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Original Research Article

Intraovarian platelet-rich plasma injection: a potential path to genetic parenthood for women with low ovarian reserve

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ABSTRACT

Background: The incidence of women with low ovarian reserve (LOR) presenting for ART is increasing. Infertility management is challenging since oocyte numbers are related to IVF success. The use of intraovarian platelet rich plasma (IOPRP) is emerging as a promising technique for ovarian rejuvenation. This study evaluates role of IOPRP in improving ovarian reserve markers, ovarian response and reproductive outcomes in women with LOR keen to achieve genetic parenthood.
Methods: This prospective observational cohort study was done on 85 women of Indian ethnicity 25-50 years, Poseidon group 3 and 4, infertility >3 years wih at least 1 previous IVF failure. One ml of PRP prepared by double centrifugation technique was injected into each ovary transvaginally. AMH, AFC, FSH, ovarian response measured pre and post IOPRP.
Results: At 8 weeks post PRP a statistically significant increase in AMH (0.57±0.33 ng/ml vs 0.96±0.49 ng/ml p<0.001), AFC (4.11±1.81 vs 7.81±3.35 p<0.001), number of oocytes retrieved (3.29±2.22 vs 5.52±3.66 p<0.001) and number of usable embryos (1.11±1.21 vs 2.33±2.12, p<0.001) was seen. Of women who underwent IVF 57.1% achieved clinical pregnancy. Overall Live birth rate was 38.09%, 8 women conceived without IVF with a live birth rate of 40%. Poseidon group 3 showed a greater improvement.
Conclusions: The study suggests that IOPRP treatment increases ovarian reserve markers and response and may be a viable alternative to donor oocytes in women with LOR wanting genetic parenthood.

Keywords: Intraovarian PRP, Low ovarian reserve, Poor ovarian response, Poseidon criterion, Donor oocyte

INTRODUCTION

The incidence of LOR in women of reproductive age presenting for assisted reproductive technology (ART) has been increasing steadily in recent years. In women over 35 years a decline is oocyte numbers and quality is expected.[1,2] However, a growing number of women under 35 years seeking infertility treatment are found to have a LOR and premature ovarian insufficiency (POI). Genetic, autoimmune, lifestyle and environmental factors have been implicated, though the precise reason is yet to be elucidated.[3] An aging ovary displays a decline in the primordial follicle stockpile, vascular insufficiency and a decrease in biological competence of the oocyte, resulting in reduced fertility.[4,5]

LOR leads to a poor ovarian response (POR) in *in-vitro* fertilization (IVF) cycles, a low oocyte yield and subsequently an adverse pregnancy outcome. The incidence of POR in IVF is estimated at 15-20%.[6] Management of infertile women with POR is challenging since oocyte numbers are related to IVF success.[7] The prognosis-based POSEIDON criteria are being used for characterization of POR patients to reduce heterogeneity in study protocols.[8]

The paradigm that ovaries have a fixed number of oocytes which decline with time [9]was challenged by Jonathan Tilly who suggested that there are dormant follicles and embryonic stem cells in the ovary (OSC's) that can be activated and could lead to enhancement of the follicular pool.[10] Ovarian activation or rejuvenation has thus become an area of intense research and numerous experimental treatments like surgical ovarian activation, intra-ovarian infusion of stem cells (ASCOT) or PRP, have been proposed.[11,12] Among these treatments, the infusion of autologous IOPRP stands out as the least invasive, making it a promising therapeutic option.

PRP, a concentrate of growth factors and cytokines was first used by Whitman et al in oral and maxillofacial surgery.[13] It is now widely used in many streams of medicine and has been a great success in the fields of dermatology and orthobiologics. Platelets have an inherent property of healing and repair due to the presence of growth factors and cytokines in their alpha granules, which are activated when tissue damage occurs. These factors promote cell differentiation, angiogenesis and inflammatory change.[5,14,15] The use of IOPRP for ovarian rejuvenation was first advocated by Pantos in 2016.[16] Subsequently, other authors have reported that IOPRP improves ovarian reserve (OR) markers, increases oocyte numbers, and improves pregnancy rates in patients with POR.[17-22] An improvement in embryo ploidy due to reduction in reactive oxygen species (ROS) has also been proposed.[23,24] Most studies indicate that IOPRP could be a viable option for treatment of patients with LOR and POI, unwilling to accept IVF with donor oocytes. Controversial results have been reported by some authors suggesting that there is no improvement in either OR markers or pregnancy outcome and that women with POI have 5-10% of getting pregnant even without any intervention.[25-27]

Aim

Aim of the study was to evaluate the efficacy of IOPRP in improving ovarian reserve biomarkers and reproductive outcome in women of Indian ethnicity belonging to POSEIDON group 3 and 4, unwilling to use donor oocytes.

Primary outcome: Assessment of improvement in ovarian reserve markers (AMH, AFC, FSH) and ovarian response (number of OR and usable embryos) after IO-PRP.

Secondary outcome: To analyze any improvement in clinical pregnancy, livebirth and miscarriage rate post IO-PRP.

METHODS

A prospective observational cohort study was conducted to assess ovarian reserve markers and IVF outcome in women of Indian ethnicity classified as POSEIDON group 3 and 4. The study was conducted at mother and child hospital and ferticity fertility clinics, New Delhi, India, between January 2020 to June 2023.

Inclusion criteria

Infertile women in the age group of 25-50 years, women classified as POSEIDON group 3 and 4. (AMH≤1.2 or AFC ≤5/ ≤3 oocytes retrieved in a previous cycle. Group 3<35 years, group 4 >35 years), women with at least one failed IVF cycle and women with ≥3 years of infertility were included.

Exclusion criteria

Women with endometriosis or any ovarian pathology, active infection, POI post gonadotoxic therapy, history of previous childbirth, endocrine disorders, thrombocytopenia, congenital abnormalities and patients with history of intake of antiplatelet or anticoagulant medications were excluded from the study.

PRP preparation and procedure

PRP was prepared by a double centrifugation technique to separate the pellet of platelets from the whole blood. 30 ml of blood was drawn and mixed with 10ml of ACD-A solution. After 5-10 minutes at room temperature first centrifugation was done at 200g for 10 minutes, the plasma layer and buffy coat containing platelets was transferred to a fresh conical tube and centrifuged at 500g for 8 minutes. The resulting pellet of platelets was mixed with 2-4 ml of supernatant and used for treatment directly allowing for spontaneous activation in the tissue. External activators like calcium chloride were not used as external activation reduces the duration of action. Platelet count was done before and after preparation. A platelet concentration of more than 6 times the baseline was achieved in all patients.

Intraovarian injection

The procedure was performed under short general anaesthesia within half an hour of PRP preparation, in the follicular phase of the cycle. One ml of PRP was injected into the ovarian cortex and medulla at multiple (approximately 4-5) sites transvaginally, under ultrasound guidance, using a 35 cm 17G single lumen needle. The needle was pre-loaded and 0.5- 1ml of plasma was pushed in after the PRP to prevent loss in the needle dead space. No adverse effects were reported. Patients were discharged after a short observation period.

Patient assessment and follow-up

Serum anti mullerian hormone (AMH) and follicle stimulating hormone (FSH) levels and antral follicle count (AFC) were determined on day 2 or 3 of the menstrual cycle prior to PRP injection and at first and second menstrual cycle following PRP. Patients who had an AFC of <3 and AMH ≤0.2 ng/ml at the second estimation went through another one or 2 cycle of PRP before COS. Since

the duration of action of released growth factors is limited, multiple cycles may enhance action. After 3 cycles of IOPRP, controlled ovarian stimulation (COS) was carried out irrespective of increase in AFC or AMH.

Controlled ovarian stimulation and IVF

Controlled ovarian stimulation was carried out from day 2 of the second menstrual cycle after IOPRP, approximately 6-8 weeks after PRP injection. A flexible GnRH antagonist protocol was used, the starting dose was based on patient's age, BMI, ovarian reserve and previous ovarian response. COS was done with recombinant follicle-stimulating hormone (follitropin-alfa Gonal-f®, EMD Serono, Inc.,) and Menopur (highly purified HMG-Ferring Pharmaceutical Ltd.) in the ratio of 2:1. GnRH antagonist (Cetrolix, Intas Pharmaceuticals Ltd.) was started according to the flexible protocol. A dual trigger with Injection human chorionic gonadotropin 5000 IU and triptorelin 0.2 mg s/c was used and transvaginal ultrasound guided ovum pick up performed 34 hours later under a short anaesthesia.

Embryo development: Intra-cytoplasmic sperm injection (ICSI) was used to achieve fertilization for all patients. All embryos were cultured to blastocyst stage and pre implantation genetic testing for aneuploidy (PGT-A) was offered when good quality blastocysts were available. Embryos were cryopreserved and frozen embryo transfers (FET) were carried out subsequently in a hormone replacement (HRT) cycle. A single embryo was transferred if a euploid embryo was available, in other patients the preference was to transfer 2 embryos.

FET and luteal phase support: For HRT 6 mg /day of estradiol valerate was started from cycle day2/3 after a baseline ultrasound and increased as per individual requirement. Progesterone was started when the endometrial lining reached 7 mm and the serum progesterone (P4) value was less than 0.9 ng/ml. For luteal phase support (LPS) progesterone was give as aqueous based injection 50 mg s/c daily and vaginal pessary 400 mg twice a day. LPS was increased if serum P4 level on day of FET was below 15ng/ml as per our clinic protocol.

Pregnancy confirmation: Serum ß-HCG level of more than 25 mIU/ml was used for pregnancy confirmation. Clinical pregnancy was diagnosed by ultrasound visualization of one or more gestational sacs. Miscarriage was defined as clinical pregnancy loss before 12 weeks of gestation and live birth was defined as the delivery of a live baby after 24 weeks of gestation.

Statistical analysis

The presentation of the categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means±SD and as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Shapiro-Wilk test. The cases in which the data was not normal, we used non parametric tests. The comparison of the variables across follow up which were quantitative and not normally distributed in nature were analysed using Wilcoxon signed rank test and variables which were quantitative and normally distributed in nature were analysed using paired t test. Spearman rank correlation coefficient was used for correlation of age with increase in AMH, AFC and ovarian reserve and usable embryos. The data entry was done in the Microsoft excel spreadsheet and the final analysis was done with the use of statistical package for social sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

RESULTS

Eighty-five women who fulfilled the inclusion criteria were enrolled in our study. Average age of the participants was 37.75±3.8 and the mean BMI was 25.98±4.59 (Table 1) Of these 7 women were lost to follow-up and 2 opted for IVF cycle with donor oocytes. Ovarian reserve assessment was completed in 76 women. Ten patients elected to go for either follicular monitoring and timed intercourse (TIC) or ovulation induction (OI) and IUI in the period before starting COS and 3 women discontinued treatment. IVF was performed in 63 women. In 8/63 (12.6%) patients no oocyte was retrieved despite an increase in AMH levels. Of the women in whom at least one mature oocyte was aspirated, 47 (74.6%) had one usable embryo after the PRP intervention (Figure 1).

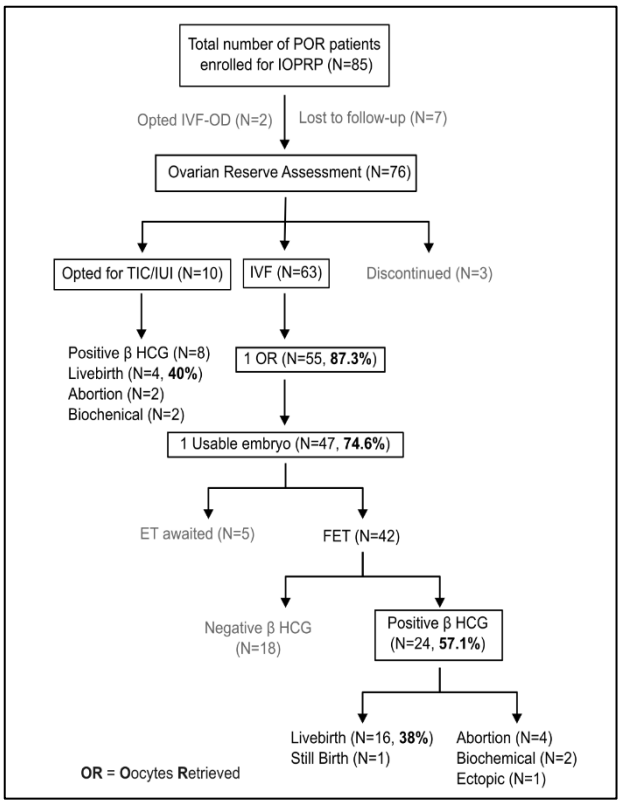

Figure 1: Study population and the clinical outcomes.

Table 1: Demographic characteristics of the study population.

Demographic characteristics	Mean±SD	Median (25 h-75th percentile)
Age (in years)	37.75±3.8	38 (35-40)
Body mass index (kg/m^2)	25.98±4.59	25 (22-28.5)

Six to eight weeks post PRP instillation we found a statistically significant increase in AMH values (0.57±0.33 ng/ml vs 0.96±0.49 ng/ml respectively p<0.001) and AFC (4.11±1.81 vs 7.81±3.35 respectively p<0.001). We did not notice a significant change in the FSH levels post PRP (11.9±16.57 vs 8.93±6.13 p=0.166 respectively). We also found a statistically significant increase in number of oocytes retrieved (3.29±2.22 vs 5.52±3.66 respectively p<0.001) and usable embryos formed (1.11±1.21 vs 2.33±2.12 p<0.001) after PRP (Table 2).

Of all the women who developed embryos after PRP treatment 42 underwent FET, 24/42 (57.1%) achieved a clinical pregnancy, 16/42 (38.09%) had a livebirth, (4/24) 16.7% had a miscarriage at 5-7 weeks of gestation and 8.3% (2/24) had a biochemical pregnancy. There was one ectopic pregnancy and one patient underwent an MTP for congenital abnormalities in the fetus. Five women have not come back for FET so far due to personal reasons.

PGT-A was performed in 20 women who had biopsiable blastocysts. Of these 55% women (11/20) had at least one euploid embryo. Eight of these 11 women underwent a euploid transfer and five (62.5%) went on to deliver at term. One patient had a biochemical pregnancy and another required a termination of pregnancy at 16 weeks for congenital anomaly (Table 3).

Of the 10 women who elected to try follicular monitoring with TIC or OI with IUI, eight achieved conception PR (80%). Majority of them conceived within 1-3 months (mean time 1.87 months) after the PRP procedure and 40% (4/10) went on to have a live birth. The miscarriage rate was 25% (2/8) and biochemical pregnancy rate was 25% (2/8) (Table 3). Duration of infertility in these patients ranged from 3-7 years, number of previous failed IVF were 1-2, mean pre-PRP AMH was 0.45 ng/ml (0.09-0.74 ng/ml) and the average age was 38 years (33-42 years) (Table 4).

We observed a significant negative correlation between age and the increase in AMH, AFC, and OR, indicating that women belonging to Poseidon group 3 tend to experience greater improvements in their ovarian reserve markers post-PRP treatment particularly the AMH values (rs=-0.273).

We did not find a correlation with BMI (Table 5).

Table 2: AMH, AFC, FSH, OR, usable embryos values pre and post IO-PRP.

Clinical variables	Mean±SD		Median (25th-75th percentile)		P value
	Pre-PRP	Post PRP	Pre-PRP	Post-PRP	
AMH (ng/ml)	0.57±0.33	0.96±0.49	0.59 (0.37-0.88)	0.99 (0.64-1.28)	<0.0001†
AFC	4.11±1.81	7.81±3.35	4 (3-5)	8 (5-10)	<0.0001*
FSH	11.9±16.57	8.93±6.13	7.7 (5.49-11.3)	7.95 (6.35-9.4)	0.166*
OR	3.29±2.22	5.52±3.66	3 (2-5)	6 (3-7.75)	<0.0001*
Usable embryos	1.11±1.21	2.33±2.12	1 (0-2)	2 (0.5-3)	<0.0001*

†Paired t test, *Wilcoxon Signed ranks test.

Table 3: Reproductive outcome of 42 frozen embryo transfers and 10 non-IVF patients.

Outcome	Patient proportion
Outcome for FET	
Clinical pregnancy	24/42 (57.1%)
Live birth	16/24 (38.09%)
Miscarriage	4/24 (16.7%)
Biochemical pregnancy	2/24 (8.3%)
Blastocysts biopsied	20/47 (26.5%)
Euploid blastocyst	11/20 (55%)
Live birth with 8 euploid embryos	5 /8 (62.5%)
Outcome for TIC/IUI	
Clinical pregnancy rate	8/10 (80%)
Live birth	4/8 (50%)
Overall live birth	4/10 (40%)
Miscarriage	2/8 (25%)
Biochemical pregnancy	2/8 (25%)

TIC: Timed intercourse, IUI: Intra-uterine insemination

Table 4: Demographic characteristics of the patients who conceived naturally/IUI post IO-PRP.

Clinical variables	Mean (Min-max)
Age (in years)	38.25 (33-42)
Duration of infertility (in years)	4.6 (3-7)
Number of menstrual cycles taken to achieve pregnancy after PRP	1.87 (1-3)
Pre PRP FSH (mIU/ml)	8.53 (4.1-13)
Pre PRP AFC	3.6 (2-6)
Pre PRP AMH (ng/ml)	0.45 (0.09-0.74)

Table 5: Correlation of age and with AMH, AFC and OR.

Clinical variables	AMH	AFC	OR
Age (in years)			
Correlation coefficient	-0.273	-0.299	-0.278
P value	0.024	0.013	0.029
Body mass index (kg/m^2)			
Correlation coefficient	-0.072	0.106	-0.015
P value	0.554	0.384	0.906

DISCUSSION

It is ironical that though longevity of life has increased in the last two centuries biological aging of the ovary appears to have accelerated. Golezar et al estimated that globally 3.7% women presented with POI and 12% women suffered early menopause (menopause before the age of 45 years.[28,29] Understandably, the number of women with LOR seeking ART is increasing. Majority of these young women are unwilling to undergo IVF with donor oocytes and would prefer to try an experimental treatment to have a child who is genetically their own, however slim the chances of success.

Numerous adjuvants and ovarian stimulation protocols have been advocated for enhancing oocyte numbers in LOR and POI patients, but none have met with much success.[30] Of the many regenerative therapies for rejuvenation and /or reactivation of ovarian function that have been proposed in recent years, infusion of autologous PRP into the ovary seems to be the most promising. Its advantage lies in the fact that it is prepared from the patient's own blood so precludes immune intolerance, is easy to prepare and is minimally invasive. Platelets are involved in tissue regeneration and healing and this property has been harnessed for use successfully, in many streams of medicine.

Ovulation is associated with local epithelial injury and tissue repair and the molecular events associated with tissue repair appear to be similar to those required for ovarian rejuvenation.[17] Platelets contain a number of growth factors which have a role in follicular growth and oocyte maturity namely, the transforming growth factor-beta 1 (TGF -β), growth differentiation factor-9 (GDF-9), vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IGF-1). GDF-9 is involved in oocyte maturation and has been found to be mutated in POI.[31] Growth factors important for vascular support, and ovarian function-the platelet-derived growth factor (PDGF) and bone morphogenic proteins (BMP) are also present in platelets.[23]

The results of our study are in concurrence with studies done by other authors who reported an increase in biomarkers of ovarian reserve and an increase in number of oocytes retrieved after IOPRP. The CPR and LBR achieved in these studies were in the range of 20% and 7% respectively.[19-22,25] Our study showed a significant increase in AMH and AFC, the number of oocytes retrieved and usable embryos. 87.4% of our patients post PRP had at least 1 oocyte recovered and 74.6% had at least one usable embryo. We observed a CPR of 57.1% and LBR of 38.09% and miscarriage rate was 16.7%. The most heartening aspect of IOPRP treatment is the enhancement of fertility parameters that allow for spontaneous pregnancy, probably due to rejuvenation or restoration of the ovarian niche. 80% of women who conceived with timed intercourse or IUI post PRP, did so within 1-3 months of the PRP procedure, 40% of them had a live birth. Spontaneous conceptions post IOPRP have been reported many of studies.[16,19,18,31]

No improvement in either OR markers, oocyte numbers or PR was reported in the multicentric study done by Herlihy et al.[26] Strangely COS for IVF was started in the cycle immediately after IOPRP. The timeline of PRP action in ovarian reserve enhancement in most studies is approximately 2-3 months though Melo et al reported an earlier rise.[21,33] This is in accordance with the physiological time line determined for follicular recruitment, 120 days for the primary follicles to reach the secondary follicle stage, and 71 days from the secondary to the early antral stage.[34] The increase in AMH in our study too occurred at 6-8 weeks after PRP and a decline of AMH was observed in patients beyond 3 months. This points to activation of dormant secondary follicles-a stage

in folliculogenesis when theca vascularization is initiated. This would in theory, allow for better delivery and action of the growth factors and cytokines. In some patients despite an increase in AMH no oocyte was recovered, this was observed in 12.6% of our patients. The fact that AMH is secreted by granulosa cells and not the oocyte could explain this outcome. In menopausal patients the return of menstrual function observed, points to an improvement in steroid secretion by the granulosa cells which in turn would lead to a drop in FSH.[31]

Though the exact mechanism of action of IOPRP is unknown many hypothesis have been put forward. It is believed that PRP can restore the ovarian microenvironment and promote development of primitive and primary follicles to pre-antral stage.[32] The angiogenic properties in PRP correct ovarian hypoperfusion, improve tissue oxygenation and aid ROS clearance thereby reducing degeneration and atresia and promoting an improvement in mitochondrial function.[35,36] Positive effects on vascular density of ovarian tissue grafts have been reported in in-vitro experiments.[37] It has also been suggested that IOPRP treatment could enhance ovarian function both by stimulating dormant follicle and inducing differentiation of potential stem cells into new oocytes thus improving both quantity and quality.[33] The timeline observed in most studies for AMH increase after PRP does not support the theory of stem cell differentiation.

Oxidative stress is associated with chronic low-grade inflammation which is implicated in ageing.[38] The increased ROS associated with a functionally aging ovary leads to altered communication between the oocyte and granulosa cells, telomere shortening, mitochondrial dysfunction and meiotic errors in the oocyte.[4,39] Decrease in ROS enhances vascularity and functionality of the ovarian niche thereby improving mitochondrial function and meiotic aberrations in the oocyte which in turn leads to improvement in embryo ploidy.[23] Twenty women in our study had biopsiable blastocyst and underwent PGT-A. The 55% (11/20) of them had at least one euploid embryo, and 2/20 (10%) had a low-grade mosaic for transfer, despite very low AMH and oocyte numbers, pointing to the probable role of an improvement in the ovarian microenvironment by IOPRP.

It has been suggested that the mechanical effect of the injection may be the mechanism behind the increase in oocyte numbers acting perhaps by disrupting the HIPPO signals.[11] A recent double blind RCT where patients and controls underwent 3 cycles of retrieval reported an increase in number of mature oocytes in successive egg retrievals however the increase was significantly more in the PRP arm.[40] The PRP in this study was injected at the time of 1st OPU when very little ovarian tissue is visible because of the stimulated follicles, leading perhaps to a sub-optimal dispersion of growth factors into the dormant follicles or preferential diffusion into the aspirated follicles resulting in enhancement of luteal function rather than activation of dormant follicles.

It has been argued that women with POI have 5-10% chance of getting pregnant even without any fertility treatment.[25-27] Our study reports a LVBR of 38% with IVF and 40% in the TIC and IUI group. Considering that success rates of less than 5% are reported with IVF in LOR patients, this increase is very relevant.[33]

We did not use activated PRP in our study as duration of growth factor action is shorter and its efficacy over non-activated PRP has not been proven.[5] Our study suggests that it may not be necessary to add that extra step in IOPRP preparation.

We acknowledge that IOPRP is still in its nascent stage, and several concerns need to be addressed. These include the standardization of preparation and procedure. Risks of procedure include, infection, abscess formation, vascular injury, ovarian tissue necrosis and the possibility of malignancy due to increased cellular proliferation.[5,41]

Limitations of the current study, such as its small size and lack of control groups, highlight the need for caution. Women in this category are often reluctant to be relegated to a no-intervention group, hence the patient's previous IVF cycle parameters were used for comparison.

CONCLUSION

The ability of IO-PRP to improve ovarian reserve biomarkers along with ovarian response, and reproductive outcomes, makes it a viable alternative to IVF with donor oocytes in women belonging to POSEIDON group 3 and 4. Our study showed an increase in AMH, AFC and number of oocytes retrieved. A CPR of 57.1%, MR of 16.7% and a LBR of 38.09% was achieved in women who underwent IVF post IO-PRP. LBR achieved with simpler treatments like OI and IUI or just follicular monitoring and TIC subsequent to IOPRP was in the range of 40% which is very encouraging and reassuring. Though large randomized controlled trials are required to confirm these findings, offering IOPRP to women with LOR desperate to have a genetic child may be considered.

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