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Review Article

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The Effectiveness of Autologous Platelet-Rich Plasma PRP In the Therapy of Infertile Women with Poor Ovarian Reserve POR, A Retrospective Chart-Review Study.

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Introduction

Platelet-rich plasma (PRP), also known as autologous platelet gel, is "autologous blood with concentrations of platelets above baseline levels, which contains at least seven growth factors". plasma rich in growth factors (PRGF), and platelet concentrate (PC), is a high concentration of autologous platelets suspended in a small volume of plasma after centrifugation [1]. More than 800 types of protein molecules, cytokines, hormones, and chemo-attractants are carried by the platelets [2]. When platelets get activated, numerous biologically active proteins that stimulate cell proliferation, growth, and differentiation are released. Activated platelets also release various types of growth factors like platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), fibroblast growth factor (FGF), epidermal growth factor (EGF), insulin-like growth factor (IGF-1), and hepatocyte growth factor (HGF) [3] Table 1.

Cell ratios in normal blood contain only 6% platelets, however, in PRP there is a concentration of 94% platelets. With its rich growth factor composition, has been already proven beneficial in regenerative therapy [4]. Some of the specific beneficial effects of PRP are accelerated angiogenesis and anabolism, inflammation control, cell migration, differentiation, and proliferation were identified by a few previous studies [5, 6]. As a result, PRP is nowadays used in various clinical scenarios that required improved tissue regeneration [7-9]. In maxillofacial surgery, neurobiology, orthopedics, sports medicine, and ophthalmology [3, 10]. Potential benefits of PRP have also been studied in the field of gynecology; a study revealed PRP can increase endometrial thickness and improve the pregnancy outcome with a thin endometrium [10]. According to Colombo GVL, PRP has the potential to reduce implantation failures by increasing the expression of adhesion molecules, and ovarian rejuvenation and folliculogenesis reactivation in peri-menopausal women [11].

To enhance the chance of pregnancy to whom having limiting factors limiting factor for the success of any treatment modality for infertility as in "Poor ovarian reserve (POR)" which associated with a reduction in quantity and quality of oocytes in women of reproductive age group. It may be age-related as seen in advanced years of reproductive life or may occur in young women due to diverse etiological factors.

Since the regulation of local health authority documented egg donation as a forbidden approach, Thus, the majority of women with POR need to undergo in vitro fertilization to achieve pregnancy, When the poor ovarian reserve overlapped with the problem of infertility in women, the interest in using assistive technologies to modify the results of ART in women with POR increased, and one of these therapeutic methods was rejuvenation Ovarian PRP, as sensational novel therapy has the potential to put a full stop to our long search for the question of poor ovarian reserve and getting a genetically linked baby. We review PRP to evaluate the effectiveness in the therapy of infertile women with poor ovarian reserve.

Table 1: Factors, released by platelets, effects the ovary.

Factor	References	Factor	References
CCL5 Chemokine (C-C Motif) Ligand 5	*Ledee et al. (2008). Machlus et al. (2016)*	BMPS (Bone Morphogenic Protein)	*Hussein et al. (2005). Kalén et al. (2008). Demiray et al. (2017)*
	Ben-Ezra et al. (1990). Reizel et al. (2010)	IL-8 Interleukin-8	*Arici (1996). Huang et al. (2017)*
Serotonin	*Amireault and Dubé (2005). Brenner et al. (2007). Henriksen et al. (2012). Cloutier et al. (2018)*	PF4/CXCL4 Platelet factor 4	*Deuel et al. (1981). Pervushina et al. (2004) Huang et al. (2016)*
PDGF platelet-Derived Growth Factor	*Hart et al. (1990). Nilsson et al. (2006). Valeri et al. (2006). Pinkas et al. (2008). Pascuali et al. (2015). Yeh et al. (2016)*	TGF-β1 Transforming Growth Factor Beta 1	*Assoian et al. (1983). Dragovic et al. (2007). Meyer et al. (2012)*
P-Selectin (CD62)	*Geng et al. (1997). Merten and Thiagarajan (2000)*	S1P Sphingosine-1-Phosphate	*Ono et al. (2013). Cheng et al. (2015). Urtz et al. (2015). Pors et al. (2020)*
SDF-1α/CXCL12 Stromal-cell Derived Factor 1 Alpha/Chemokine (C-X-C motif) ligand 12	*Kryczek et al. (2005). Holt et al. (2006). Massberg et al. (2006)* *Nishigaki et al. (2011)*	GM-CSF Granulocyte-Monocyte Colony Stimulating Factor	*Raidem et al. (2003). Lee et al. (2008). Peralta et al. (2013)*
VEGF Vascular endothelial growth factor	*Shweiki et al. (1993). Wynendaele et al. (1999). Duncan et al. (2008). Italiano et al. (2008)*	TIMP-4 Tissue Inhibitor Of Matrix Metalloprotease	*Radomski et al. (2002). Bu et al. (2006)*
TSP-1 Thrombospondin-1	*Jaffe et al. (1982). Disdier et al. (1989). Bender et al. (2019). Rival et al. (2019). Zaslavsky et al. (2010)*	FGF Fibroblast Growth Factor	*Nilsson et al. (2001). Pintucci et al. (2002)* *Ben-Haroush et al. (2005)*

Material and Methods

ESHRE consensus and Bologna criteria were acknowledged toward a uniform definition of POR in our study to choose the sample. Bologna criteria recommend the presence of at least two of the following three features for diagnosis of POR:

i. Advanced maternal age (≥40 years) or any other risk factor for POR.
ii. A previous POR (≤three oocytes with a conventional stimulation protocol).
iii. An abnormal ORT (i.e., AFC, 5–7 follicles or AMH, 0.5–1.1 ng/ml).

Subjects

223 women with low ovarian reserve were recruited "Sample size: 223" according to ESHRE and Bologna Criteria from 1st August 2017 to 1st April 2021 at The British-Syrian IVF and Fetal Medicine Centre, all women undergoing PRP treatment constituted the study population. The FSH, LH, E2, and AMH levels were determined before the PRP treatment to monitor the ovarian function changes if any, in addition to the routine tests of TSH, FT4, Prolactin, and CBC (FBC). Our study includes FSH, E2, AMH only.

Methods

Platelet-rich plasma (PRP) is prepared from fresh whole blood, which is collected from a peripheral vein, stored in acid citrate dextrose solution A (ACD-A) anticoagulant, and processed to increase platelets by separating various components of blood, hence the injected fluid prepared from autologous blood by centrifugation using Dr. PRP kits and equipment (USA). The consent form was given and signed.

Under sedation women had been undergone PRP intra-ovarian injection with 1,5 ml in each ovary using an egg collection needle, guided by vaginal ultrasound scan, The injections were repeated to those who had more than one failed ICSI previously with a willingness to do so after consenting them. Antagonist protocol was used for ovarian stimulation using HMG (Menopure, Ferring). The presence of developing follicles and oocytes collection was confirmed by a vaginal ultrasound scan.

2-4 months following PRP, the Ovarian reserve reviewed according to AFC and FSH level and E2 level prior and after PRP immediately prior to ICSI attempts, several retrieved oocytes, in addition, to review results of fertilization rate and Clinical Pregnancy rate (CPR), Miscarriage rate and we looked at the natural conception rate i.e., after the ICSI failed PRP attempt, the AFC showed no deference.

All candidates exposed to blood sample (CBC: Full Blood Counts) immediately prior to each attempt of PRP and all candidates out of the initial normal range of platelets level (200-450

per microliter) +/- hemoglobin less than 11 were excluded from our study, also who did not achieve the PRP criteria i.e., level of platelets must be at least 1,000,000 of platelets/in 5ml of plasma activation status.

Detailed history taking to couples including general health, Obstetrics and gynecology history, libido, sexual health, past fertility, any failed IVF attempt, sexual activity and previous exposure to surgery, drugs, mumps infection, and irradiation, physical examination. Vaginal and abdominal if indicated Ultrasound scan by an expert was taken, FSH, E2 while some other hormones which may influence the procedure e.g., TSH, FT4, and prolactin not included in this study but focused on FSH, E2 and AMH level. AMH was initially taken to cover the poor responder criteria however all couples of Male factors, Endometriosis factor and uterine factors were excluded.

Statistical analysis

The categorical variables were presented as frequencies and percentages and continuous variables were presented as mean ± standard deviations. The statistical difference between the initial FSH, E2, and post-procedure FSH and E2 for all patients included in this study were calculated by paired samples Wilcoxon Tests.

The analysis was performed in a 95% confidence interval using Statistical Package for Social Science (SPSS), version 25 (IBM, Armonk, NY, USA). Two authors (RA and ZK) independently scrutinized the titles and abstracts of the electronic searches according to the predefined eligibility criteria.

According to age factors, we divided the total sample into 3 groups: group 1 all women less than 38 years old, Group 2 all women between 38-42, group 3 women over 43: The mean ± SD age of all respondents was 37.825 years ± 6.5,

Table 2: Result by age category

	Sample Size	Positive bHCG No&Rate	Cancellation No& Rate
G1: <38	101 (45.29%)	17 (7.62%)	18 (8.07%)
G2: 38-43	81 (36.32%)	7 (3.14)	12 (8.38)
G3: >43	41 (18.39)	4 (1.97%)	19 (8.52)
Total	223 (100%)	28 (12.56)	49 (21.97)

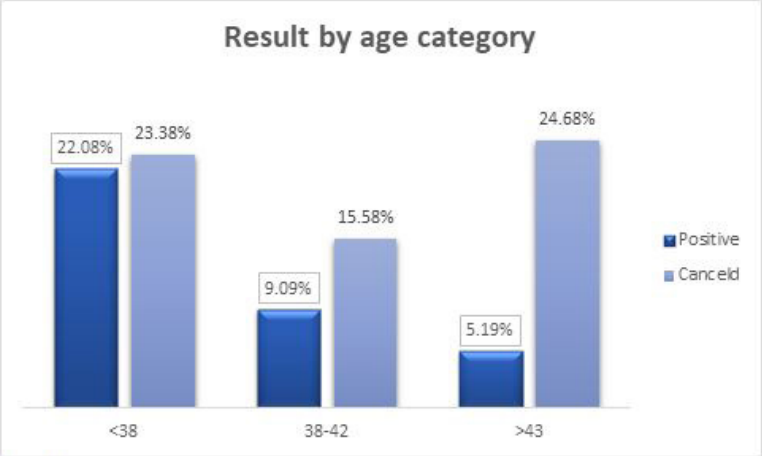

Figure 1: Result by age category

To understand the efficacy of our study we review our recorded data from 1st August 2017 to 1st April 2021 to whom did not receive any juvenile treatment with the same criteria as above i.e. (AMH less than 1.1 with FSH higher than 8.5)

Table 3: Result by age category (Control)

	Sample Size	Positive bHCG	Cancellation
G1C: <38	430 (43.97%)	31 (7.2%)	76 (17.67%)
G2C: 38-42	328 (33.54%)	20 (6%)	88 (26.8%)
G3C: >43	220 (22.49%)	4 (1.8%)	113 (51.36)
Total	978 (100%)	55 (5.6%)	277 (28.32)
G: group C: control			

According to reproductive history: If we consider the number of previous pregnancies into consideration (G4: no previous pregnancy) the total 91/223 (40.81%) out of those 10 were pregnant following ICSI (11.2%), while those who had previous 1 or more pregnancies G5 were 132/223 (59.19%) and 18 were pregnant following ICSI (13.4%), as we can see the cancellation rate in G4 is 29.87% and 33.77% in G5.

Table 4: Result by G/P

	No	Positive bHCG	Cancellation
G4 (G0/P0)	91 (40.81%)	11 (14.29%)	23 (29.87%)
G5 (G> = 1)	132 (59.19%)	17 (22.08%)	26 (33.77%)

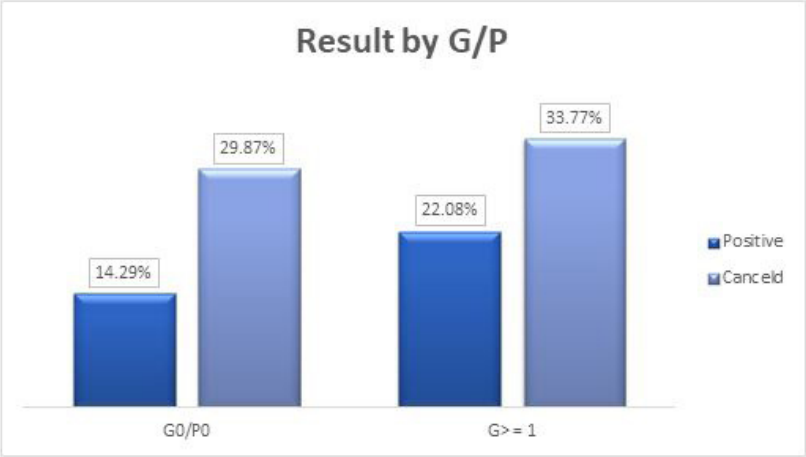

Figure 2: Result by G/P

Our recorded data (data pool of our center) from 1st August 2017 to 1st April 2021 to whom did not receive any juvenile treatment with the same criteria as above i.e. (AMH less than 1.1 with FSH higher than 8.5 and no other factors I.e., male factor, endometrial and uterine factors)

Table 6: Result by G/P (Control)

	No	Positive bHCG	Cancellation
G4C (G0/P0)	459 (46.93%)	24 (5.22%)	82 (17.8%)
G5C (G> = 1)	519 (53.07%)	31 (5.97%)	195 (37.5)
G: group C: control			

We extracted the number of collected oocytes before the PRP attempt and after, we found the total number of collected oocytes Before PRP attempts: 422 and after: 615, while the fertilization 377/ 615 (fertilization rate 61.30 % comparing with non-treated couples 32.7%), Fertilization failure rate showed FTF before PRP 39.81% (168/ 422) comparing with failed to fertilize rate 16.14% (36/ 223).

As for the mean of previse IVF attempts 4 ± 2, and number of ET was 283.

Table 7: Num of Oocytes before & after, FTF

	No of Oocytes in the last attempt before	No of Oocytes per attempt after	No of fertilized Oocytes	Previse Failed to Fertilize
Mean	1.89	2.76	1.69	0.75
Std. Deviation	1.35	1.98	1.37	0.83
Sum	422	615	377	168

Table 8: Num of IVF & ET

	No of previous IVF attempts	No of embryos transferred
Mean	3.57	1.27
Std. Deviation	1.67	0.98
Sum	795	283

Results

This Retrospective chart-review study was done to assess the effectiveness of intra-ovarian infusion of PRP in sub-fertile women in terms of improvement in ovarian reserve parameters and outcomes after assisted reproduction versus with no treatment.

Data showed that the miscarriage rate was 21.73% (5/23 positive result), also some women achieved pregnancy naturally regardless of assisted conception failure attempts, the total number was 7 while 5 ended up with delivery and 2 miscarriages.

We lost contact with most women who had IVF/ICSI attempt following PRP to assess the accumulation success rate with Natural conceptions.

Also, we reviewed suboptimal elevated FSH levels and high FSH > 15.1 in view of the number of collected eggs with their results.

Table 9: FSH levels and its results

FSH LEVEL	Patients	Collected Oocytes	Positive bHCG	Miscarriage	Cancelation
8.51-10.5	30	105 (24.88%)	6 (20%)	1 (0.54%)	0 (0%)
10.51-15.00	101	228 (54.03%)	17 (17.7%)	5 (2.24%)	8 (0.4%)
Over 15.01	92	89 (21.09%)	5 (5.1%)	4 (1.79%)	41 (18.39%)

Average FSH before PRP was 16.62 mIU/ml and after PRP was 16.032mIU/ml, we found a decrease in the Average value of the post-treatment level of serum FSH from the respective pretreatment level. The Average difference was 0.5, to be statistically significant (p-value 0.0).

While an increase in serum E2 with PRP infusion was found to be statistically not significant (p-value 0.077) (E2 before PRP is 35.105pg/ml while after PRP 36.229) [1].

We have not repeated AMH after PRP, whoever the Average of AMH: 0.424ng/ml prior to PRP injection.

Table 10: Statistics: FSH, E2, AMH

	AMH	FSH before Treatment	FSH after Treatment	E2 before Treatment	E2 after Treatment
Mean	.4243	16.6264	16.0318	35.1054	36.2297
Std. Deviation	.31394	8.05651	10.64103	12.14682	10.47757
Minimum	.01	9.50	1.00	7.00	11.00
Maximum	1.00	60.01	125.80	87.00	72.00

Shapiro-Wilks Normality Test. The Shapiro-Wilks test for normality is a test designed to detect all departures from normality. The test rejects the hypothesis of normality when the p-value is less than or equal to 0.05

Table 11: Tests of Normality (FSH, E2)

	Shapiro-Wilk		
	Statistic	df	Sig.
FSH before Treatment	.770	222	.000
FSH after Treatment	.521	222	.000
E2 before Treatment	.971	222	.000
E2 after Treatment	.979	222	.002

Wilcoxon signed-rank test is used to compare two related samples, matched samples, or to conduct a paired difference test of repeated measurements on a single sample to assess whether their population mean ranks differ.

Table 12: Wilcoxon Signed Ranks Test (FSH, E2)

	FSH after Treatment - FSH before Treatment	E2 after Treatment - E2 before Treatment
Z	-4.587-	-1.766-
Asymp. Sig. (2-tailed)	.000	.077

Wilcoxon signed-rank test is used to compare two related samples, matched samples, or to conduct a paired difference test of repeated measurements on a single sample to assess whether their population mean ranks differ.

Table 13: No PRP and its results

No PRP	Pt No	N0 oocytes	Positive	Misc	Cancelation
1	10	17 (1.7%)	0	0	6 (60%)
2	83	269 (3.24%)	12 (14.4%)	1	11 (13.25%)
3	127	323 (2.54%)	15 (11.8%)	4	31 (24.4%)
4	3	6 (2%)	1 (33.3%)	0	1 (33.3%)

7 women got pregnant naturally out of those 2 were miscarried.

Correlation

Correlation is a statistical measure that tells us about the association between the two variables. It describes how one variable behaves if there is some change in the other variable. If the two variables are increasing or decreasing in parallel, then they have a positive correlation between them and if one of the variables is increasing and another one is decreasing then they have a negative correlation with each other. If the change of one variable has no effect on another variable, then they have a zero correlation between them.

Both Pearson and Spearman are used for measuring the correlation but the difference between them lies in the kind of analysis we want. Pearson correlation evaluates continuous variables, While the Spearman correlation does not require that the variables be continuous, and when there are nominal variables, the sign has no meaning in the direction of the relationship.

Table 14: Correlation levels

Correlation coefficient value	Correlation Type
0	Null
[0, -0.4]	Low Negative
[-0.4, -0.7]	Moderate Negative
[-0.7, 1]	High Negative
-1	Perfect Negative
[0, 0.4]	Low Positive
[-0.4, 0.7]	Moderate Positive
[0.7, 1]	High Positive
1+	Perfect Positive

By studying the correlation matrix between the Initial hormone values and other quantitative variables according to the Pearson coefficient, we found several results, the most important of which are:

- There is a significant correlation between AMH and each of (FSH, Previous Failed to Fertilize). and it's a moderate negative correlation
- There is also a significant correlation between the AMH and each of (Number of Oocytes, Number of fertilized Oocytes, the number of embryos transferred), and it's a high positive correlation.
- There is a significant correlation between FSH and each of (Number of Oocytes, Number of fertilized Oocytes, and the number of embryos transferred), and it's a moderate negative correlation.
- There is also a significant correlation between FSH and Previous Failed to Fertilize, but it is a weak positive correlation
- There is a significant correlation between the E2 and Previous Failed to Fertilize, but it is a weak positive correlation.

Table 15: Pearson Correlation

		FSH	E2	IVF	Oocytes	FTF	N PRP	fertilize Oocytes	ET
AMH	Pearson	-.573-**	.017	-.082-	.771**	-.413-**	-.074-	.735**	.713**
	Sig	.000	.796	.225	.000	.000	.273	.000	.000
FSH	Pearson		-.128-	-.105-	-.566-**	.261**	.072	-.520-**	-.545-**
	Sig		.056	.119	.000	.000	.284	.000	.000
E2	Pearson			.146*	-.006-	.054	-.072-	-.029-	-.009-
	Sig			.030	.929	.421	.286	.666	.898
** Correlation is significant at the 0.01 level (2-tailed).									
* Correlation is significant at the 0.05 level (2-tailed).									

By studying the correlation matrix between the Initial hormone values and other quantitative variables according to the Spearman coefficient, we found several results, the most important of which are:

- There is a significant correlation between AMH and each of (Fertilized pregnancy result, Continuity of pregnancy). but it's a weak correlation
- There is also a significant correlation between the AMH and each of (Number of Oocytes, Number of fertilized Oocytes, the number of embryos transferred). and it's a high positive correlation.
- There is a significant correlation between FSH and each of (Fertilized pregnancy result, Continuity of pregnancy). but it's a weak correlation.

Table 16: Spearman Correlation

		result	Continuity pregnancy	Miscarriage	Spontaneous Pregnancy
AMH	Spearman	-.346-**	-.326-**	-.075-	.071
	Sig.	.000	.000	.263	.290
FSH	Spearman	.334**	.250**	.005	-.069-
	Sig.	.000	.000	.936	.304
E2	Spearman	-.063-	-.038-	-.023-	-.006-
	Sig.	.348	.573	.736	.929
** Correlation is significant at the 0.01 level (2-tailed).					

The variable of incidence of pregnancy result is not independent of the variable of the age categories neither the variable of Initial FSH levels, as the P-Value is less than 5% and therefore we reject the null hypothesis that the variables are independent.

This means that there is a relationship between the pregnancy result in different age categories, and there is relationship between the Fertilized pregnancy result in different Initial FSH levels.

Table 17: Chi-Square Tests (Age categories Vs Results)

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	20.906	4	.000
Likelihood Ratio	18.810	4	.001
Linear-by-Linear Association	6.054	1	.014
N of Valid Cases	223		

Table 18: Chi-Square Tests (FSH levels Vs Results)

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	50.596	4	.000
Likelihood Ratio	56.561	4	.000
Linear-by-Linear Association	28.043	1	.000
N of Valid Cases	223		

Regression

In statistical modeling, regression analysis is a set of statistical processes for estimating the relationships between a dependent variable (often called the 'outcome' or 'response' variable) and one or more independent variables (often called 'predictors', 'covariates', 'explanatory variables' or 'features'). this allows the researcher to estimate the conditional expectation of the dependent variable when the independent variables take on a given set of values.

Regression analysis is primarily used for two conceptually distinct purposes. First, regression analysis is widely used for prediction and forecasting. Second, in some situations, regression analysis can be used to infer causal relationships between the independent and dependent variables.

In statistics, logistic regression is a model that is used to predict the probabilities of the different possible outcomes of a binary dependent variable, given a set of independent variables (which may be real-valued, binary-valued, categorical-valued, etc.). while multinomial logistic regression is a classification method that generalizes logistic regression to multiclass problems, i.e., with more than two possible discrete outcomes.

An increase of a one-unit in the rate of the AMH leads to a 3.35% percent decrease in the probability of a negative result versus a positive result. A one-unit increase in the rate of the AMH leads to a 12.22% percent decrease in the probability that the result will be abolished versus a positive result. That is, the increase in the AMH positively affects the result.

An increase of a one-unit in the rate of the FSH leads to a 0.16% percent increase in the probability of a negative result versus a positive result. A one-unit increase in the rate of the FSH leads to a 0.33% percent increase in the probability that the result will be abolished versus a positive result. That is, the increase in the FSH negatively affects the result, even if it was a simple possibility.

Table 19: Regression AMH & Results

Multinomial Logistic Regression			
Fertilized pregnancy result[a]	B	Sig	Asymptotic Significance (2-sided)
Negative	Intercept	3.683	.000
	AMH	-3.355-	.000
Canceled	Intercept	4.697	.000
	AMH	-12.229-	.000
[a]The reference category is: Positive.			

Table 20: Regression FSH & Results

Multinomial Logistic Regression			
Fertilized pregnancy result[a]		B	Sig
Negative	Intercept	-.569-	.531
	FSH before Treatment	.165	.018
Canceled	Intercept	-4.805-	.000
	FSH before Treatment	.338	.000
[a]The reference category is: Positive.			

Discussion

We understand that our study covered the suggestion of items PRP inclusion which should include platelet count, activation status, activation agents, the origin of PRP, volume infused, an anticoagulant used, AMH level, detailed reporting of the participant's fertility history (Lloyd Atkinson et al, 2021 published in ESHRE).

Short communication at the ESHRE Annual Meeting indicated that infusion of PRP into the ovary of the premenopausal women led to the resumption of the menstrual cycle by direct injection of PRP into ovaries [2]. Other studies have reported increased AMH and decreased FSH levels in previous non-responders, leading to folliculogenesis, significant levels of oocyte retrieval, and in a handful of cases, spontaneous pregnancy (Sfakianoudis et al. 2018: Farimani et al. 2019. Pantos et al. 2019. Hsu et al, 2020).

The cancellation rate was higher in couples who did not receive any juvenile treatment from 1st August 2017 to 1st April 2021, Miscarriage rate and clinical pregnancy rate also natural conception rate regardless to the fact that the latter was subjective and we lost to follow up some of patients to be able to compare.

Conclusion

Autologous platelet-rich plasma (PRP) could improve the outcome of Ovarian Poor Responder Outcomes in the therapy of infertile women with moderate elevation of FSH level. Intra-ovarian autologous PRP infusion increases the ovarian reserve parameters resulting in increased collected oocytes, fertilization rate, as well as the formation of embryos which increase the chance of pregnancies. Whoever Long term safety of PRP must be robustly assessed (Harper et al, 2012), particularly in view of ART itself may increase the risk of birth defects (Luke et al, 2020),

There is a great need for future, high-quality randomized controlled trials to estimate its efficacy in terms of clinical pregnancy and live birth rate. Also, there is a need to identify an optimum level of serum AMH or another marker of ovarian reserve for the success of intra-ovarian PRP infusion and identify the subpopulation that would get the most benefit from PRP [12-16].

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13. Cytokine signalling is increasingly being shown to be involved in the interrelationship among the oocyte, granulosa and thecal cells, with dysfunction in this ecosystem resulting in deficiencies in follicle maturation, ovulation and luteinisation (Orisaka et al., 2006 12 ; Field et al., 2014 13)
14. Orisaka, M., Mizutani, T., Tajima, K., Orisaka, S., Shukunami, K. I., Miyamoto, K., & Kotsuji, F. (2006). Effects of ovarian theca cells on granulosa cell differentiation during gonadotropin-independent follicular growth in cattle. Molecular Reproduction and Development: Incorporating Gamete Research, 73(6), 737-744.
15. Field, S. L., Dasgupta, T., Cummings, M., & Orsi, N. M. (2014). Cytokines in ovarian folliculogenesis, oocyte maturation and luteinisation. Molecular Reproduction and Development, 81(4), 284-314.
16. A number of the cytokines that regulate follicle development are released by platelets through secretion of their alpha and dense granule contents during platelet activation (Table II).