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Review Article

Regenerative approaches in ovarian rejuvenation: hope for fertility restoration

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ABSTRACT

Ovarian aging is a progressive biological process marked by a decrease in the amount and quality of oocytes, resulting in decreased fertility, diminished ovarian reserve (DOR), premature ovarian insufficiency (POI), and menopause. Multiple molecular processes, including as oxidative stress, mitochondrial dysfunction, telomere shortening, DNA damage, apoptosis, and hormone imbalance, all contribute to poor ovarian function and follicular depletion. Conventional fertility therapies and assisted reproductive technologies focus on the effects of ovarian malfunction rather than improving ovarian activity itself, with little success in women with low ovarian reserve. Recently, ovarian rejuvenation has emerged as a viable regenerative method for enhancing the ovarian microenvironment, awakening dormant follicles, and restoring endocrine and reproductive function. This study looks at the biology of ovarian aging, the pathophysiology of ovarian dysfunction, and recent breakthroughs in ovarian rejuvenation treatments such as platelet-rich plasma (PRP) treatment, stem cell-based therapy, in vitro activation (IVA), and ovarian tissue transplantation (OTT). PRP therapy has the potential to improve ovarian reserve markers such as AMH, FSH, and AFC, whereas mesenchymal stem cell therapy may promote angiogenesis, reduce inflammation, and support follicular survival via paracrine mechanisms. IVA and OTT are also novel fertility preservation and restoration procedures for women with DOR and POI. Although first results are intriguing, existing evidence is limited due to small sample sizes, a lack of standardized techniques, and insufficient long-term safety data. More large-scale randomized clinical trials are needed to determine the efficacy, safety, and therapeutic application of ovarian rejuvenation therapy in reproductive medicine.

Keywords: Ovarian rejuvenation, PRP therapy, stem cell therapy, diminished ovarian reserve, premature ovarian insufficiency, ovarian tissue transplantation

INTRODUCTION

The ovary is an important reproductive organ responsible for gamete production and hormone secretion. It contains a limited number of primordial follicles formed before birth, which progressively decline throughout the reproductive lifespan.[1,2] Folliculogenesis is regulated by gonadotropins, leading to follicle maturation, oestrogen production, and ovulation followed by corpus luteum formation and progesterone secretion. Ovarian function is also reflected by biomarkers such as Anti-Müllerian hormone (AMH), and its impairment can lead to conditions including diminished ovarian reserve (DOR) and premature ovarian insufficiency (POI).[2]

Ovarian aging involves a progressive decline in oocyte quantity and quality, driven by mechanisms such as oxidative stress, mitochondrial dysfunction, telomere shortening, and DNA damage.[3,4] Reduced ovarian vascularity further disrupts folliculogenesis and hormonal balance. Clinically, this manifests as DOR or POI, leading to reduced fertility.[5,6] Current treatments, including ovulation induction and assisted reproductive technologies, mainly address infertility symptoms rather than restoring ovarian function and often require repeated cycles with limited success in DOR and POI.[5,7]

Ovarian rejuvenation seeks to solve the issue by stimulating follicle growth and regeneration of ovarian milieu. The theory behind ovarian rejuvenation lies in the regenerative capacity of the organ that can be stimulated by various procedures. As pointed out recently, ovarian rejuvenation provides a promising area of reproductive medicine.[8] The objective of this review is to provide a comprehensive analysis of the recent theories and advances in ovarian rejuvenation, with special emphasis on the biological underpinnings, recent advancements in treatment approaches, and clinical uses.

OVARIAN BIOLOGY AND AGING

There is a global trend of delaying childbirth into the thirties and forties, when fertility declines due to ovarian aging.[9] The ovary ages faster than many organs, with a finite pool of primordial follicles that decreases from before birth throughout life.[10] This leads to reduced oocyte number and quality, increasing infertility, pregnancy complications, and chromosomal abnormalities such as trisomy 21, along with higher miscarriage risk. Ovarian aging ultimately results in menstrual irregularities, infertility, and menopause.[9] Given the vital role, ovarian hormones, especially oestrogen, play an important role in numerous metabolic, cardiovascular, skeletal, and neurological processes. A decline in the functioning of ovarian hormones has significant consequences not only for fertility and reproductive health but also for overall systemic health. Therefore, a deeper comprehension of ovarian aging offers a special window into the biology of longevity and aging.[10]

Folliculogenesis and ovarian reserve

During foetal development, many germ cells are produced, but most are lost before birth, leaving a finite pool of primordial follicles that forms the ovarian reserve.[11] Oogonia proliferate by mitosis and differentiate into oocytes, which enter meiotic prophase and become enclosed within primordial follicles.[12] Females are born with about 2 million primordial follicles, declining to approximately 400,000 by menarche.[13] Folliculogenesis is the process by which these dormant follicles are activated and mature into ovulatory follicles capable of producing fertilizable oocytes. In each menstrual cycle, a group of follicles is recruited, with usually one dominant follicle proceeding to ovulation.[11]

As follicles develop, they form an antrum containing follicular fluid. Granulosa cells differentiate into mural granulosa cells, involved in steroid production, and cumulus cells, which support the oocyte.[12,13] FSH and LH are essential for antral follicle growth and maturation. FSH stimulates granulosa cell proliferation, oestrogen production, and LH receptor expression. After ovulation, granulosa and theca cells form the corpus luteum, which secretes progesterone and supports early pregnancy.[9,13]

Molecular mechanisms of ovarian aging

The ovary functions as a natural biological clock, and its progressive decline is known as ovarian aging.[14] This process is driven by mechanisms such as telomere shortening, genomic instability, oxidative stress, mitochondrial dysfunction, impaired DNA repair, cohesin defects, crossover maturation inefficiency (CMI) chromosomal abnormalities and meiotic spindle disruption.[10] Age-related decline in oocyte quality is mainly due to increased meiotic nondisjunction, leading to aneuploidy and poor pregnancy outcomes.[3]

Oxidative stress plays a key role in ovarian aging. Reactive oxygen species (ROS) and reactive nitrogen species produced during aerobic metabolism damage DNA, accelerate follicular loss, and impair mitochondrial DNA (mtDNA), creating a cycle of increasing oxidative stress that promotes follicular atresia and reduced oocyte quality.[14,15]

Disruption of signalling pathways, particularly hyperactivation of the PI3K/AKT/mTOR pathway, contributes to premature depletion of ovarian reserves.[10] Mitochondrial dysfunction further impairs oocyte maturation, fertilization, and embryo development, accelerating ovarian insufficiency and pregnancy failure.[15] Apoptosis is another major mechanism of ovarian aging, causing follicular atresia and loss of ovarian function. Oocyte apoptosis reduces germ cell numbers, while granulosa cell apoptosis disrupts ovarian metabolism. Increased apoptosis also elevates cell-free DNA and ROS levels, further amplifying cellular damage and ovarian decline.[14]

Hormonal changes with aging

The hypothalamic-pituitary-ovarian (HPO) axis regulates female reproductive function through the pulsatile release of GnRH, which stimulates the anterior pituitary to secrete FSH and LH. These hormones control follicular development, ovulation, and the production of oestrogen, progesterone, inhibin, and AMH.[9] Age-related fertility decline is associated with dysfunction across the hypothalamic-pituitary-gonadal axis.[16] As ovarian follicles decrease in number and quality, the production of inhibin B and AMH declines, reflecting reduced ovarian reserve.[9] In response to decreased ovarian sensitivity, FSH levels rise and serve as a marker of ovarian insufficiency, while LH levels may increase or fluctuate, often

contributing to ovulatory dysfunction.[16] Older women also exhibit a reduced LH response to GnRH, suggesting pituitary involvement in reproductive ageing. Declining oestradiol production impairs endometrial function, lowers implantation rates, and contributes to anovulation, menstrual irregularities, and reduced oocyte quality.[9] Oestrogen deficiency further accelerates bone resorption, decreases bone formation and bone mineral density, and weakens bone strength, thereby increasing the risk of osteoporosis and fractures.[17]

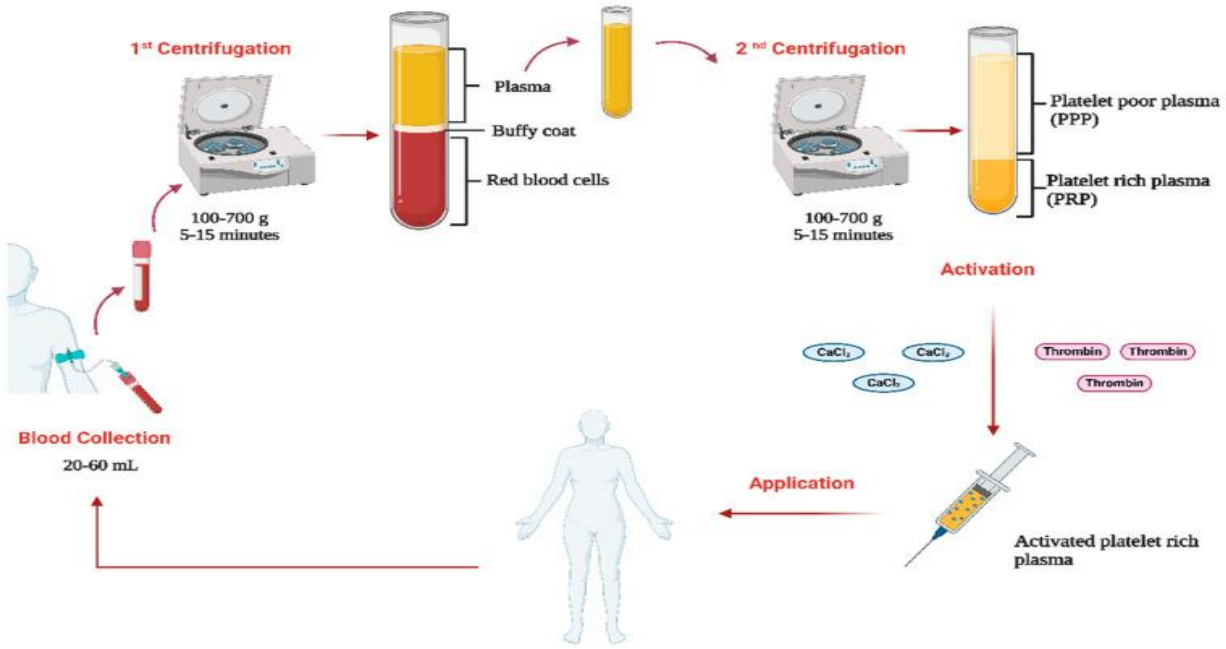

Figure 1: Preparation protocol of human PRP.[37]

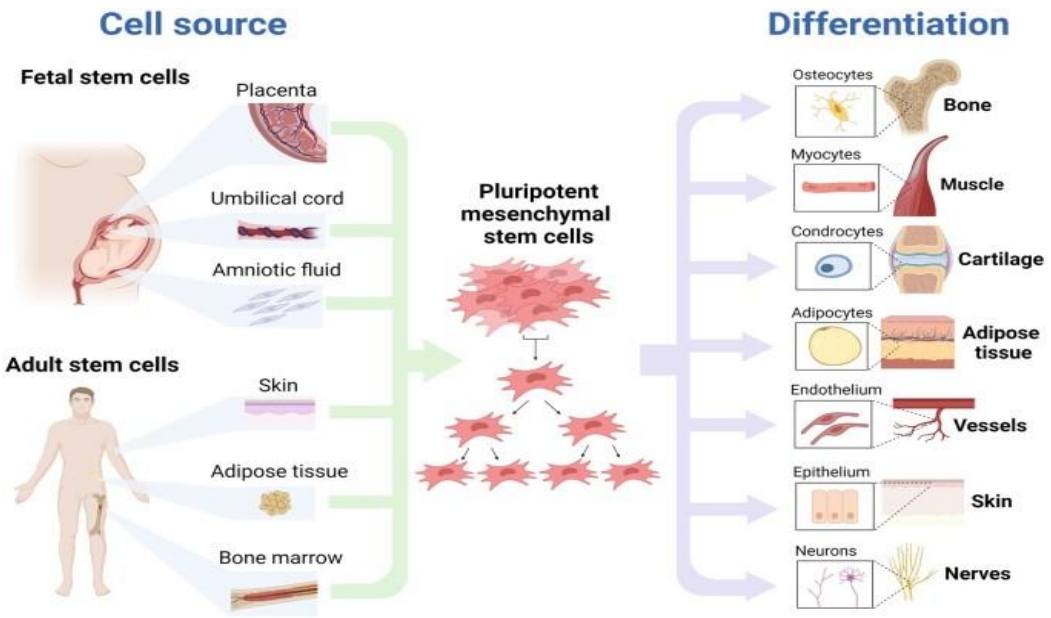

Figure 2: Sources of mesenchymal stem cells and their capacity for differentiation.[44]

PATHOPHYSIOLOGY OF OVARIAN DYSFUNCTION

According to the World Health Organization, infertility affects around 48 million couples and 186 million people globally, making it a serious public health concern.[18] Female infertility is multifactorial, commonly resulting from hormonal imbalance, reproductive tract abnormalities, age-related decline in oocyte quality, and lifestyle factors. Among these, ovarian dysfunction is a major cause of reduced fertility in women of reproductive age, disrupting endocrine balance and normal reproductive

processes. Normal reproductive function is regulated by the integrated HPO axis and its co-ordinated neuroendocrine and ovarian hormonal signalling.[19]

Diminished ovarian reserve

DOR is characterized by an age-inappropriate reduction in oocyte number and quality, leading to poor ovarian stimulation response, low IVF success rates, and an increased risk of foetal aneuploidy.[9] Its etiology is multifactorial, involving aging, genetic factors, environmental exposures, lifestyle habits, medications, and iatrogenic causes. Increased granulosa cell apoptosis contributes to follicular depletion, while conditions such as Turner syndrome, BRCA1/2 mutations, chemotherapy, smoking, and endocrine-disrupting chemicals further accelerate ovarian reserve decline and ovarian aging.[20–22] Clinically, ovarian reserve is assessed using biomarkers and imaging techniques. Among these, serum AMH levels and antral follicle count (AFC) are the most reliable indicators of ovarian reserve.[21,22] AMH reflects the pool of follicles in the gonadotropin-independent phase, while cycle day 3 FSH serves as an indirect marker influenced by inhibin B and oestradiol feedback, supporting early follicular development and oocyte quality.[23]

Premature ovarian insufficiency

POI is a medical disorder in which ovarian follicles become exhausted and no longer function normally as reproductive and endocrine organs in women under the age of 40. Hypergonadotropic hypogonadism develops before the age of 40 in about 1-2% of women.[24,25] Primary amenorrhea may be the initial symptom in up to 10% of instances of POI.[28] This syndrome frequently leads to subfertility or infertility because it is connected with hypoestrogenism, which causes monthly abnormalities and pregnancy failures.[24] POI may have a spontaneous or induced basis. Spontaneous POI can be caused by genetic, autoimmunological, inflammatory, enzyme deficiency, metabolic, or, most commonly, idiopathic factors. Oncological treatments such as surgery (bilateral oophorectomy), chemotherapy, and radiotherapy are the leading causes of induced POI.[26]

Iatrogenic and environmental causes

The developing ovary is particularly vulnerable during prenatal and neonatal periods, when exposure to endocrine-disrupting chemicals (EDCs) can have long-term effects on ovarian function. EDCs, present in cosmetics, agrochemicals, plastics, and food products, can disrupt reproductive function through receptor-mediated hormonal interference or direct cytotoxic effects on ovarian cells.[27] Environmental toxins such as per- and polyfluoroalkyl substances (PFAS) increase ROS production, impair mitochondrial function, and trigger oocyte apoptosis via intrinsic pathways, leading to structural and functional ovarian damage.[28] Smoking is another well-established environmental risk factor associated with earlier menopause and impaired ovarian function. Chemotherapy and radiation damage ovarian tissue and blood supply, causing follicular loss and reduced steroid production.[29]

CONCEPT AND BIOLOGICAL MECHANISMS OF OVARIAN REJUVENATION

Ovarian rejuvenation aims to restore ovarian function by improving the ovarian microenvironment rather than replacing hormones. Ovarian aging and DOR are linked to oxidative stress, mitochondrial dysfunction, DNA damage, reduced vascularization, and telomere shortening, supporting the idea that niche modification may reactivate dormant follicles.[30,31] The “reactivation theory” suggests that primordial follicles may persist but fail to mature due to disrupted endocrine and paracrine signalling.[30] Approaches such as platelet-rich plasma (PRP) and mesenchymal stem cell (MSC) therapy aim to restore this niche. PRP releases growth factors and cytokines that promote cell growth, angiogenesis, and tissue repair.[30] MSCs act mainly through paracrine effects, secreting bioactive molecules that reduce apoptosis, inflammation, and improve vascular support within the ovary, thereby enhancing endocrine and reproductive function.[32] However, despite promising preclinical results, these therapies remain experimental, with limited clinical evidence for consistent fertility restoration.[33]

PRP THERAPY

Platelet-rich plasma is an autologous blood-derived product obtained by centrifugation, resulting in a plasma fraction with a high concentration of platelets.[34] PRP contains growth factors such as TGF-β, IGF, VEGF, and EGF, which promote angiogenesis, cell proliferation, and tissue regeneration.[35] Additionally, platelet α-granules release bioactive proteins that stimulate regenerative processes through paracrine signalling, particularly by influencing mesenchymal stem cells.[36]

PRP exerts its effects through platelet activation (natural or via thrombin/calcium chloride), leading to release of growth factors that regulate both timing and duration of healing responses.[37] These factors promote chemotaxis, cell recruitment, proliferation, and differentiation. Key mediators such as PDGF, IGF-1, and TGF-β support tissue repair, while VEGF, bFGF, and FGF enhance angiogenesis and blood supply. PRP also forms a temporary extracellular matrix (vitronectin, fibronectin, fibrin) that supports cell migration and tissue regeneration.[37] It further reduces inflammation by lowering TNF-α and IL-1β and increases anti-inflammatory mediators, while promoting collagen deposition and tissue remodelling.[38].

In reproductive medicine, PRP is being investigated for improving ovarian function and follicular development through angiogenic, proliferative, and immunomodulatory effects. It is also applied as an adjunct in ART, particularly

IVF, for patients with DOR, POI, or menopause.[39] Intraovarian PRP has shown potential to restore ovarian activity, including resumption of menstruation and spontaneous pregnancies in menopausal women.[40] PRP may help restore ovarian function damaged by chemotherapy or radiation by improving ovarian tissue health with growth factors, potentially supporting fertility recovery and increasing the chances of future pregnancy or successful egg preservation. PRP has been reported to improve ovarian reserve indicators, including increases in AMH and antral follicle count, along with reductions in FSH and LH and elevated oestradiol levels, while early evidence also suggests spontaneous pregnancy rates of approximately 7.4%–10% following treatment.[41] In women with poor ovarian reserve, a 2 mL PRP injection improved AMH and AFC while decreasing FSH levels.[42]

Autologous intraovarian PRP offers several potential advantages, including being a minimally invasive, non-hormonal, and autologous treatment with a low risk of immune reaction, while potentially improving ovarian function, egg quality, and IVF response, restoring fertility in DOR or ovarian failure cases, and serving as a safe adjunct to other fertility treatments.[38] Intraovarian PRP is considered a low-cost alternative to MSC therapy with potential benefits for ovarian rejuvenation and menopausal symptoms, but its long-term safety, optimal use, and mechanisms are still not well understood.[8]

STEM CELL THERAPY

Stem cell therapy is a promising regenerative approach for ovarian disorders such as POI and DOR.[43] Stem cells possess self-renewal and differentiation capacity and are classified into embryonic, foetal, adult, and induced pluripotent types (Figure 2).[44] Among them, MSCs, derived from various adult and perinatal tissues, are widely studied for ovarian regeneration. MSCs support ovarian repair by enhancing follicular survival, improving angiogenesis, improve hormonal balance and reducing cellular damage without affecting embryo quality.[44]

MSCs restore ovarian function mainly via paracrine effects, releasing growth factors, cytokines, and chemokines that promote angiogenesis, improve nutrient supply, and support follicle survival.[32] They may also transfer mitochondria to enhance cell energy and viability. Delivery routes include intraovarian injection, intravenous infusion, and ovarian artery administration.[43] Bone marrow-derived stem cells may aid ovarian repair through differentiation and paracrine actions, potentially restoring menstrual function, improving hormone levels, and in some cases enabling spontaneous pregnancy.[45] They also help reduce granulosa cell apoptosis and support hormone production.[46]

MSC therapy shows potential benefits in POI, including improved hormone levels, follicle counts, and menstrual recovery, but evidence remains limited due to small, non-controlled studies.[45] Larger randomized trials are needed, though it is considered a possible option when conventional treatments are inadequate. Stem cell-based ovarian rejuvenation remains experimental due to safety concerns including immunogenicity, tumorigenic potential, and unknown long-term outcomes.[47] Additional limitations include ethical and regulatory constraints, as well as variability in stem cell sources, dosing, and delivery methods. Currently, there are no standardized clinical guidelines, although emerging research is exploring safer strategies such as gene-modified stem cells and MSC-derived exosomes.[48]

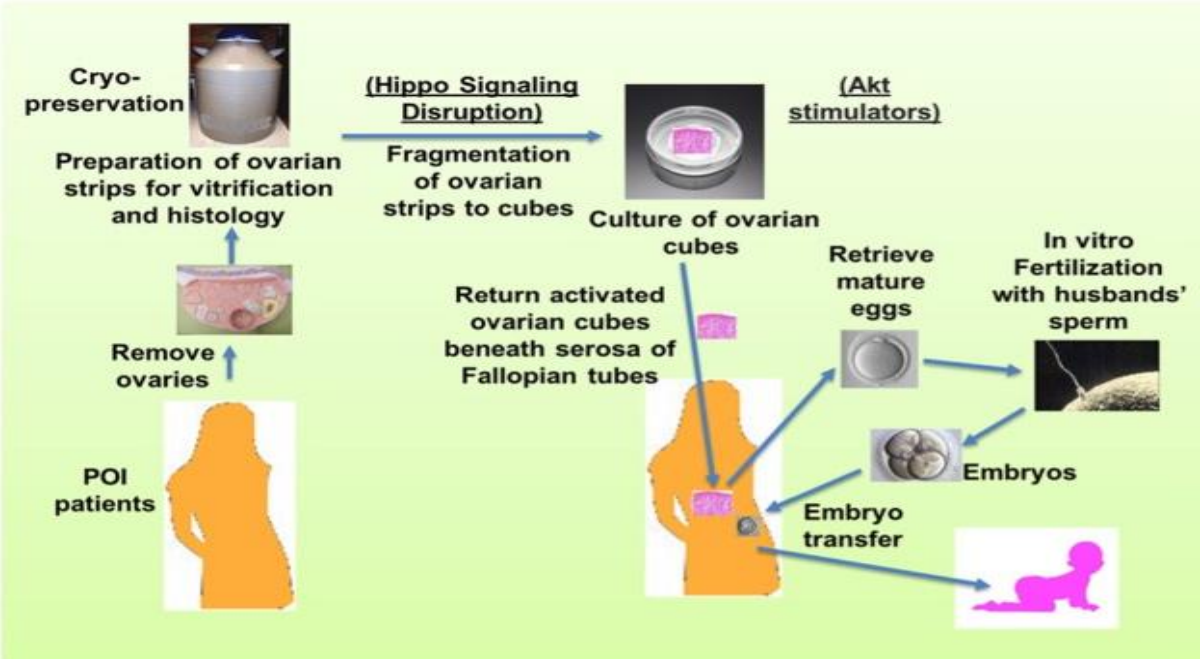

Figure 3: In vitro activation procedure for follicle activation in POI patients.[49]

IN VITRO ACTIVATION

In reproductive biology, IVA stimulates dormant follicles to resume growth through ex vivo ovarian tissue manipulation and reimplantation. It modulates key pathways such as PI3K–Akt activation and Hippo pathway disruption to promote follicular activation in DOR and POI patients.[49] PI3K–Akt signalling is enhanced using PI3K activators or PTEN inhibitors to support primordial follicle survival and activation, while ovarian tissue fragmentation disrupts the Hippo pathway, activating YAP/TAZ signalling and further promoting follicle growth.[49,50] IVA involves laparoscopic retrieval of ovarian cortical tissue, fragmentation, and reimplantation near the ovary or fallopian tube to support follicle development.[51] Drug-free IVA is increasingly preferred in DOR and early POI due to reduced invasiveness and lower risk of follicle damage, and is considered for fertility preservation in women with limited ovarian reserve.[52]

In a review of 51 POI patients undergoing IVA, follicular development occurred in 29.4%, with 4 pregnancies reported after combined fragmentation and pharmacological activation.[53] In a study of 11 DOR/POR patients, IVA improved AFC, with 68.7% fertilization, 56.9% high-quality embryos, resulting in 1 live birth, 2 ongoing pregnancies, 1 miscarriage, and cryopreserved embryos.[51] However, overall pregnancy rates remain low, and only a small proportion achieve pregnancy.[6] IVA is a promising fertility strategy for POI, DOR, and cancer patients with preserved ovarian tissue.[49]

OVARIAN TISSUE TRANSPLANTATION

Ovarian tissue cryopreservation (OTC) and transplantation can restore both fertility and endocrine function, with ovarian activity lasting for several years after transplantation. More than 130 live births have been reported following ovarian tissue transplantation (OTT). This approach is particularly valuable for prepubertal girls and patients requiring immediate cancer treatment, as it does not require ovarian stimulation or oocyte retrieval.[55] Additionally, successful restoration of ovarian function after transplantation suggests its potential role in ovarian rejuvenation. A human case report showed that auto transplantation of cryopreserved ovarian tissue could restore ovarian function in a menopausal woman, indicating possible ovarian rejuvenation.[49] The first successful case of fresh OTT in humans was reported in 2005 involving monozygotic twins.[55]

OTC is mainly done by slow freezing and vitrification. Slow freezing is the most widely used method, involving controlled-rate cooling and storage in liquid nitrogen at −196°C, while vitrification rapidly freezes tissue to minimize ice crystal formation and cryoinjury. Cryopreservation can be performed as whole-ovary preservation, which maintains the ovarian blood supply but is technically challenging, or ovarian cortical tissue preservation, where cortical strips containing primordial follicles are frozen for later transplantation.[56]

OTT can be carried out at orthotopic or heterotopic sites. Orthotopic transplantation restores tissue to the ovary or ovarian fossa, enabling follicular development and potential natural conception. Heterotopic transplantation places tissue at extra-pelvic sites, such as the forearm or abdominal wall, allowing easier access and monitoring when orthotopic transplantation is not feasible.[57]

Ovarian function usually returns within a few months after orthotopic transplantation, but the graft's activity is often temporary. Its functional lifespan varies widely among individuals, typically lasting from a few years.[58] Live birth rates after ovarian tissue transplantation are encouraging but still limited per case and depend on age, disease, and graft quality. A major issue is loss of primordial follicles due to ischemia–reperfusion injury before blood supply is restored, which reduces ovarian reserve and graft lifespan. There is also a risk of reintroducing malignant cells in patients with blood-related or metastatic cancers, which is a major safety concern and limits its use in some cancer patients.[59]

CONCLUSION

Ovarian rejuvenation is an emerging field in reproductive medicine that could potentially help women with DOR or POI regain their ovarian function and increase their fertility. Emerging approaches such as PRP therapy, stem cell therapy, IVA, and ovarian tissue transplantation have demonstrated potential in enhancing follicular development, hormonal function, and reproductive capacity. While stem cell therapy has regenerative potential by enhancing the ovarian microenvironment and perhaps activating dormant follicles, PRP therapy offers a minimally invasive approach that may encourage tissue regeneration through growth factors. Similar to this, IVA has made it possible for patients with ovarian insufficiency to activate their remaining follicles, and ovarian tissue transplantation has emerged as a crucial method of preserving fertility, especially for cancer survivors. However, despite promising first results, these methods are still mostly experimental because of the paucity of clinical data, the absence of standardized procedures, and worries about long-term safety and effectiveness. To confirm their efficacy and determine their place in standard fertility treatment, further extensive research and clinical trials are necessary.

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