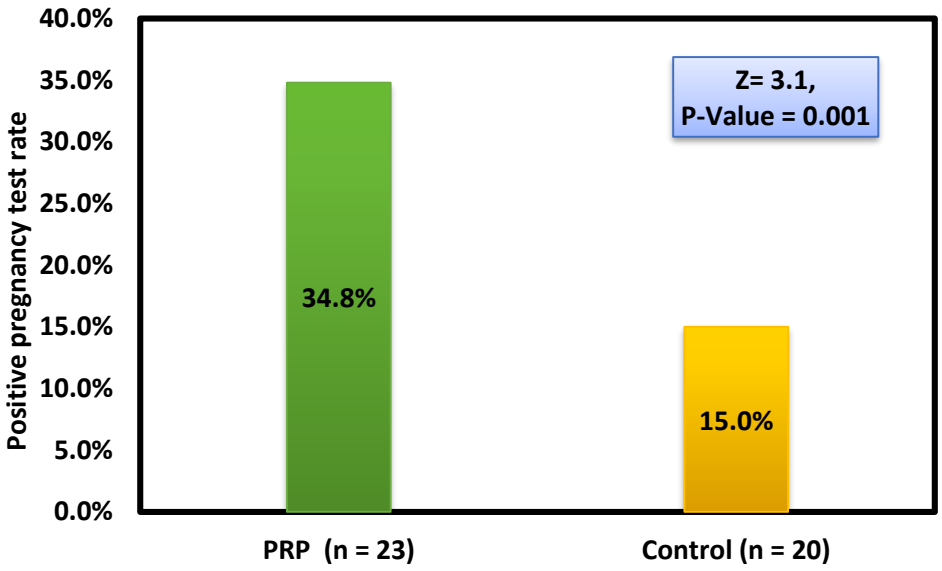

Figure (4): Comparison of Positive pregnancy test rates between both groups using Z statistics.

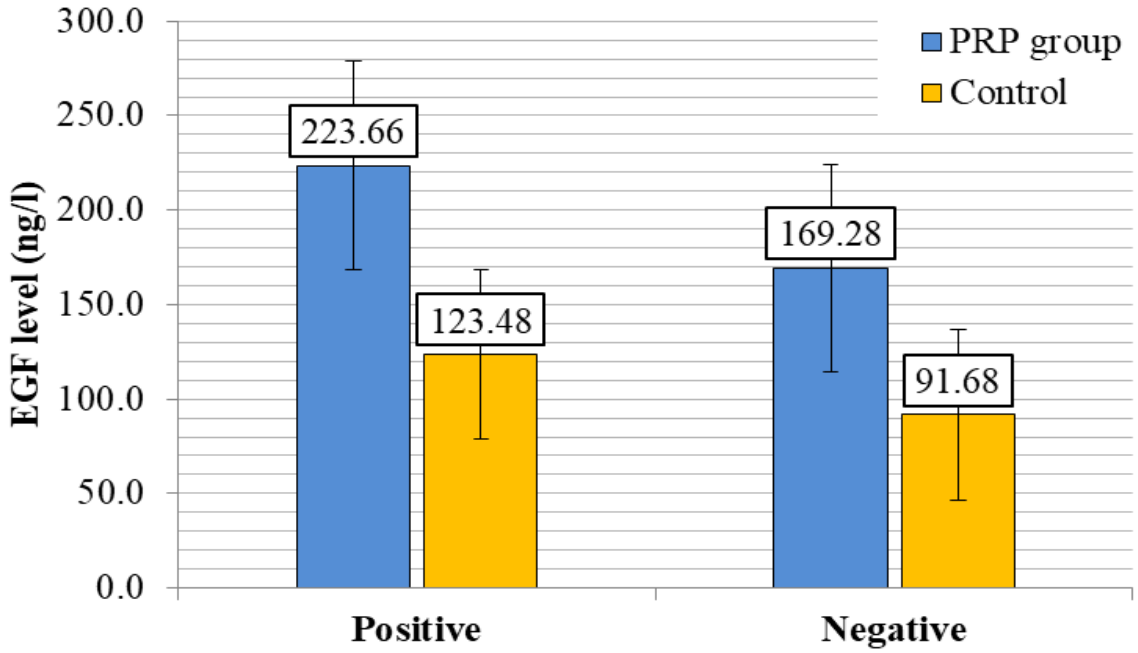

Figure (5): Comparison of mean EGF according to results of pregnancy tests in Discussion

Upon platelet activation in PRP, the platelet granules are degranulated and release the cytokines and growth factors (GF) that will improve the pericellular microenvironment. These GF comprise EGF, fibroblast GF (FGF), VEGF, platelet-derived GF, hepatocyte GF, insulin-like GF 1, 2 (IGF-1, IGF-2), matrix metalloproteinases 2, 9, and interleukin 8 (Andia and Abate [26]). These factors signify signaling molecules that bind to specific receptors on target cell surfaces, supporting cell differentiation, maturation, and proliferation and they are commonly concomitant with positive cell signaling (Makrigiannakis, et al. [27]). In the current study, the endometrial thickness on the day of IUI was significantly higher in the PRP group compared with the control group This is agreed by the study by (Chang, et al. [11]) evaluated the role of autologous PRP in thin endometrium in five patients experiencing frozen embryo transfer cycles. The ET amplified at 48 to 72 h after PRP infusion in all the patients and extended >7 mm on day of progesterone

administration. (Garcia-Velasco, et al. [28]) also refers to the use of autologous PRP as a prospective mode of improving ET in females with refractory endometrium. Consistently another two groups of researchers in their pilot study involved patients with a history of canceled cycles due to insufficient endometrial growth (<7 mm), they recognized that PRP was effective for endometrial growth in patients with a thin endometrium (Zadehmodarres, et al. [29]). Other scientists considered PRP treatment for destroyed endometrium, and they concluded that the intrauterine infusion of autologous PRP motivated and accelerated endometrial regeneration and reduced fibrosis in a murine model (Jang, et al. [30]). The EGF enhances angiogenesis and chemotaxis of endothelial cells and mesenchymal cells mitosis (Barrientos, et al. [31]). For the mean EGF, it was significantly greater in the PRP group (188.2 ± 87.4) than that lof controls (96.7 ± 33.6). This is agreed with the study that explores VEGF, EGF, platelet-derived growth factors, and Transforming growth factor β1 were all significantly higher in PRP samples than in the whole blood baseline samples (Karimipour, et al. [32]). Human endometrial tissue contains receptors for EGF, it encourages endometrial tissue re-establishment and play a role by paracrine land autocrine and are accompanying with endometrial receptivity, embryo implantation, and development (Anitua, et al. [33]). In a study searched the relationship between endometrial thickness and EGF expression, they found that EGF expression in the endometrium in the mid-luteal phase and endometrial thickness had a significant positive correlation signifying that EGF may enable endometrial growth due to its mitogen activity. These results recommend strong proof for the positive association between IVF-embryo transfer pregnancy outcome and endometrial thickness (Song, et al. [34]). It is usually established that endometrial thickness, hormones, and cytokines are significant factors in

regulating endometrial receptivity. These various factors synchronize and mediate cell-matrix and cell-cell interactions, thereby augmenting endometrial receptivity and confirming the success of embryo implantation (Ponsuksili, et al. [35]). In the current study, the pregnancy rate in the PRP group was 8/23 (34.8%) significantly higher compared to 3/20 (15%) in the control group. This is agreed with other studies which found that intrauterine PRP infusion upsurge pregnancy rate in ICSI frozen cycles, so we will compare our study with those studies because there is no previous study on PRP in IUI. (Farimani, et al. [36]) employed a single-blind pilot study to support the hypothesis that PRP intrauterine administration probably will rise pregnancy outcomes of frozen-thawed embryo transfer, they attained clinical pregnancy lof 66.6%. The same also established by (Molina, et al. [37]) who achieved an experimental trial using PRP to increase the quality of endometrial and implantation rates in patients who have refractory endometrium and investigated that growth factors expression in the endometrium of women with repeated implantation failure is fewer than normal fertile women. According to this hypothesis, local infusion of PRP that contains several growth factors and cytokines may increase endometrial receptivity land implantation. (Fujiwara, et al. [38]). The growth factor included in our study is EGF. For EGF, the mean level of cases with a positive pregnancy test in the PRP group was significantly greater than that of positive pregnancy test controls. EGF is expressed both in decidual land trophoblastic cells and affects implantation in several ways. The EGF prompts trophoblast invasion, differentiation, and proliferation, hence it is considered a key regulator for the process of implantation. It has been shown to increase matrix metalloproteinase-2, matrix metalloproteinase-9 activity in trophoblastic cells, thus inducing cell invasion (Staun-Ram, et al. [39]). This is also agreed by a study that considers the

exogenous EGF effects on implantation rate of in vitro developing blastocysts in rats and it was established that the implantation rate of developing blastocysts was significantly larger in the existence of EGF matched with the control blastocysts in vitro (Aflalo, et al. [40]). Another study approved that Electron microscopy together with immunohistochemistry demonstrated that the EGF expression in the glandular and luminal epithelium is extreme when completely developed pinopodes are present, highlighting the role of EGF in the invasion and attachment processes of human implantation (Cha, et al. [17]).

6. Conclusion

The PRP intrauterine infusion could be an effective alternative treatment for patients with thin endometrium since PRP significantly improve endometrial thickness. Endometrial receptivity marker (EGF) was increased after the use of PRP significantly. The pregnancy rate in women with infertility undergoing IUI was improved significantly after using the intrauterine infusion of PRP.

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Author Contribution

Abaid WA, performed the study, Al-Obaidi MT, and Abood MS supervised the work.

Conflict of Interest

The authors declare no conflict of interest.

Ethical Clearance

The study was approved by the Ethical Approval Committee.

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