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A Study to Assess the Effectiveness of Intra-Ovarian Infusion of Autologous Platelet-Rich Plasma in Patients with Poor Ovarian Reserve or Ovarian Insufficiency

[1]Emrana Rahman, Director, Janm IVF Centre, Bhagalpur, Bihar, India

Corresponding Author: Emrana Rahman, Director, Janm IVF Centre, Bhagalpur, Bihar, India

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Abstract

The development of autologous platelet-rich plasma (PRP) therapy for infertile patients with premature ovarian failure is a breakthrough. A systematic search was conducted using pertinent search terms in electronic databases like Medline to examine the effectiveness of intra-ovarian infusion of autologous PRP on the improvement of ovarian reserve parameters and subsequent artificial reproductive technique (ART) cycle outcomes in infertile women with poor ovarian reserve or premature ovarian insufficiency. Our systematic analysis includes all different types of research that assessed the effects of intra-ovarian infusion of PRP in subfertile women for diminished ovarian reserve (DOR) or premature ovarian insufficiency (POI), except for case series, case reports, and review articles. Each qualified study's data was taken out and cross-checked by the authors. The effects of intraovarian PRP infusion on ovarian rejuvenation are promising, and the outcomes of the succeeding intracytoplasmic sperm injection (ICSI) cycle are positive. In terms of an improvement in ovarian reserve parameters (increase in serum anti-mullerian hormone or antral follicle count or decrease in serum follicular stimulating hormone), PRP intervention was found to be effective. After intra-ovarian PRP infusion, ICSI cycle performance was found to be improved when compared to their prior cycle without PRP infusion in terms of the total number of oocytes retrieved, number of two-pronuclei embryos, number of fertilization rate, number of cleavage stage embryos, number of good quality embryos, and cycle cancellation rate.

Keywords: PRP, ICSI. ART, POI, DOR

Introduction

The primary limiting factor for success in both spontaneous conception and assisted reproductive technology (ART) is a gradual fall in the amount and quality of the oocyte reserves related to ovarian ageing [1]. These older oocytes are also more likely to make mistakes during cell division and DNA synthesis, which increases the likelihood of aneuploidy and congenital abnormalities in the offspring [Figure 1; 1].

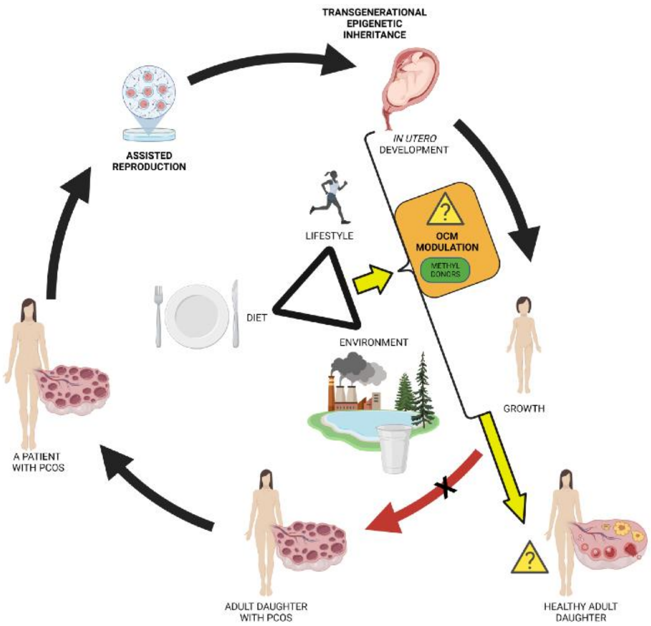

Figure 1: Epigenetics and Translation in oocyte maturation and embryo development.

Numerous therapeutic approaches, such as antioxidant dietary supplements comprising vitamins C and E, melatonin, dehydroepiandrosterone (DHEA), and coenzyme Q10, have been attempted to address this problem in the absence of a cure for ovarian senescence [2]. Their overall efficacy is still lacking, and the evidence to support them is equivocal [3]. Currently, in vitro fertilization (IVF) is frequently used in conjunction with an oocyte donation program or adoption to address infertility caused by ovarian insufficiency [4]. Recently, methods for restoring ovarian function have been thoroughly researched and may help these people have healthy, genetically related babies.

Researchers are examining the effects of platelet-rich plasma (PRP) in the treatment of disorders including diminished ovarian reserve, premature ovarian failure, etc. because it has been used successfully in regenerative medicine. [5]. The development of autologous PRP therapy reveals a ground-breaking strategy with encouraging outcomes. However, there isn't much research out there right now that deals with this problem. To investigate the effects of intra-ovarian injection of autologous PRP on ovarian rejuvenation, this systematic review was carried out. Infertile women with poor ovarian reserve or premature ovarian insufficiency were the target population for this study, which aimed to determine the effectiveness of intra-ovarian infusion of autologous platelet-rich plasma (PRP) on the improvement of ovarian reserve parameters and the subsequent artificial reproductive technique (ART) cycle outcomes.

Methodology

In order to determine whether intra-ovarian PRP injection in sub-fertile women improves ovarian reserve measures and outcomes following assisted reproduction, a systematic study was conducted.

We complied with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Handbook for Systematic Reviews of Interventions. Within a year, a thorough search was conducted in electronic databases like Medline. We used search terms like "In Vitro Fertilisation" OR "IVF" OR "Intracytoplasmic Sperm Injection" OR "ICSI" OR "Embryo transfer" AND "Platelet-Rich Plasma" OR "PRP" OR "Autologous Platelet-Rich Plasma" OR "Platelet-Rich Plasma" and "premature ovarian failure" OR "decreased ovarian reserve" OR "premature menopause" etc.).

Inclusion Criteria

Our systematic analysis includes all studies that assessed the effects of intra-ovarian PRP injection in sub-fertile women for diminished ovarian reserve (DOR) or premature ovarian insufficiency (POI). Case-control studies, cohort studies, clinical trials, and other types of studies were all included in this study.

Exclusion Criteria

This systematic review examined information on ovarian reserve measures and intracytoplasmic sperm injection (ICSI)/in vitro fertilization (IVF) cycle features. We omitted case series, case reports, and review papers from our analysis.

Selection of studies, data extraction, and quality evaluation

In accordance with the predetermined eligibility criteria, two writers independently examined the titles and abstracts of the electronic searches. Full articles for pertinent research were obtained. The three authors and the two authors extracted the data from each study that was eligible and cross-checked it. Using the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) methods for assessing the risk of bias in prospective observational studies, the quality of the included studies was evaluated in accordance with the criteria [6]. Three studies were determined to have a low risk of bias. This is illustrated in the Appendix.

Meta-analysis

The lack of available studies and the heterogeneity of the included outcomes precluded the meta-analysis from being used as intended.

Results

The Literature Search Summary

907 publications were found after the initial electronic literature search. After removing duplicates and unrelated papers, we discovered 15 pieces of research that might be suitable. Eleven articles were cut after reviewing the full texts of those 15 articles. In the end, four studies [7–10] were included in our systematic review.

Characteristics of the study

We have incorporated trials that assessed the efficacy of PRP in infertile women with low ovarian reserve, early ovarian failure, or menopause [11] into this systematic review. Three of the four included studies were quasi-experimental (uncontrolled before and after investigations), while one was a non-randomized clinical trial. AMH, FSH, and antral follicle count (AFC) measurements of the ovarian reserve were compared in all investigations before and after PRP injection. In the two studies, the ICSI cycle's results were analyzed [12–13].

Ovarian reserve specifications

Serum Anti-Mullerian Hormone (AMH) levels increased following PRP therapy for the cohorts with poor ovarian response, early ovarian insufficiency, perimenopause, and menopause, respectively, according to the study by Sfakianoudis et al. [14]. With p-values <0.0002 in each group, the difference was determined to be statistically significant.

The median value of the post-treatment level of blood AMH (in ng/ml) was higher than the corresponding pre-treatment level, according to Melo et al. [15]. The increase in serum AMH with PRP infusion was discovered to be statistically significant (p-value <0.002), with a median difference of 0.4 (0.42 to 0.56).

The studies also revealed that there was a statistically significant difference in the level of serum AMH following intra-ovarian PRP infusion (p-values of <0.02 and <0.0015 for the respective studies) [17], discovered that platelet count is a parameter that is likely to predict AMH response to intra-ovarian PRP injection.

All the study's cohorts had lower serum FSH levels after receiving PRP treatment [16]. All cohorts had statistically significant decreases in blood FSH levels, with the exception of the group of women with inadequate ovarian reserve (p-value = 0.1341) (p-values for the cohorts with early ovarian insufficiency, perimenopause, and menopause, respectively, were 0.0002, 0.0023, and 0.0002). According to Melo et al., the median post-treatment levels of serum FSH decreased, with the difference being statistically significant (p-value -0.001), with a median difference of 5.4 (6.2 to 4.8) [15]. The study indicated that the median pretreatment and posttreatment serum FSH concentrations (all values in mIU/ml) were 41.9±24.7 and 41.6±24.7, respectively [21].

AFC, or Antral Follicle Count

The studies demonstrated an increase in antral follicle count (AFC) after PRP treatment, and this increase was statistically extremely significant with p-values of <0.0002 in each study. Once more in the trial, the average antral follicle count values for pretreatment and posttreatment were discovered to be 0.4±0.4 and 1.6±1.3, respectively, demonstrating a statistically significant increase (p-value= 0.02) [20,21].

Results from the ICSI Cycle

ICSI cycle after PRP, using the previous cycle as a control [21]. They found that the cancellation rate (30% versus 63.3%; p-value< 0.0191) and the average number of retrieved oocytes (3.37±1.54 versus 1.20 ±0.76; p-value <0.0001) were all higher in the post-PRP ICSI cycle than in the control cycle. They also found that the average number of mature oocytes (2.97±1.38 versus 1.00±0.79; p-value <0.0001), number Additionally, more high-quality embryos were created during the post-PRP ICSI cycle than during the control cycle, but this difference was not statistically significant.

The post-PRP ICSI cycle performed better than the control cycle in terms of the total number of retrieved oocytes (median value of 5.0 ranging from 2.0 to 9.0 versus median value of 3.0 with a range of 0.0-6.0; p-value-0.002), fertilisation rate (median value of 0.5 ranging from 0.33-1.0 versus median value 0.5 ranging from 0.0-1.0; p-value <0.0002), and the number of good qualities [20].

After PRP, RT was attempted in 201 women who had at least one antral follicle, of whom 130 (64.7% were stimulated) underwent oocyte retrieval [19]. Out of this, at least one cleavage-stage embryo was retrieved in 82 women (40.8% of stimulated cycles), and fresh embryo transfer or embryo cryopreservation was carried out. Morphologically, these embryos were in grade 1/2.

Oocytes were recovered on average at a rate of 1.81 ±1.30. In women who had embryo development, the mean numbers of two-pronuclei (2 PN) and cleavage-stage embryos were 1.24 ±0.49 and 1.18 ± 0.39, respectively. 57 of the 82 women who generated embryos underwent embryo transfer, whereas 25 decided to maintain cryopreserved embryos for a future transfer.

Discussion

The data analysis for this systematic review included 660 subfertile women who had intra-ovarian PRP injections as an intervention across four studies. The ovarian reserve parameters (an increase in serum AMH or antral follicle count or a decrease in serum FSH) were observed to improve after PRP intervention. In three of the four investigations that were included, the ICSI cycle's result was investigated. When compared to their previous cycle without PRP infusion, the results of the ICSI cycle were found to be improved after the intra-ovarian PRP infusion in terms of the total number of oocytes retrieved, the number of two-pronuclei embryos, the fertilisation rate, the number of cleavage stage embryos, the number of good quality embryos, and the cycle cancellation rate.

According to a study, women without antral follicles at the time of PRP injection had a lower likelihood of responding to therapy than those with one or two antral follicles [19]. Likewise, women in the top and lowest quartiles of serum FSH and AMH had lower response rates. The researchers concluded that PRP aids in reactivating preantral and/or early antral follicles and that the amount of a woman with POI's response is probably influenced by the number of follicles still present in her ovaries [19]. In order to determine the subgroup that will benefit most from PRP infusion, more well-controlled research is clearly required. However, currently, we are unable to generalize this conclusion.

Numerous studies have shown that the administration of PRP can lessen postoperative blood loss, infection, and the need for narcotic painkillers. Additionally, PRP plays a part in the expedited osteogenesis, wound, and soft tissue repair [22–23]. The granules in platelets contain a number of significant growth factors, including transforming growth factor- (TGF-), 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, and hepatocyte growth factor (HGF), which serves as the foundation for the tissue-regenerating properties of PRP [24].

The same growth factors are also thought to be essential for tissue regeneration, cell proliferation, angiogenesis activation, and cell migration and differentiation [25]. It's important to note that research has revealed an antagonistic link between growth hormone and IGF-1 concentrations and ageing [26]. Particularly, the use of PRP in ovarian rejuvenation has not received extensive research. Only a few studies [27] have investigated this subject so far. According to their research, PRP can significantly reduce the risk of ischemia and reperfusion injury in rats after bilateral adnexal torsion and surgical detorsion [28]. They concluded that an increase in VEGF played a major role in this activity.

A few case series studies that evaluated the use of PRP for treating a thin endometrium, recurrent implantation failure, and poor response to controlled ovarian stimulation found positive outcomes [29]. An infertile woman with premature ovarian failure had an autologous PRP intra-ovarian injection, which led to a biochemical pregnancy and eventual miscarriage [30]. Similar occurrences of live birth in patients with poor responses after PRP infusion have also been documented [31]. Additionally, several research back the idea that PRP therapy aids in the development and maturation of follicles.

Recently, several case series that were similar to our investigation and indicated the effectiveness of intra-ovarian PRP injection. In the case series, the intra-ovarian infusion of PRP resulted in a rise in the pretreatment serum AMH. Although the difference between the trials was statistically insignificant (p-values <0.4544 and <0.15, respectively), the rise in serum AMH levels was statistically significant (p-value 0.0394) [32,33].

Similar to this case series, the intra-ovarian injection of PRP lowered the pretreatment serum FSH values [34]. All of the aforementioned investigations found this drop to be statistically significant, with p-values of 0.0311, 0.02, and 0.0052, respectively. A rise in the post-treatment mean values of AFC (1 ± 1 and 2 ± 1.40, respectively) in their case series [35]. With a p-value of 0.0698, this was not, however, determined to be statistically significant.

Strength And Limitation

The performance of ICSI cycles in women with low ovarian reserve or early ovarian failure is evaluated in this systematic review along with the impact of intra-ovarian PRP infusion on ovarian reserve measures. However, significant restrictions must be considered when interpreting the results of this systematic study. The main limitations are the small amount of research and the lack of homogeneity among the included studies. We were unable to do a meta-analysis due to this. Pregnancy traits such the clinical pregnancy rate, miscarriage rate, chemical pregnancy rate, and live birth rate haven't been assessed in most studies. ICSI cycle performance has only been assessed in a small number of trials. Finally, none of them included RCTs, and many of the studies are quasi-experimental studies. However, these restrictions are expected when performing a systematic review because intraovarian PRP injection is a very new and uncommon form of treatment for infertility. Furthermore, our study's positive findings have opened the door for undertaking more organized, randomized controlled studies in the future.

Conclusion

According to our comprehensive review, intra-ovarian autologous PRP infusion boosts the ovarian reserve parameters, which in turn raises the yield of mature oocytes, the rate of fertilization, and the production of high-quality embryos. Therefore, this astonishing revolutionary therapy is a particularly remarkable discovery in the field of reproductive medicine since it may put an end to our lengthy search for the relationship between having an insufficient ovarian reserve and having a genetically related child. Future, high-quality randomized controlled trials are needed to determine its effectiveness in terms of clinical pregnancy and live birth rate. Additionally, it is necessary to determine the subpopulation that would benefit from PRP the most and the ideal amount of serum AMH or another indicator of ovarian reserve for the effectiveness of intra-ovarian PRP injection.

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