The use of Autologous Platelet-Rich Plasma (PRP) versus no Intervention in Women with Low Ovarian Reserve Undergoing Fertility Treatment: A Non-Randomized Interventional Study

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- Abstract
- Purpose to Investigate the Impact of a 3-Month Course of Intra Cortical Injections of Autologous Platelet-Rich Plasma (PRP) upon ovarian Reserve Markers versus no Intervention in Women with Low Ovarian Reserve Prior to Undergoing Assisted Reproductive Technology (ART).

Methods:

- Prospective Controlled, Non-Randomized Study in Venezuela in Women with Abnormal Ovarian Reserve Markers
- **Primary outcomes**: were the change in FSH, AMH and AFC Pre- and Post-Treatment.
- **Secondary outcomes:**

1 Included the Number of oocytes

2 Biochemical/Clinical Pregnancy Rates

3 Miscarriage and Live Birth Rates.

Results:

- Eighty-three women were included, of which 46 Received PRP Treatment and 37 Underwent no Intervention.
- Overall Median Age was 41 Years (IQR 39–44).
- Biochemical Pregnancy (26.1% versus 5.4%, P = 0.02)
- Clinical Pregnancy (23.9% versus 5.4%, P = 0.03)
- There was no difference in the Rates of First Trimester Miscarriage and Live Birth between Groups.

Conclusion:

- PRP Injections are Effective and Safe to Improve Markers of low Ovarian Reserve Prior to ART

- Further Evidence is required to Evaluate the Impact of PRP on Pregnancy Outcomes.

Introduction

- Female Fetus peaks at 6 Million in the Second Trimester of Gestation and Steadily Declines Thereafter
- At Birth, Both Ovaries Contain 1–2 Million oocytes,
- The Rate of Follicle Degeneration Increases After the Age of 37 Years,
- Only 1000 oocytes, on Average, are Present at the Time of the Menopause

- Aging oocytes :

1 Errors in DNA Synthesis

2 Increased Rates of Aneuploidy

There is no known Effective Treatment to prevent, Delay or Reverse Ovarian Senescence.

- **Environmental factors reduce oocyte numbers and quality:**

1 Cigarette Smoking

2 Dietary Habits

3 Exposure to Chemo and Radio-Therapy.

Improving Ovarian Reserve

1.Antioxidant Diet:

- ✓ Vitamin C
- ✓ Vitamin E

2. Melatonin

3. De Hydro Epi Androsterone (DHEA)

4. Coenzyme Q10

The Applicability of PRP:

1 Therapeutic Agent in Nerve Injuries

2 Myocardial Infarction

3 Cosmetic Surgery

4 Eye Disease

5 Sports Medicine to Treat Ligament and Tendon Lesions

6 Very Few Studies have Investigated the Potential Applicability of PRP in Ovarian Tissue Regeneration

PRP in ART :

- women with a Thin Endometrium
- Recurrent Implantation Failure(RIF)
- poor Response to Controlled Ovarian Stimulation

Materials and methods

- **Inclusion criteria**:

1 Female age 38 years old and above

2 FSH, day 3 of the menstrual cycle) > 12 mIU/mL

3 Anti-Müllerian Hormone (AMH) < 0.8 ng/mL

4 Normal Uterine Cavity

- **Exciosion criteria**:

1 History of Pelvic Inflammatory Disease

2 Clinical/Biochemical Hyper Androgenism(PCO)

3 Tubal Factor Infertility

5 Endometriosis

6 Platelet or Thromboxane Synthesis Disorder

7 Severe Male Factor Infertility.

The Effect of PRP:

1. Release Multiple Bioactive Molecules and Growth Factors.
2. Induce Clotting
3. Inflammation
4. Neovascularization
5. Focal Tissue Repair

Plt Concentration in PRP:

- Concentrate Derived from Centrifuged Whole Blood with Platelet Concentrations up to seven times Higher than Circulating Serum, in Regenerative Medicine

PRP may be consist of:

- Growth Factors
- Transforming Growth Factor-β
- Insulin-like Growth Factors 1 and 2 (IGF-1 and IGF-2)
- Vascular Endothelial Growth Factor (VEGF)
- Epidermal Growth Factor (EGF)
- Basic Fibroblast Growth Factor
- Hepatocyte Growth Factor (HGF)

Patient Allocation

Women Planning to Undergo Fertility Treatment :

1 Timed intercourse

2 IUI

3 IVF/ICSI

Ovarian PRP injection:

- Participants Between Days 7 and 9 of the Menstrual Cycle for Three Consecutive Cycles (cycles 1, 2 and 3).
- Follicle Development Takes Approximately 90 to 120 days
- 5 Blood collection Tubes Containing Sodium Citrate 3.8% were filled with 4.5 mL of Blood Each and Centrifuged at 270g for 10 min. Following Centrifugation, 100 µL of the platelet-rich supernatant were transferred from each of 4 of the Original Blood Tubes and Mixed with 0.1 mL of 10% Calcium Chloride.

Controls

- Women who Receive Treatment with PRP were allocated to the Control Group, Measuring Ovarian Reserve Parameters in Cycles 1 and 4.

Conception

- Women in Both Groups were Followed up for a Total of 12 months
- IVF Short GnRH-Antagonist Protocol
- FSH from Day 3 of the Cycle:225 to 300 IU+HMG 75 to 150 IU FOR 10–12 days De-pending on Age, BMI, FSH and AFC

Outcome variables

- **The primary outcome :**

- ✓ AFC (TVS)
- ✓ FSH
- ✓ AMH (ELISA)
- ✓ in cycles 1 and 4 All samples containing baseline ovarian reserve markers

- **Secondary outcomes:**

- ✓ Number of Oocytes Collected and Fertilization Rates During IVF/ICSI
- ✓ rates of biochemical pregnancy
- ✓ clinical pregnancy
- ✓ ongoing (12 weeks' gesta- tion and above) pregnancy
- first trimester miscarriage (< 12 completed weeks' gestation
- live birth (≥ 24 completed weeks' gestation) per participant.

Table 2 Comparison of ovarian reserve parameters pre- and post-treatment

	PRP ($n=46$)				Control ($n=37$)			
	Pre-treatment	Post-treatment	*P* value	Median difference (95% CI)	Baseline	Follow-up 3 months	*P* value	Median difference (95% CI)
AMH (ng/mL)	0.62 (0.47 to 0.76)	1.01 (0.9 to 1.3)	< 0.001	0.5 (0.43 to 0.57)	0.68 (0.41 to 0.78)	0.58 ± (0.39 to 0.76)	0.15	−0.025 (−0.07 to 0.02)
FSH (mIU/L)	13.6 (12.9 to 17.5)	9.07 (8.3 to 10.5)	< 0.001	−5.5 (−6.3 to −4.9)	14.9 (13.1 to 17.8)	15.0 (13.4 to 17.9)	0.23	0.25 (−0.06 to 0.89)
Total AFC (*n*)	4 (3 to 5)	7 (6 to 8)	< 0.001	3.0 (3.0 to 3.5)	5.0 (2.0 to 6.0)	5.0 (2.0 to 5.0)	0.1	−0.5 (−0.5 to 0)

Values represent *n* (%) or median (IQR)

PRP, autologous platelet-rich plasma; *AMH*, anti-Müllerian hormone; *FSH*, follicle-stimulating hormone; *AFC*, antral follicle count

Pregnancy outcomes

- Treatment with PRP was significantly linked with higher biochemical (P = 0.02) and clinical pregnancy rates (P = 0.03)
- Although the Rates of First Trimester Miscarriage and Live Birth did not differ Between Treatment Groups
- A subgroup Analysis According to ART Modality (timed intercourse/IUI versus IVF/ICSI) did not Identify any Differences in Pregnancy Outcomes Between those who had Previously been treated with PRP and those who had Undergone no Intervention