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EFFECTS OF AUTOLOGOUS PLATELET-RICH PLASMA ON RECEPTIVITY, IMPLANTATION AND PREGNANCY IN THIN ENDOMETRIUM, WITHOUT FETAL TRANSMIT

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ABSTRACT

Background: Thin endometrium (TE) is a major challenge in infertility medicine and despite several methods that have been described for management, there is little consensus on the most effective one. **Objective:** The purpose of this study was conducted to evaluate the effectiveness of platelet-rich plasma (PRP) in improvement of receptivity, implantation, and, pregnancy rate in thin endometrium(TE) implantation that favoring the crosstalk between the embryo and the uterus improving the embryo-maternal dialogue. **Study design:** The study was prospective trial which condcted in department of obstetrics and gynecology, Tishreen University Hospital, Lattakia, Syria approved by the ethics committee of Tishreen University, and all participants signed an informed written consent. **Results:** 27 patients 5 patients had chemical pregnancies with 3 ongoing pregnancies, only 2 miscarricage, and 3 live birth. PRP application day was relevant with a significant probability of achieving pregnancy when the first PRP infusion was carried out at 10th day, and the second one at 12th day of the menstrual cycle. **Conclusions**: According to this study, it seems that Intrauterine autologous platelet- rich plasma (PRP) infusion is a safe, easily accessible, effective, and inexpensive therapy that could collaborate in fertility treatments, which improve thin endometrium by optimizing the receptivity, implantation and outcome in TE patients.

KEYWORDS: Platelet-rich plasma, receptivity, implantation, Thin endometrium, Pregnancy rate.

INTRODUCTION

Adequate endometrial growth is an integral step in endometrial receptivity and embryo idiopathic or resulting from an underlying pathology, a thin endometrium of <7 mm is linked to a lower probability of pregnancy.[1]

Embryo implantation is a very dellcat and well-orchestrated process that is governed by the interaction between several maternal and embryonic factors, ultimately resulting in adherence of the blastocyst to the endometrium.[2,3,4,5]

For a short period of time during the normal menstrual cycle, the endometrium represents the fertile "soil" for the implanting embryo.[6] The human endometrium undergoes complex changes', which culminate at the mid-luteal phase of the menstrual cycle when it becomes suitable to host the blastocyst.[7,8,9] These changes occur at the morphological, biochemical, and molecular levels; any fault may result in failed implantation.[10,11,12,13,14]

Implantation is crucial in reproduction

The etiologies for endometrial insufficiency are varied; it may be damaged, non-receptive, or non-proliferative among other causes. Previous studies have demonstrated a positive correlation between endometrial thickness (EMT) and embryo implantation rates.[15,16] which has led to the general clinical practice. the patient's endometrium thickness remains below 7 mm it is as a thin endometrium.

EMT and embryo implantation may be plimproved by endometrial scratching.[17,18,19] however, it is an invasive procedure with contradictory results.

Thin endometrium(TE)defind as a poor endometrial quality, may be caused low blastocyst competence, or asynchronicity between embryo and endometrium,

Therefore, endometrial quality is of paramount importance for embryo receptivity and implantation.[20,21,22]

To address issues of receptivity and asynchronicity between endometrium and embryo, efforts have been made to characterize the endometrial receptivity at various stages in the reproductive cycle.[23] recent studies have challenged the efficacy of receptivity profiling, suggesting that the technology is invasive and its applicability is limited.

Moreover, effective treatments for poor receptivity and thin endometrium are lacking.[24,25,26]

In this sense, new techniques should be directed toward the improvement of implantation, and promote the dialogue between the embryo and the endometrium that starts even before implantation. Also, the embryo-maternal crosstalk should be enhanced, favoring the processes of apposition, adhesion, and implantation.[27] In clinical practice, appropriate endometrium thickness suggests an optimal endometrial growth and receptivity that acts as a biosensor for embryo quality, it is noticeable that an endometrial thickness less than 6 mm is associated with a lower probability of pregnancy.[28]

Recently the use of plasma-rich platelet (PRP) has arisen as an intersting option in repeated implantation failure (RIF) and thin endometrium (TE)

PRP is prepared from fresh whole blood that contained several growth factors and cytokines including fibroblast growth factor (FGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VGEF), transforming growth factor (TGF), insulin-like growth factor I, II (IGF-I, II), connective tissue growth factor (CTGF) and interleukin 8 (IL-8).

PRP has been investigated as a therapeutic approach for several medical disorders including nerve injury, ocular epithelial defects, alopecia, cardiac muscle injury, osteoarthritis, and tendinitis. Despite the wide use of PRP in several fields in medicine, it's efficacy in obstetrics and gynecology is limited.[27-,34]

To the best of our knowledge, this study is the first randomzed trial in syria, to evulate and investigate whether intrauterine infusion of PRP could improve pregnancy outcome in women with (TE) without fatel transmet, and without previous recurrent implantation failure (RIF).

METHODS

The patients who participated in this study were referred to the department of obstetrics and gynecology in Tishreen University Hospital in Lattakia, Syria, between October 2021 and November 2022, all the patients had Thin endometrium.

The age group included in the study was 24 – 41 yrs, Thin endometrium (TE), i.e., less than 6 mm endometrium after hormone replacement therapy (HRT).

This inclusion criteria were used age below 45yrs, body mass index (BMI) below 30 kg/m^2

The exclusion criteria were

Any hematological, immunological, or hormonal disorders, chromosomal and genetic abnormalities and uterine abnormalities (acquired or congenital).

Laboratory evaluation of thrombophilia, antiphospholipid antibodies, hormonal disorders, hematological and immunological disorders in women.

All patients were treated with hormonal therapy protocol as usual in the clinical practice for endometrial preparation, administering E2 valerate orally.

PRP preparation and application

The volume of peripheral blood required to outcome approximately 2ml of prepared PRP for infusion the patient was 20ml.

For PRP obtention, 20ml of venous blood was drawn from the patients in sodium citrate tubes.

Tubes were centrifuged immediately at 1200 rp for 12 min to separate red blood cells, then plasma was centrifuged again at 3300 rpm for 7 min to obtain PRP that contained platelet 4-5 times more than peripheral blood

The whole plasma column was aspirated avoiding the buffy coat containing the leucocytes, the releas supernatant was collected for the instillation.

Approximately one week after estrogen administration, 2ml PRP was instilled into the intrauterine cavity. the PRP was aspirated into a tomcat catheter,and infused into the uterus under ultrasonography guidance, administration of PRP was performed at the10th,12th day of the menstrual cycle ,the EMT was measured by ultrasonography evry pre each PRP infusion, and after 48-72 hrs,until the EMT lining reached the target thickness over 7mm. with substituted hormonal therapy, Endometrial preparation begins on the second day of menstruation with 4-6 mg/day of estradiol valerate, luteal phase support is started with progesterone (Utrogestan) 400 mg ,twice daily. the medication is maintained until the serum levels of beta-human chorionic gonadotropin (β-hCG) measurement are performed (between 17,19 ds after ovulation), and if this is positive until the 12th week of pregnancy. The primary studied outcomes were endometrial thickness, pregnancy rate, and miscarriage rate.

Statistical analysis

Data collected were analyzed.

We used mean ± SD to assess quantitative parameters and Percentages To assess Qualitative parameters.

We used Kolomogroc-Smirnov Test to check normality of the Data, Paired Samples T-Test to study the difference in mean between groups.

A p-value of <0.05 was established as a statistical significance level.

RESULTS

PRP increased the endometrial growth respecting the initial thickness in all cases.[27]

Participants had a thin endometrium TE less than7 mm at ovulation day in previous cycles, were entered into this study. All of them were able to complete the study and their data were analyzed.

Table 1: Charasteristics of Patients in our Study.

N.	Age (Years)	BMI (kg/m^2)	Thickness Before Injection (mm)	Thickness After 1st Injection (mm)	Thickness After 2nd Injection(mm)	Chemical Pregnancy 5	Abortion 2	Live Birth 3
1	27	20.7	5.70	6.30	7.70			
2	41	25.6	6.20	6.90	7.60			
3	27	17.7	5.00	5.70	7.30			
4	25	19.6	6.80	7.70	8.10			
5	37	23.3	6.70	7.10	7.90			
6	40	23.7	5.80	7.30	8.20			
7	27	21.5	6.70	8.20	9.20	+		+
8	31	17.7	4.80	6.60	7.40			
9	40	23.7	6.70	8.00	9.30			
10	34	20.7	6.80	7.40	7.90			
11	25	17.7	4.90	6.00	7.50			
12	24	16.2	5.50	6.70	7.80			
13	24	16.9	6.90	8.00	9.30			
14	35	21.5	5.80	7.70	9.10			
15	28	20.7	4.90	6.40	8.60			
16	40	27.5	6.20	7.20	7.80			
17	27	16.2	6.70	7.30	8.70	+		+
18	41	28.2	6.70	8.00	9.30			
19	27	17.7	5.60	7.30	8.70	+	+	
20	37	18.8	6.90	8.20	9.70	+	+	
21	26	16.2	5.50	7.70	8.90			
22	35	17.7	5.90	6.10	7.30			
23	37	29.0	6.10	7.50	8.10			
24	40	23.3	6.30	7.30	8.90			
25	41	20.7	6.90	7.00	7.50			
26	41	22.6	5.10	6.20	7.10			
27	27	17.7	6.70	8.00	9.70	+		+

Table 2: Baseline characteristics The average age of the women participating in the study was 32.74 ± 6.48 years with average BMI 20.85 ± 3.68 Kg/m^2 and average Infertility Duration of 3.4 ± 3.01 years.

Parameter	***Minimum***	***Maximum***	***Mean ± SD***
Age (years)	24	41	**32.74 ± 6.48**
BMI (Kg/m^2)	16.2	29	**20.85 ± 3.68**
Infertility Duration (Years)			**3.4 ± 3.01**
Parameter		*N (%)*	
Primary Infertility		**7 (25.9%)**	
Secondary Infertility		**12 (44.5%)**	
Repeated Abortion		**7 (25.9%)**	
Asherman		**1 (3.7%)**	
Endometeriosis		**2 (7.4%)**	
Fibroids		**0 (0%)**	

Table 3: Statistical characteristics of Endometria Thickness Before and after PRP Injection.

Parameter	*Minimum*	*Maximum*	*Mean ± SD*
Thickness before Injection (mm)	4.8	6.9	**6.07 ± 0.713**
Thickness after 1st Injection (mm)	5.7	8.2	**7.18 ± 0.722**
Thickness after 2nd Injection (mm)	7.1	9.7	**8.32 ± 0.803**

Table 4: Dependent T-Test for mean difference in Endometrial Thickness before and after 2nd PRP Injection.

Thickness Before injection Mean ± SD (mm)	Thickness after 2nd injection Mean ± SD (mm)	Mean Difference ± SD	Confidence Interval		P Value
			Lower	Upper	
6.07 ± 0.713	8.32 ± 0.803	2.25 ± 0.76	1.99	2.55	**<0.001**

Table summarizing study the outcome distributed according to the indication.

Regarding endometrium thickness, for all 27 patients analyzed, the mean measured beforePRP application was 6.07 ± 0.71 mm; this value increased to 7.18± 0.72 mm after the first PRP infusion, and to 8.32± 0.80 mm after the second PRP infusion we showed that day of PRP application was a relevant fact, and there was a statistically significant probability of achieving pregnancy when the first PRP infusion was carried out at10th dy,and the second infusion with PRP was performed at 12th dy of the women's menstrual cycle.

Table 5: Study the outcome.

Endometrial thickness	8. 32 ± 0.80
Chemical pregnancy	5/27 (18.5%)
Clinical pregnency	3/27 (11.1%)
miscarrige rate	2/27 (7.4%)
Live birth	3/27 (11.1%)

A chemical pregnancy implies a positive β-hCG, and an ongoing pregnancy is defined as a pregnancy with a detectable heart rate at 12 weeks of gestation 5 participants were chemical pregnancy, The chemical pregnancy rate was 18.5%, considering the total number of patients (5 positive β-hCG out of 27 women 3 clinical pregnancy, The rate was 11.1%, 2 early miscarriage, The rate was 7,4%, 3 live birth, The rate was11.1%, were recorded.

DISCUSSION

Since every day research to find a new approach to serve this main factor (window of implantation) endometrium is the main factor for implantation and pregnany.

Despite expanding experience in advanced technologies and great. improvement in infertility treatment.[35,36]

The receptive endometrium is the main factor for implantation and pregnancy.

In a normal menstrual cycle in human, endometrium becomes receptive during the mid-secretory phase around days 19-23 that is described as window of implantation.[37,38] During this period, cytokines, growth factors, prostaglandins, and adhesion molecules are expressed and inconsistency of these proteins could impair implantation and pregnancy.[39,40]

Sak and co-workers investigated that expression of growth factors in the endometrium of women with (RIF) is less than normal fertile women.[41,42]

So our study focus on this free thin endometrium, that without present fatel transmit,or pravious (FIT), to study the degree of it is normal response with the tigger of immuno factors alone, plasma - Rich Platelet(PRP), as a new trial, to study the improve quality of endometrium to receptivity and implantation alone,so to improve the chance of pregnancy, to study the outcome of pregnancy.

As the local infusion of (PRP) that contains several growth factors and cytokines may improve endometrial receptivity and implantation. (PRP) collected from an autologous blood sample that has been enriched with platelets about 4-5 times more than circulating blood.

Recently, Chang reported the efficacy of (PRP) intrauterine infusion in endometrial growth in the refractory thin endometrium.[43]

Just recently, Reghini suggested the efficacy of (PRP) for the treatment of inflammatory response in chronic degenerative endometritis in mares. In this trial, 13 mares with endometrium classified as chronic degenerative endometritis and 8 mares with normal endometrial histology were selected to investigate the PRP therapy effect. The mares were inseminated with fresh semen in two consecutive cycles in a crossover study design. Each mare served as its own control and the treatment was performed with intrauterine (PRP) infusion four hrs after artificial insemination. They concluded that (PRP) was effective in modulating the exacerbated uterine inflammatory response to semen in mares with chronic degenerative endometritis.[44]

Miwa et al. elegantly described that with increased impedance across the radial uterine arteries, there is resultant decrease in (VEGF) expression and subsequent poor vascular development, resulting in thin endometrium.[45] however, found that the most commonly reported cut of 7 mm was associated with a significant drop in the probability of pregnancy.[46]

The implantation process is a consequence of an inflammatory and anti-inflammatory equilibrium and an imbalance could lead to refuse of endometrial receptivity.[47] The positive effect of (PRP) on implantation and gestation should occur via its anti-inflammatory molecules in the case of undetected or silent endometritis and even working over a possible underlying infection, thanks to the anti-microbial role of(PRP).[48]

Precisely, in clinical practice, the positive effect of(PRP)infusion on pregnancy achievement has been widely proven, improving reproductive outcomes of women with TE.[49]

Table 6: Comparison results of the endometrial thickness (only) before and after PRP infusion of our study with international studies.

STUDY	Type Of Study	Participants	Age	Day of PRP	Average EMT Before PRP	Average EMT After PRP	linical Pregnancy Rate
Our study 2023	Pilot	27	32.74 ± 6.48	10 - 12	6.07 ± 0.71 mm	8.32 ± 0.80	3/27
Change al. 2015	Pilot	5	35.0 ± 4.0	10	6.22 mm	7.52mm	5/5
Zadehmodarres et al. 2017	Pilot	10	35.0 ± 5.0	11 – 12	7.52 mm	N / A	5/10
Nazariet al.2016	Pilot	20	36.0 ± 3.0	16 – 18	N / A	N / A	18/20
Tandulwadkar et al.2017	Pilot	64	31.0 ± 9.0	15 – 16	7.22 mm	N / A	39/64
Eftekhar et al.2018	RCT	66	32.5 ± 2.0	13	8.67mm + 0.64 mm	8.04mm+0.27mm	14/33(s)vs. 8/33(c)
Hounyoung et al.2019	Pilot	20	37.5 ± 7.5	12,15,18	6.0mm + 1.1 mm	N / A	6/20
Nazariet al .2019	RCT	60	33.11 ± 3.77	11 – 12	7.21mm	5.76mm	12/30(s)vs . 2/30 (c)
Change et al.2019	RCT	64	33.5 ± 1.5	10	7.65mm + 0.22mm	6.52mm+0.31mm	15/34(s)vs . 6/30 (c)

CONCLUSION

The results of our study is encouraging, inspite of the small study population in TE, it could be considered a good starting point to expand our study, and other future research. randomized controlled clinical trials, and study of outcome in terms of live birth rates are needed to confirm our observations

Abbreviations

TE : Thin endometrium
PRP : Plasma rich platelat
β-hCG : Beta-human chorionic gonadotropin.
BMI : Body mass index

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