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03 (69) 2025 : 001-007 • RESEARCH ARTICLE

Rejuvenating the ovaries: A review of innovative strategies for fertility restoration

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SUMMARY

Modern women are delaying having children, which increases their risk of developing ovarian insufficiency. Over the course of her reproductive life, a woman's ability to procreate is mostly determined by the number of follicles in her ovaries and the quality of the oocytes that are produced within them. Advance age is a major risk factor for reducing the amount and quality of viable eggs. Thus, it is vitally critical to develop innovative methods for safely restoring ovarian function. Ovarian rejuvenation is a new term that has acquired popularity recently. This review will concentrate on the knowledge gained in recent years regarding ovarian aging, potential ways of treatment, and extending the ovaries' lifespan. New treatments are being investigated, including stem cell therapies, mitochondrial enhancement therapy, and, most recently, PRP injections. In any case, further research is needed to determine the optimal dosages, minimize danger, and maximize the effectiveness of the interventions.

Keywords: Ovarian rejuvenation; Platelet-rich plasma; Fertility; Woman infertility; Primary ovarian insufficiency treatment

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Word count: 3573 **Tables:** 00 **Figures:** 00 **References:** 47

Received: 20.06.2025, Manuscript No. gpmp-25-170655; **Editor assigned:** 23.06.2025, PreQC No. P-170655; **Reviewed:** 15.07.2025, QC No. Q-170655; **Revised:** 23.07.2025, Manuscript No. R-170655; **Published:** 29.08.2025

INTRODUCTION

Globally, women are delaying childbirth because of the socioeconomic changes of the previous century, which have increased their employment rates and pushed them to prioritize their careers and achieving their professional objectives [1,2]. Since ancient times, female age has been recognized as a determinant of reproductive result. Because of the decreased ovarian reserve and deteriorating egg quality, it is a major risk factor for female infertility [3,4]. Unlike other organs, the ovaries have a limited period of time to function at their best. In addition to natural aging, some women suffer from Premature Ovarian Insufficiency (POI), which can lead to Premature Ovarian Failure (POF). It is considered a form of infertility where the menopausal state manifests prior to the physiological age [5]. As a result, the necessity for Assisted Reproductive Technologies (ART) is increasing. *In vitro* fertilization is still the first-line treatment, although low-quality eggs can potentially make it ineffective [6,7]. Despite the possibility of conceiving using donated eggs, there may be serious financial and psychological issues with such a solution. Therefore parents are not persuaded by this choice [8]. Additionally, there is the option to cryopreserve the egg at a younger age, however not many individuals do so, due to the high expense and the fact it does not guarantee a pregnancy [6,7]. As a result, biomedical researchers and the pharmaceutical sector are now increasingly interested in studying anti-ovarian aging [2]. New approaches that facilitate the recruitment of primordial germ cells and the generation of *de novo* oocytes would be welcomed, given the growing skepticism over the efficacy and safety of hormone replacement therapy and classical IVF techniques [9]. Women may be better equipped to make decisions regarding their reproductive health earlier if they have a better grasp of the molecular mechanisms of female reproductive aging and possible coping mechanisms [10]. "Ovarian rejuvenation" is a novel phrase that has acquired prominence in recent times. It is a type of regenerative medicine uses several techniques to revitalize and restore function to the premenopausal or menopausal ovary [11].

MATERIALS AND METHODS

For the purpose of writing this paper, we searched databases such as PubMed, PMC, Google Scholar, and Scopus for relevant documents. Abstracts were screened

to assess the relevance. Full-text examination was performed for articles that met the inclusion criteria. Keywords such as: ovarian rejuvenation, fertility, woman infertility, primary ovarian insufficiency, platelet-rich plasma were used for a search. The information was then summarized and written as an overview. In preparing this work, the authors used ChatGPT for the purpose of assesing the grammatical and syntactical correctness of the article and as well as formatting. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

RESULTS

Ovarian aging

Factors and mechanisms contributing to ovarian aging:

Only 1-2 million oocytes are present in women at birth, and by adolescence, that number declines to 400,000 [1,6]. At the average age of 51 years old, menopause occurs, leaving less than 1000 primordial follicles that are no longer capable of supporting ovulation [10]. Meanwhile, age-related mutations leads to the depletion of ovarian reserve as shown by decreasing serum AMH and primordial follicle number as well as increased follicle stimulating hormone (FSH) [3].

Oxidative stress, mitochondrial dysfunction, impairment of ovarian vascularization, fibrosis telomere shortening, DNA damage and related genetic mutations, misaligned chromosomes, disturbed communication in ovarian microenvironment and epigenetic changes can all contribute to poor oocyte quality as people age [12]. Inflammatory fibrosis is another component associated with ovarian aging. It is a result of age- related changes in the homeostatic immune system [13]. In the ovary, it is characterized with a greater proportion of monocytes, collagen fibers, and macrophages [6]. The aging of the surrounding follicular somatic cells, which supply nutrients and regulatory substances to promote oocyte growth and development, is another potential cause of ovarian insufficiency [14].

Primary ovarian insufficiency and primary ovarian failure:

The key characteristics of the disorders known as primary ovarian insufficiency and primary ovarian failure include oligomenorrhea or amenorrhea, elevated gonadotropin levels, hypoestrogenism and low anty-Müllerian hormone. POI and POF are linked various factors, including autoimmune disorders, endocrine dysfunction, chemotherapy, radiation treatment, unilateral ovarian absence, previous ovarian surgery, aneuoploidy, environmental toxicants or smoking. [7,15-17]. Also genetic defects, such as Turner syndrome, trisomy X, isochromosome deletions, fragile X syndrome and single mutations in genes associated with fertility can lead to ovarian insufficiency. POF affects 1 in 100 women under 40 and 1 in 250 women under 35 [15]. In patients, laparoscopy reveals a lack of follicle formation, and malfunctioning ovaries result in an estrogen shortage [12]. Cigarette smoking is the primary non-genetic risk factor that has been shown to shorten the menopause by roughly three years [10].

Mitochondrial malfunction and telomere attrition:

One of the signs of aging is mitochondrial malfunction. Age-related declines in mitochondrial DNA (mtDNA) copy number and function are consistent across a range of tissues. During ovarian aging, a lower mtDNA copy number has also been documented [1,18]. The accumulation of spontaneous mitochondrial damage is induced by increasing Reactive Oxygen Species (ROS) in oocytes. Protective mechanisms against ROS-damaged proteins, DNA and metabolism are less reliable in older ovaries [2]. ROS comprise hydrogen peroxide, superoxide, and hydroxyl as byproducts of mitochondrial oxidative phosphorylation. Overproduction of ROS overwhelms the body's antioxidant defenses, causing damage to the mitochondria and nuclear DNA [10].

Finally, telomere attrition is one of the major routes implicated in the process of ovarian aging [12]. In order to preserve genome integrity, telomeres—protective caps at the ends of linear chromosomes—avoid chromosome fusion and degradation [6]. Loss of telomerase activity and buildup of ROS leads to thelomere shortnening in ovaries. Compared to women with shorter telomeres, individuals with longer telomeres went through menopause up to three years later [10]. Additionally, people with ovarian insufficiency have substantially lower telomarase activity in their granulose cells compared to those without reproductive issues [6].

Stem cells

Characteristics and mechanism of action:

It has long been believed that female animals do not have germ-line stem cells in the ovaries. The expression of germ-cell markers by extra-follicular cells, however, has called into question this conventional wisdom and is providing promise for the novel therapeutic approaches [10]. According to their definition, stem cells are cells that come from a multicellular creature and have the ability to differentiate (potency) into other cells of the same kind as well as other cell types [19].

Researchers concentrated on human clinical trials using various types of stem cells following the successful outcomes of animal studies [11,12,15,19]. There are several kind of stem cells, such as Bone Marrow-Derived Stem Cells (BMDSCs), amniotic fluid Mesenchymal Stem Cells (MSCs), induced Pluripotent Stem Cells (iPSCs), umbilical cord MSC (UCMSCs), menstrual blood-derived Stromal Cells (MenSCs), Adipose tissue Derived MSC (ADMSCs), amniotic fluid Mesenchymal Stem Cells (MSCs), stem cells from Extra-Embryonic Tissues (ESCs). [11,15]. Although they don't alter the quality of embryos, adult stem cells secrete variety of growth factors, cytokines and chemokines that encourage follicular growth, boost ovarian angiogenesis, improve follicle and stromal cell proliferation, tissue repair and decrease cell apoptosis and follicular atresia [12,19-21]. According to reports, autologous MenSC injected intraovarianly enhanced the number of antral follicles, Anti-Müllerian Hormone (AMH) levels, and spontaneous pregnancy rates in experimental group [11].

Research on the effectiveness of stem cells:

The production of hematopoietic, mesenchymal, and endothelial SC is possible with bone marrow derived stem

cells (BMDSC) [6]. Two spontaneous conceptions were reported by Indian researchers [20] following treatment with autologous bone marrow-derived stem cells. Laparoscopic intraovarian instillation of ABMDSC along with PRP was used to treat two individuals with a history of infertility and low ovarian reserve. The left ovaries of the first patient and both ovaries of the second patient exhibit excellent response on follow-up ultrasonography. Both the ovary's volume and follicle count increased. Patients spontaneously conceived within two years of the surgery.

In Egypt, another effective study was conducted. Gabr H, et al. [22] used autologous Mesenchymal Stem Cells (MSCs), which were delivered into the ovarian tissue *via* laparoscopy and into the ovarian artery *via* catheter. The study involved 30 POI women. In 26 of the 30 patients, the follow-up examination (48 weeks after the procedure) revealed a decrease in FSH levels and an increase in estrogen and AMH levels. Eighteen cases showed signs of ovulation, with ovum sizes ranging from 12 to 20 mm. One of the patients conceived spontaneously.

A team of Spanish researchers [23] created a second trial to assess how Autologous Stem Cell Ovarian Transplantation (ASCOT) affected the ovarian reserve of 17 women. Six pregnancies and three healthy newborns were accomplished, and 81.3% of women experienced improvements in ovarian function biomarkers (AMH and AFC).

The procedure of MSC treatment is costly, time-consuming, and labor-intensive. Additionally, In it carries certain possible dangers, including the possibility of infection, GVHD, and tissue specialization of MSCs [11]. More study is required to determine the optimal stem cell origin choice, reduce the risk of adverse effects, and provide less invasive infusion procedures [15,21].

PRP

Characteristics and mechanism of action:

The concentrated platelet preparation known as Platelet-Rich Plasma (PRP) has restorative qualities because of the different growth factors it contains [7,24]. Like stem cells, PRP administered intraovarianly has demonstrated the ability to raise Antral Follicle Count (AFC), lower blood FSH levels, enhance oocyte retrieval, improve AMH levels, and encourage spontaneous conception [5,11,25,26].

In women with early ovarian insufficiency and very low ovarian reserve, Platelet-Rich Plasma (PRP) therapy has been utilized as a supplement to fertility therapies when combined with *In Vitro* Fertilization (IVF) as an intraovarian injection [27,28]. Through centrifugation and the separation of its various components, Platelet-Rich Plasma (PRP) is produced from whole blood, which comprises plasma (55%), red blood cells (41%), platelets, and white blood cells (4%). Red blood cells are eliminated, and plasma with five to ten times the concentration of growth factors is produced. PRP's growth factors have been demonstrated to be crucial in promoting collagen synthesis, bone cell proliferation, fibroblast chemotaxis, macrophage activation, angiogenesis, stimulating the migration (chemotaxis) and proliferation (mitogenesis) of different cell types; and stimulating immune cells to migrate toward the area of injury. Differentiation, mesenchymal and epithelial cell cytokine secretion and improving oocyte quality [24-27, 29]. In traditional "ovarian rejuvenation," autologous (activated) Platelet-Rich Plasma (PRP) is surgically injected into ovarian tissue using either a transvaginal ultrasound-guided injection or a laparoscopy [30].

Research on the effectiveness of PRP:

New research is emerging all the time. There are a lot of successful case studies in the literature [3,24,31]. Melo P, et al. [32] conducted one of the earliest prospective controlled, non-randomized comparative studies. Of the 83 women who were part of the study, 46 were treated with PRP, whereas 37 did not get any kind of intervention. Women who had PRP treatment saw a significant improvement in FSH, AMH, and AFC at the 3-month follow-up, while the control group showed no change. Additionally, the PRP group had higher overall rates of biochemical pregnancy and clinical pregnancy, but the groups did not vary in the rates of live birth and first-trimester miscarriage.

In their trial, Athanasios, et al. treated 253 women between the ages of 22 and 56 with autologous PRP injection. Most subjects showed improvements in their hormone profiles at the two-month follow-up rate. 15% of the women with advanced ages in this pilot trial had their menstrual cycle restored, and 17% of the women were able to conceive.

120 patients were tracked for three months in a different prospective, controlled, non-randomized pilot research using intraovarian PRP injection [33]. According to the results, the POR group's ICSI cycle performance and hormonal profile and ovarian reserve markers get significantly better. In 60% of POI patients, menstruation recovered, and AMH, FSH, and AFC levels improved. In the menopausal group, 43 percent experienced either a return of menstruation or a drop in FSH. Eighty percent of perimenopausal women experienced regular menstruation, better hormone levels, and AFC. Within the study groups, both natural and IVF conceptions were accomplished.

182 patients with low ovarian reserve participated in this registered, prospective clinical research [34], which was published in 2020. Before and after PRP, with a three-month follow-up, the following parameters were measured: AMH, FSH, E2, and platelet count. After treatment, 28% of patients showed improved serum AMH, with a median increase of 167% and an average peak of AMH at 4 weeks. Women under 42 and those above 42 showed improvements in AMH. The follicular impact and pregnancy outcome were not measured.

Albanian researchers conducted the extensive trial [35]. The study comprised 510 women. Higher AFC, higher serum AMH, lower serum FSH, and more developed oocytes, cleavage, and blastocyst stage embryos were the outcomes of PRP treatment. Overall, PRP improved the parameters of ovarian reserve, resulting in a 20.5% pregnancy rate and a 12.9% SI/LB rate.

The randomized, controlled trial conducted by Herlihy NS, et al. [36] yielded different results. After meeting the requirements for inclusion, 83 patients were randomly assigned to either have an autologous intraovarian PRP injection (n=41) or no intervention (n=42). There were no observable differences in blastocysts, euploid blastocysts or the number of MII oocytes recovered per

cycle. Likewise, there were no changes in the incidence of sustained implantation or the probability of acquiring at least one euploid blastocyst. AMH and AFC did not change between the groups after therapy.

Twelve POR patients who were chosen using the Bologna group 4 criteria participated in another research conducted at Tehran University [26]. The mean Antral Follicular Count (AFC) increased significantly in those who had undergone aPRP. The number of oocytes, AMH, and FSH in the case and control groups did not significantly alter before or after the intervention

Consequently, intraovarian PRP injection is a practical, affordable, and useful substitute for MSC therapies. PRP holds potential for ovarian regeneration and the alleviation of menopausal symptoms [11]. The benefits of "ovarian rejuvenation" by PRP have been emphasized in recent articles, but its acceptability has been constrained by the lack of data from randomized, placebo-controlled clinical trials [29,37,38]. Standardized preparation, injection, and follow-up protocols are needed to further evaluate the potential benefits of autologous intraovarian PRP injection for female reproduction [27,39,40].

Other methods

Treatments for improving mitochondrial quality:

Since mitochondria play a significant role in ovarian aging, many researchers concentrate on them when identifying potential treatments. POI patients have the lowest quantities of mtDNA, more mitochondrial DNA abnormalities, a malfunctioning electron transport chain, and impaired metabolism [1,10]. Supplementing with CoQ10, a lipid-soluble quinone that functions as an efficient antioxidant that inhibits DNA oxidation and lipid peroxidation, has long been used to improve infertility outcomes and is linked to a higher clinical pregnancy rate [41]. According to a meta-analysis [41], oral CoQ10 supplementation may improve clinical pregnancy in infertile women undergoing ART treatments when compared to placebo or no treatment, with no impact on the rate of live births or miscarriages.

The use of the androgen prohormone Dehydroepiandrosterone (DHEA) is another issue [42]. DHEA has been shown to increase the number of oocytes recovered, the rate of high-quality embryos, and the rate of embryo implantation [43]. However, DHEA is still not frequently advised because of a lack of sufficiently strong randomized controlled trials and its link to androgenic side effects include hirsutism, acne and skin changes [42].

Plants naturally produce resveratrol, a polyphenolic compound that can be found in red wine and skin of red grapes. Research has indicated that resveratrol has a wide range of possible health advantages, including anti-aging, anti-inflammatory, increasing the number and quality of oocytes [1,44]. Resveratrol's effects vary with time and dosage. A large dose of resveratrol causes embryo death, but a moderate amount enhances ovarian function and oocyte quality. Taiwanese researchers [2] examine the effects on female mice of 2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-Glucoside (THSG), a resveratrol glycosylated derivative. In both young and old mice, THSG enhanced or prolonged the expression of genes related to ovarian maintenance and renewal. Although the outcomes from animal models are encouraging, their possible use is limited by the dearth of randomized, double-blind, placebo-controlled trials [44].

Age-related decreases in NMN, an intermediary of the metabolic cofactor nicotinamide adenine dinucleotide (NAD+/NADH), may also be a contributing factor to ovarian aging. According to research, in older animals, nicotinamide mononucleotide treatment revitalizes oocyte quality, resulting in fertility restoration. NMN has these advantages for the growing embryo as well, as supplementation counteracts the negative impact of mother age on developmental milestones [45]. Trials are now being conducted to determine a safe and effective dosage [10].

In order to address low egg quality in IVF, Mitochondrial Replacement Therapy (MRT) employing donor ooplasm is currently an experimental procedure [1]. Heterologous transfer raised some ethical and safety concerns and have been discontinued due to the established risk of heteroplasmy, thus autologus germline mitochondrial energy transfer is currently being tested [18]. However, compared to initial expectations, the autologous germline mitochondrial energy transfer (AUGMENT) has not shown as many positive results and is not a practical way to enhance the quality of IVF embryos [10,18].

Other options including oocyte spindle transfer, germinal vescile transfer, and gene editing technologies are also available, but these raise a lot of ethical issues and are currently not advised [1].

Lifestyle- related treatment:

Lifestyle-related concerns are one of the treatment lines. Obesity is regarded as a risk factor that contributes to the buildup of ROS and, consequently, ovarian aging. Due to altered meiotic spindle formation and mitochondrial dynamics, obesity appears to have an impact on both the egg and the preimplantation embryo. In reproductive organs, too many free fatty acids can be harmful, causing cellular damage and a persistent low-grade inflammatory state [46,47]. It is well established that Calorie Restriction (CR) and regular exercises, as well as diet high in fruits and vegetables and low in saturated fat can postpone the aging-induced functional deterioration of bodily tissues and improve the clinical pregnancy rate [1,10].

The primary obstacle to using antioxidants in human reproductive aging at the moment is determining the best time, frequency, and dosage, as well as any potential negative effects of long-term use [18].

DISCUSSION

Modern methods for so-called ovarian rejuvenation are taken into consideration in this review. Although there are numerous encouraging studies [20,22,23] that demonstrate how stem cells might enhance ovarian function biomarkers (AMH and AFC) and hence result in a successful pregnancy, some research reveal no benefits following the use of such techniques. The high expense of these techniques and perhaps conflicting research findings are the main challenges. Various stem cell therapies are being explored on POI women globally. However, most of them are still ongoing, therefore results have not yet been announced. The development of standardized MSC production standards remains a significant issue.

The most promising option is the injection of plasma-rich platelets, as numerous studies have shown to be successful [26,33,34,36]. Nevertheless, other research indicates no distinctions between the experimental and control groups. For example, Spanish researchers [37] reached the ambiguous conclusions. A randomized, double-blind, placebo-controlled study with 60 POR patients categorized by POSEIDON groups 3 and 4 was conducted. According to the findings, both experimental groups consistently produced more oocytes throughout subsequent egg retrievals. Nevertheless, when compared to the control group, PRP injection did not result in an increased proportion of euploid blastocysts or better pregnancy rates.

Furthermore, research highlighting the role of mitochondria in ovarian aging suggests using supplements like DHEA or CoQ10. The main problem is that the trials are too small and non-randomized to verify efficacy and safety.

In order to get the most useful results, properly randomized trials with a large experimental group are required.

LIMITATIONS

Not all of the research conducted over the years was covered in the article. A meta-analysis of other studies from around the world must be produced in order to make the results as reliable as possible.

CONCLUSION

Two of the most researched pathogenetic causes of infertility include maternal age and decreased ovarian reserve. Women are choosing to have children later and later as the world evolves, and medicine needs to adapt to these developments. Given the multitude of factors that contribute to ovarian aging, there are numerous areas that we may concentrate on to enhance ovarian reserve and oocyte quality, enabling women to fulfill their ambition of becoming mothers. Novel techniques are being considered, including stem cell therapies, mitochondrial enchancment therapy, and recently, the most promising PRP injections. In any case, further research on it is needed to determine the optimal dosages, reduce risk, and maximize the impact of the interventions.

FUNDING STATEMENT

This research received no external funding.

ANIMAL AND HUMAN RIGHTS STATEMENT

No animal or human studies were carried out by the authors for this article.

SCIENTIFIC RESPONSIBILITY STATEMENT

All authors declare that they have participated sufficiently in the work to take public responsibility for the content. All authors have read and approved the final version of the manuscript and agree to its submission.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. **Chiang JL, Shukla P, Pagidas K, et al.** Mitochondria in ovarian aging and reproductive longevity. *Ageing Res Rev.* 2020;63:101168.
2. **Lin HY, Yang YN, Chen YF, et al.** 2, 3, 5, 4′-Tetrahydroxystilbene-2-O-β-D-Glucoside improves female ovarian aging. *Front Cell Dev Biol.* 2022;10:862045.
3. **Sills ES.** The scientific and cultural journey to ovarian rejuvenation: background, barriers, and beyond the biological clock. Medicines. 2021;8:29.
4. **Zhang Y, Bai J, Cui Z, et al.** Polyamine metabolite spermidine rejuvenates oocyte quality by enhancing mitophagy during female reproductive aging. *Nat Aging.* 2023;3:1372-1386.
5. **Ahmadian S, Sheshpari S, Pazhang M, et al.** Intra-ovarian injection of platelet-rich plasma into ovarian tissue promoted rejuvenation in the rat model of premature ovarian insufficiency and restored ovulation rate *via* angiogenesis modulation. *Reprod Biol Endocrinol.* 2020;18:78.
6. **Polonio AM, Chico-Sordo L, Córdova-Oriz I, et al.** Impact of ovarian aging in reproduction: from telomeres and mice models to ovarian rejuvenation. *Yale J Biol Med.* 2020;93:561.
7. **Park HS, Ulin M, Cetin E.** Ovarian rejuvenation using platelet-rich plasma: a promising option for women in early menopause to have a baby. *Reprod Sci.* 2020;27:1983-1984.
8. **Petryk N, Petryk M.** Ovarian rejuvenation through Platelet-Rich autologous Plasma (PRP)—a chance to have a baby without donor eggs, improving the life quality of women suffering from early menopause without synthetic hormonal treatment. *Reprod Sci.* 2020;27:1975-1982.
9. **Sills ES, Tan SL.** Population dynamics, plasma cytokines and platelet centrifugation: technical and sociodemographic aspects of 'ovarian rejuvenation'. *Clin Pract.* 2023;13:435-441.
10. **Zhu Z, Xu W, Liu L.** Ovarian aging: mechanisms and intervention strategies. *Med Rev.* 2023;2:590-610.
11. **Sadeghi MR.** Ovarian Rejuvenation: Turning Dreams into Reality. *J Reprod Infertil.* 2024;25:31
12. **Polonio AM, García-Velasco JA, Herraiz S.** Stem cell paracrine signaling for treatment of premature ovarian insufficiency. *Front Endocrinol.* 2021;11:626322.
13. **Bukovsky A.** Novel methods of treating ovarian infertility in older and POF women, testicular infertility, and other human functional diseases. *Reprod Biol Endocrinol.* 2015;13:10.
14. **Wang H, Huang Z, Shen X, et al.** Rejuvenation of aged oocyte through exposure to young follicular microenvironment. *Nat Aging.* 2024;4:1194-1210.
15. **Sheikhansari G, Aghebati-Maleki L, Nouri M, et al.** Current approaches for the treatment of premature ovarian failure with stem cell therapy. *Biomed Pharmacother.* 2018;102:254-262.
16. **Sheshpari S, Shahnazi M, Ahmadian S, et al.** Intra-ovarian injection of bone marrow-derived c-Kit+ cells for ovarian rejuvenation in menopausal rats. *BioImpacts.* 2021;12:325.
17. **Garavelas A, Mallis P, Michalopoulos E, et al.** Clinical benefit of autologous platelet-rich plasma infusion in ovarian function rejuvenation: evidence from a before-after prospective pilot study. Medicines. 2023;10:19.
18. **Labarta E, De los Santos MJ, Escribá MJ, et al.** Mitochondria as a tool for oocyte rejuvenation. *Fertil Steril.* 2019;111:219-226.
19. **Cacciottola L, Vitale F, Donnez J, et al.** Use of mesenchymal stem cells to enhance or restore fertility potential: a systematic review of available experimental strategies. *Hum Reprod Open.* 2023;2023:hoad040.
20. **Tandulwadkar S, Mishra S, Jain H, et al.** Ray of hope for decreased ovarian reserve: India's first two spontaneous conceptions after autologous bone marrow-derived stem cells therapy for ovarian rejuvenation. *J Obstet Gynaecol India.* 2022;72:458-460.
21. **Herraiz S, Pellicer N, Romeu M, et al.** Treatment potential of bone marrow-derived stem cells in women with diminished ovarian reserves and premature ovarian failure. *Curr Opin Obstet Gynecol.* 2019;31:156-162.
22. **Gabr H, Elkheir WA, El-Gazzar A.** Autologous stem cell transplantation in patients with idiopathic premature ovarian failure. *J Tissue Sci Eng.* 2016;7:27.
23. **Herraiz S, Romeu M, Buigues A, et al.** Autologous stem cell ovarian transplantation to increase reproductive potential in patients who are poor responders. *Fertil Steril.* 2018;110:496-505.
24. **Shrivastava J, More A, Shrivastava V, et al.** Enhancement of ovarian reserve and oocyte quality after platelet-rich plasma instillation in a woman with diminished anti-Müllerian hormone. Cureus. 2024;16.
25. **Sills ES, Wood SH.** Epigenetics, ovarian cell plasticity, and platelet-rich plasma: Mechanistic theories. *Reprod Fertil.* 2022;3:C44-C51.
26. **Keikha F, Shahsavari S, Salari Y, et al.** One side ovarian rejuvenation: a quasi-experimental study of the effect of the autologous platelet rich plasma in poor ovarian responders in IVF. *Ethiop J Health Sci.* 2022;32.
27. **Seckin S, Ramadan H, Mouanness M, et al.** Ovarian response to intraovarian platelet rich plasma (PRP) administration: hypotheses and potential mechanisms of action. *J Assist Reprod Genet.* 2022;39:37–61
28. **Sills ES, Wood SH.** Progress in human ovarian rejuvenation: Current platelet-rich plasma and condensed cytokine research activity by scope and international origin. *Clin Exp Reprod Med.* 2021;48:311.
29. **Rickers NS, Sills ES.** Is autologous platelet activation the key step in ovarian therapy for fertility recovery and menopause reversal?. Biomedicine. 2022;12:1.
30. **Sills ES.** Ovarian recovery *via* autologous platelet-rich plasma: New benchmarks for condensed cytokine applications to reverse reproductive aging. *Aging Med.* 2022;5:63-67.
31. **Serdarogullari M, Raad G, Makieva S, et al.** Revitalizing female fertility: platelet-rich plasma–hype or hope?. *Reprod Biomed Online.* 2024;49:103813
32. **Melo P, Navarro C, Jones C, et al.** The use of autologous Platelet-Rich Plasma (PRP) *vs.* no intervention in women with low ovarian reserve undergoing fertility treatment: a non-randomized interventional study. *J Assist Reprod Genet.* 2020;37:855-863
33. **Sfakianoudis K, Simopoulou M, Grigoriadis S, et al.** Reactivating ovarian function through autologous platelet-rich plasma intraovarian infusion: pilot data on premature ovarian insufficiency, perimenopausal, menopausal, and poor responder women. *J Clin Med.* 2020;9:1809.
34. **Sills ES, Petersen JL, Rickers NS, et al.** Regenerative effect of intraovarian injection of activated autologous platelet rich plasma: serum anti-mullerian hormone levels measured among poor-prognosis *in vitro* fertilization patients. *Int J Regener Med.* 2020;2020:1-5
35. **Cakiroglu Y, Yuceturk A, Karaosmanoglu O, et al.** Ovarian reserve parameters and IVF outcomes in 510 women with Poor Ovarian Response (POR) treated with intraovarian injection of autologous Platelet Rich Plasma (PRP). Aging. 2022;14:2513.
36. **Herlihy NS, Cakiroglu Y, Whitehead C, et al.** Effect of intraovarian platelet-rich plasma injection on IVF outcomes in women with poor ovarian response: the PROVA randomized controlled trial. *Hum Reprod.* 2024;39:1495-1503.
37. **Barrenetxea G, Celis R, Barrenetxea J, et al.** Intraovarian platelet-rich plasma injection and IVF outcomes in patients with poor ovarian response: a double-blind randomized controlled trial. *Hum Reprod.* 2024;39:760-769.
38. **Sills ES.** Why might ovarian rejuvenation fail? Decision analysis of variables impacting reproductive response after autologous platelet-rich plasma. *Minerva Obstet Gynecol.* 2022;74:377-385
39. **Panda SR, Sachan S, Hota S.** A systematic review evaluating the efficacy of intra-ovarian infusion of autologous platelet-rich plasma in patients with poor ovarian reserve or ovarian insufficiency. Cureus. 2020;12.
40. **Aflatoonian A, Lotfi M, Saeed L, et al.** Effects of intraovarian injection of autologous platelet-rich plasma on ovarian rejuvenation in poor responders and women with primary ovarian insufficiency. *Reprod Sci.* 2021;28:2050-2059.

41. **Florou P, Anagnostis P, Theocharis P, et al.** Does coenzyme Q10 supplementation improve fertility outcomes in women undergoing assisted reproductive technology procedures? A systematic review and meta-analysis of randomized-controlled trials. *J Assist Reprod Genet.* 2020;37:2377-2387.

42. **Wierman ME, Kiseljak-Vassiliades K.** Should dehydroepiandrosterone be administered to women?. *J Clin Endocrinol Metab.* 2022;107:1679-1685.

43. **Zhu F, Yin S, Yang B, et al.** TEAS, DHEA, CoQ10, and GH for poor ovarian response undergoing IVF-ET: a systematic review and network meta-analysis. *Reprod Biol Endocrinol.* 2023;21:64.

44. **Podgrajsek R, Ban Frangez H, Stimpfel M.** Molecular mechanism of resveratrol and its therapeutic potential on female infertility. *Int J Mol Sci.* 2024;25:3613.

45. **Bertoldo MJ, Listijono DR, Ho WH, et al.** NAD+ repletion rescues female fertility during reproductive aging. *Cell Rep.* 2020;30:1670-1681.

46. **Broughton DE, Moley KH.** Obesity and female infertility: potential mediators of obesity's impact. *Fertil Steril.* 2017;107:840-847.

47. **Marinelli S, Napoletano G, Straccamore M, et al.** Female obesity and infertility: outcomes and regulatory guidance. *Acta Biomed.* 2022;93:e2022278.