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THE ROLE OF MULTIPLE SELF ADMINSTRATION OF PLATELET-RICH PLASMA (PRP) IN IMPROVING THIN ENDOMETRIUM THICKNESS, AND PREGNANCY OUTCOME, WITHOUT EMBRYO TRANSFER

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ABSTRACT

Background: Infertility is one of the basics of gynecological treatments, and its problems affect many couples. objective: Our study aimed to evaluate the effect (three injections) of platelet-rich plasma (PRP) as a promising adjunctive therapy in thin endometriosis (TE). which did not achieve the required thickness of 7 mm, And the possibility of its role through multiple self-injection in improving implantation rates and pregnancy rates. 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 The infusion was reinforced by being three infusions, that is, the second infusion was reinforced by the third infusion. PRPincreased the endometrial growth thickness in all cases. The biochemical pregnancy rate determined as positive beta-human chorionic gonadotropin (β-hCG) was 20%,; the ongoing pregnancy rate was 10%. So Multiple PRP application was therefore consistent with the probability of pregnancy, with an improvement in the rate. **Conclusions** The Intrauterine autologous platelet- rich plasma(PRP) infusion is a safe, easily accessible, effective, inexpensive. In our study, the results achieved a clear improvement in the thickness of the lining, and a slight improvement in pregnancy and childbirth outcomes,The small sample may be an important factor, but it itself showed an improvement in the results as a first attempt and study.

KEYWORDS: Platelet-rich plasma (PRP), three infusions, Thin endometrium, Pregnancy rate.

1. INTRODUCTION

Receptivity remains an important factor, fundamental, and confounding factor in the continuation of pregnancy or infertility. Studies and experiments remain the guide to reach more accurate results.

Therefore, we focus on the importance of acceptance, with its important mechanisms, which is the basis for the desired scientific research. the uterine lining is incredibly important for implantation of the blastocyst to take place. The question of how to measure this, termed 'uterine receptivity', has been studied extensively in the literature. The methods that have used in the past were indirect, assumptive and not reproducible. Researchers in Spain have created a new tool which has been shown to be promising for identifying molecular markers for uterine receptivity.[1]

As the blastocyst floats within the uterine cavity looking for a place to land, a dialog takes place between the blastocyst and the endometrium. In order for a successful implantation to take place, the blastocyst needs to be at the appropriate stage, and it needs to signal the uterine lining to 'accept' it. Within the uterine cavity, once ready for implantation, the microvilli present on the trophoblast cells of the blastocyst act as one side of 'velcro' to adhere it to the uterine lining. The embryo is in search of a receptive endometrium (the other half of the velcro) which will 'fasten it' to the uterine wall.[2] The hormonal preparation of the uterus plays a critical role each month in creating this environment in which the blastocyst can adhere to the endometrium in the hope that implantation will take place.

The uterine lining undergoes changes during the two phases of the menstrual cycle that prepare it for

blastocyst implantation. During the proliferative phase, it grows due to the increasing production of estrogen by the ovaries. The second phase is called the secretory phase where the production of progesterone, produced by the corpus luteum, converts the endometrial lining to a secretory one, changing the cells to prepare for implantation (a process called decidualization). Should implantation not take place, the hormone levels will fall,[3] resulting in a shedding of the lining, which results in menses. Studying the mid-secretory phase is of great importance since the window of implantation (WOI) takes place then. The sweet spot of WOI is approximately a 2-day period when the uterus is prepared to accept the implantation of a blastocyst. Conventionally, it was assumed that every woman had the same WIO, (approximately 8-10 days after ovulation) so embryo transfers would be scheduled to take place during this time.[4] This theory has recently been challenged, with researchers proposing that the WOI can vary among women.

The appearance of the lining by ultrasound in the late proliferative phase. Many studies have focused on the endometrial thickness and type (triple-line vs homogenous appearance). Although the lower limit of an acceptable lining has not been agreed-upon by researchers or practitioners (most would arguably be satisfied with a lining of 7 mm or above) that information is a reflection of the adequacy of the proliferative phase, which tells us that the lining was properly primed by estrogen, but doesn't give us any information other than that. Ultrasound in the secretary phase is not helpful,[5] as it shows a thick, homogenous lining that doesn't usually affect clinical decision-making, so is not routinely performed.

Over the last decade, different ways of studying the endometrial lining more directly have been investigated, first by attempting to identify the substances that were generated at the time of implantation, the cytokines, adhesion molecules and other proteins. To date, this line of investigation has been unsuccessful, so the focus has shifted to the stage that leads to the production of these substances, the stage of RNA transcription. Transcriptomics allows the study of gene expression by looking at the mRNA produced. It can provide a molecular profile of the status of the endometrium by telling us what genes are actually "turned on". Gene expression profiling is now widely used for other disciplines, such as tumor classification.[6]

With the relatively recent advent of DNA microarray analysis we can measure the expression of thousands of genes simultaneously, allowing us to explore which ones are expressed in the mid-secretory phase, when implantation takes place. The discovery of this technology was a major turning-point in the study of endometrial receptivity and several studies were undertaken to determine which of these genes were important during the WOI. Researchers agree that there is a specific and unique action that takes place during the process of transcription, when RNA creates the 'script' for a protein, in order for the endometrium to become receptive, but the identification of the specific genes involved was elusive until recently.[7] A group in Spain identified 238 genes related to endometrial receptivity and collected the data to create a tool, named the endometrial receptivity array or ERA (Diaz-Gimeno, et al 2011). This test purports to identify if an endometrium is receptive or not based on the mRNA profile or the endometrial gene expression. It further differentiates the non-receptive category into pre- or post-receptive) in natural or hormone-replacement (HRT) cycles, regardless of it's appearance by ultrasound or under the microscope (histological.[8]

(PRP) platelet-rich plasma

The concentrate of plasma platelets obtained by centrifugation of the patient's whole blood was named PRP. Platelets are non-nucleated cell fragments derived from megakaryocytes located in the bone marrow. Circulating anucleate platelets do not synthetize new proteins. All GFs and cytokines contained in cytoplasmic granules and delivered by platelets were produced by their mother cells, the megakaryocytes. The cytoplasm of platelets is divided in two regions: the chromomere, where granules accumulate, and the agranular hyalomere rich in cytoskeletal proteins. Platelet granules contain numerous proteins, several growth factors, and cytokines. When an injury or a cut occurs, platelets are "activated" and secrete these molecules that in turn act synergistically on local cells to promote wound healing by modifying the biological milieu to a suitable regenerative environment.[9,10]

The roles of platelets in homeostasis and preventing blood loss have been known for more than a century since they were first identified by Bizzozero in the 1880s.[11] More recently identified functions for platelets show that these cell fragments indeed participate in inflammatory processes and produce and release immunomodulatory factors.[12–17] such as soluble CD40 ligand (CD154), which perform key roles in innate and adaptive immunity crosstalk. Thus, the administration of a platelet concentrate to a recipient represents also the infusion of a huge amount of cytokines and chemokines. Last but not least, reports describe the presence of antimicrobial peptides in platelet secretory granules.[18-19]

Thus, preparation methods should be worldwide standardized to understand the putative mechanisms through which platelets or other cells present in peripheral blood are exerting their action on therapies of tissue regeneration and growth and to achieve consistent clinical outcomes.

The search for a repeatable and highly effective PRP preparation method led to the creation and optimization of protocols designed to maximize PRP regenerative and angiogenic properties.[20,21] The importance of a highly

repeatable and efficient protocol to prepare platelets for clinical use is justified by the fact that the concentration of GFs and cytokines in a given preparation is related directly to the platelet count and proteins present in plasma.[22]

2. METHODS

To the best of our knowledge, this study is the first of its kind, investigating the efficacy of plasma_rich platelate (PRP) on thin endometrium (TE) without embryo transfer.

All 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 April 2023, all the patients had Thin endometrium.

The age group included in the study was 33 – 45yrs.

Thin endometrium (TE), i.e., less than 6 mm endometrium after hormone replacement therapy (HRT).

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

The exclusion criteria were
Any hematological, immunological, or hormonal disorders.

Laboratory evaluation of thrombophilia, antiphospholipid antibodies, hormonal disorders, hematological.

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

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.

In our study We adopted
PRP was obtained from each patient and it was administreted intrauterine as three infusions administration PRPwas performed at three stages,three days: (at the8th,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.

So far, there are no studies confirming that the third injection increases the chances of pregnancy and childbirth,
We tried to focus on this, without transferring embryos.As a first study of its kind

3. 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 <0.001=0.003 was established as a statistical significance level.

4. RESULTS

PRP increased the endometrial growth respecting the initial thickness in all 10cases.

The patients had a thin endometrium (TE) less than7 mm at ovulation day in previous cycles.

Table 1: individual data of 10 women in our Study.

Table 1: individual data of 10 women in our Study.

N	Age (Years)	BMI (kg/m^2)	Thickness Before injection (mm)	Thickness After 1st injection (mm)	Thickness After 2nd Injection (mm)	Thickness After3rd Injection (mm)	hemical regnanc y	Abortion 1	Live Birth 1
1	34	20.7	5.90	6.20	6.90	9.10	+		
2	37	22.6	5.50	6.10	7.80	8.20			
3	33	27.5	4.30	5.50	6.90	7.30			
4	40	16.2	4.80	5.50	5.90	7.00		+	
5	33	17.7	5.10	6.10	7.80	8.30			
6	43	18.8	5.80	6.80	8.00	7.70	+		
7	45	20.7	6.30	6.90	7.00	8.30			+
8	41	16.2	4.70	5.00	7.00	7.00			
9	35	28.2	6.00	6.50	7.50	9.00			
10	37	20.3	5.00	6.10	7.80	10.40			

Table 2: baseline characteristics The average age of the women participating in the study was 37.8 ± 0.00 years with average BMI 18.95 ± 2.26 Kg/m^2 and average Infertility Duration of 3.2±3.02years.

Parameter	Minimum	Maximum	Mean ± SD
Age (years)	33	45	**37.8 ± 0.00**
BMI (Kg/m^2)			**18.95 ± 2.26**
Infertility Duration (Years)			**3.4 ± 3.01**
Parameter		*N (%)*	
Primary Infertility		**3 (30%)**	
Secondary Infertility		**4 (40%)**	
Repeated Abortion		**5 (50%)**	
Asherman		**0 (0%)**	
Endometeriosis		**0 (0%)**	
Fibroids		**0 (0%)**	

Table 3: Statistical characteristics of Endometria Thickness Before and after PRP Injection (of three injections).

Parameter	*Minimum*	*Maximum*	*Mean ± SD*
Thickness before Injection (mm)	4.3	6.3	5.35 ± 1.4
Thickness after 1st Injection (mm)	5.0	6.9	6.07 ± 1.21
Thickness after 2nd Injection (mm)	5.9	8.0	7.26 ± 0.2
Thickness after 3nd Injection (mm)	7.0	10.4	8.23±0.00

Table 4: Dependent T-Test for mean difference in Endometrial Thickness before and after 3rd PRP Injection.

Thickness Before infusion Mean ± SD (mm)	Thickness after 3rd infusion Mean ± SD (mm)	Mean Difference ± SD	Confidence Interval		P Value
			Lower	Upper	
5.35 ± 1.4	**8.23 ± 0.00**	**2.01 ± 1.21**	**1.99**	**2.55**	**<0.001**

Table summarizing study the outcome distributed according to the indication.

Regarding endometrium thickness, for all 10patients analyzed, the mean measured before PRP application was 5.35 ± 1.4mm; this value increased to 6.07± 1.21mm after the first PRP infusion, and to 7.26± 0.2 mm after the second PRP infusion, and to 8.23± 0.00 mm after the third PRP infusion,

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.

We had 10 patients:

Table 5: Study the outcome.

Endometrial thickness	8.23 ± 0.00
Chemical pregnancy	2/10 (20%)
Clinical pregnency	1/10 (10%)
miscarrige rate	1/10 (20%)
Live birth	1/10 (10%)

The total participants10 patients
2. participants were chemical pregnancy
The chemical pregnancy rate was 20%, (2 positive β-hCG out of 10 women);
2clinical pregnancy, The rate was 20%,
1early miscarriage, The rate was 10%,
1 live birth, The rate was10%, were recorded
The statistical analysis showed that day of PRP application was a relevant fact, and there was a statistically significant probability of achieving pregnancy when PRP infusion was carried out,of three infusion at (8th dy, 10th dy, 12th dy) of the women's menstrual cycle.

Compare the results of the two studies,
The two studies were conducted during approximately the same time of period of two groups of patients, who had a history of infertility with thin endometrium(TE)

The first study of 27 cases had studied during the period between October 2021 and November 2022, all patients had Thin endometrium.

Administration of PRP was performed at the10th, 12th day of the menstrual cycle,so Apply the adminestrations to (2 infusions).

The second study of 10cases, had studied during the period between October 2021 and April 2023, all patients had Thin endometrium.

Administration of PRP was performed at the 8th, 10th, 12th day of the menstrual cycle, so Apply the adminestrations to (3 infusions).

Table 6: study the Compare the results of the two studies.

study	Thickness Before infusion Mean ± SD (mm)	Thickness after infusion Mean ± SD (mm)	The outcome Chemical Abortion Live Birth Pregnancy
1	**6.07 ±0.71 (mm)**	**2nd 8.32 ± 0.80(mm)**	**18.5% 7.4% 11.1%**
2	**5.35± 1.4 (mm)**	**3rd 8.23 ± 0.00(mm)**	**20% 10% 10%**

So, In comparison between the results of the two studies, we find that the results were close, with no significant statistical difference, and this may be due to the small size of the sample in both studies.

We note that the results between the two studies, and increasing the number of infusions did not give higher results with a clear difference.

Comparison the results of improving endometrial thickness.

Comparing pregnancy outcomes, We found that the results were similar and that the increase in the number of infusions did not have a more effective role in pregnancy outcomes in a more significant way, Perhaps because of the small sample size, but in itself the results are important, and therefore needed Wider studies.

4. DISCUSSION

PRP is autologous blood plasma that has been enriched with platelets at about 4-5 times more than the circulating blood,[23] PRP can stimulate proliferation and regeneration with a large amount of growth factors and cytokines,[24] including PDGF, TGF, VGEF, EGF, fibroblast growth factor (FGF), insulin-like growth factor I, II (IGF I, II), interleukin 8 (IL-8) and connective tissue growth factor (CTGF). Currently.[25] PRP infusion is being increasingly used in several fields in medicine such as nerve injury, osteoarthritis, chronic tendinitis, bone repair and regeneration, cardiac muscles, alopecia, plastic surgery and oral surgery, but there is limited experience in gynecology and obstetrics (Alcaraz et al., 2015; Borrione et al., 2010; Patel et al., 2016; Yu et al., 2011).

For the first time, Chang reported the efficacy of intrauterine infusion of PRP for endometrial growth in women with thin endometrium. In that trial, PRP was infused in 5 women with inadequate endometrium who had poor response to conventional therapy during the FET cycle[26, 29].The proper response to treatment was reported in all of them, and normal pregnancy was reported in 4 women (Chang et al., 2015).

PRP is a type of leukocyte-free with a moderate and optimal platelet concentration; its clinical efficacy has been demonstrated in several medical fields.[26] Recently, the beneficial effects of PRP have been reported in gynecology, obstetrics, and reproductive medicine.[27,29] as an interesting therapeutic tool with minimal risks for disease transmission and immunogenic and allergic responses due to its autologous source endometrial thickness is a main factor for implantation and

pregnancy. Women with persistent thin endometrium often do not undergo embryo transfer,[30]. Several methods have been described for endometrial preparation but there is not any definitive method yet. In recent years, intrauterine infusion of G-CSF has been studied but inconsistent results have been reported. Some researchers reported that G-CSF favors endometrial growth and pregnancy, G-CSF is a cytokine that stimulates neutrophilic granulocyte differentiation and proliferation, it may induce endometrium proliferation and growth, thus improve pregnancy outcome. According to this hypothesis, local infusion of PRP that contains several growth factors and cytokines may improve endometrial growth and receptivity,[31]

Sak and co-workers investigated that the expression of growth factors in the endometrium of women with(RIF) is less than normal fertile women[32,33]. our study is therefore focused on this thin, free endometrium, whichis without current, orprevious fatel transfer(FIT), to study the degree of normal response, with these immune agents alone platelet-rich plasma (PRP), by enhancing the three-injection protocol.

In a study conducted in Spain 2022, where autologous plasma injection PRP was applied in three applictions, with embryo transfer, the following results were:

The average age of the wome participating in the study was 39 years endometrium thickness, for all 27 patients analyzed, the mean measure after the first PRP application was 6.3 ± 1.3 mm; this value increased to 7.4 ± 1.2 mm after the second PRPapplication and to 8.4 ± 1.6 mm after the third PRP infusion, including embryo transfer, the pregnancy rate was 59%.

5. CONCLUSION

So, the role of multiple autoinfusion of platelet rich plasma (PRP)(three infusions)

It has improved endometrial thickness and pregnancy outcomes ,and needs more follow-up and trials to obtain a higher rate of pregnancy outcomes.

Abbreviations
TE: thin endometrium
β-hCG: beta-human chorionic gonadotropin.
PRP: plasma rich platelat

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