Treatment potential of bone marrow-derived stem cells in women with diminished ovarian reserves and premature ovarian failure

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Purpose of review
We review the techniques recently tested in both animal models and humans to provide a state-of-the-art on adult stem cell ovarian transplant to achieve ovarian rejuvenation in patients with diminished ovarian reserves.

Recent findings
As the firsts reports of spontaneous pregnancies achieved after bone marrow transplantation in oncologic women with primary ovarian insufficiency, increasing evidence supports the regenerative effects of stem cell-based therapies in the ovarian niche. Adult stem cells from several origins promote follicular development, increase ovarian local vascularization, increase follicle and stromal cell proliferation and reduce cell apoptosis and follicular atresia, although they do not modify embryo quality. Therefore, residual quiescent follicles of aged or damaged ovaries might produce competent oocytes in an adequate ovarian environment. Nevertheless, further research is needed to properly evaluate underlying mechanisms, identify best cell sources and design less invasive infusion techniques.

Summary
Stem cells may be a relevant therapeutic alternative for ovary regeneration and follicular development in patients with impaired ovaries, such as poor ovarian responders or women diagnosed with primary ovarian insufficiency.

Keywords
adult stem cell, diminished ovarian reserve, follicular rescue, premature ovarian insufficiency, stem cell ovarian transplant

INTRODUCTION

Human ovaries contain a genetically determined limited pool of primordial follicles with both reproductive and endocrine functions [1,2]. The primordial follicle contains an oocyte — for the reproductive function — surrounded by granulosa cells, which fulfill the endocrine role. During reproductive life, many follicles activate and grow under stimulation with follicle-stimulating hormone (FSH), but only one becomes preovulatory during each ovulation cycle [3]. The remaining follicles constitute the ovarian reserve and can be depleted by harmful factors such as smoking [4], surgery or chemotherapy/radiotherapy [5,6], reducing a woman's reproductive potential.

The concept of a diminished ovarian reserve (DOR) first appeared when young patients exhibited similar response to controlled ovarian stimulation (COS) with gonadotropins as did older patients [7,8]. These patients eventually were termed poor ovarian responders (PORs). A more severe condition is primary ovarian insufficiency (POI), characterized by amenorrhea, hypoestrogenism and elevated serum gonadotropin levels; previously referred to

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KEY POINTS

- Infusion of human-derived stem cells could supply an adequate ovarian niche to maintain or promote follicular rescue in patients with impaired or aged ovarian reserves.
- Long-term fertility rescue has been achieved in chemotherapy-induced mouse ovaries mimicking aging, POR or POI after infusion of adult stem cell from different origins as well as several administration techniques, providing scientific evidence to design new alternatives and therapies for humans.
- Human studies propose BMDSCs, both mesenchymal and hematopoietic, which are feasible candidates to promote ovarian rejuvenation, as several pregnancies and live births have been reported after ovarian transplant of BMDSCs in women who are POR or diagnosed with POI.

as premature menopause or premature ovarian failure (POF) [9] this condition affects 1% of women below 40 years old. The main difference between PIO and menopause is the unpredictability of ovarian function, as 5–10% of women with POI may still conceive [10]. The incidence of POI increases with cancer survival, thus POI together with POR and the increasing number of women delaying motherhood pose significant challenges for reproductive medicine.

Many strategies based on COS protocols have been developed to treat impaired ovaries [11]. Unfortunately, there is no specific or successful gold-standard treatment for patients with DOR, POR and/or POI [12–18]. Within this context, cellular therapies have emerged from other medical fields [19] as alternatives to recover ovarian function. For instance, hematologic stem cell treatments have achieved endometrial regeneration and pregnancy in women with Asherman syndrome [20].

In this review, we aim to provide a state-of-the-art for the use of stem cells as a tool to optimize the remaining ovarian reserve in patients with impaired ovaries. Advantages and limitations of cell sources and administration techniques are carefully assessed in both animal and human models to provide an overview of the limited ovarian cell therapy approaches currently available in humans.

Adult stem cell-based therapies to promote follicle development

A small pool of residual quiescent follicles remains in the ovaries of women with DOR, POI or established menopause. These primordial follicles could potentially be rescued and grown to increase the final yield of oocytes, if an appropriate and supportive ovarian niche is provided by different approaches [21,22▪].

ANIMAL STUDIES

The possibility of adult stem cell-based therapies to restore ovarian function arose from animal studies, mainly in rodents with chemotherapy-induced POF. Adult stem cells from both hematopoietic and mesenchymal/stromal types have been tested, although mesenchymal cells with various origins have been the target of most preclinical approaches developed in the past decade. Mesenchymal stem cells (MSCs) display high replication capacity and in-vitro differentiation potential into chondrocytes, osteocytes and adipocytes [23], and they can be found in various adult tissues [24–30].

In the field of reproductive medicine, the ability of human MSCs to survive, engraft and proliferate into the ovaries was first assessed by Liu *et al.* [31] using human amniotic fluid MSCs in a cyclophosphamide-based POF mouse model. Direct ovarian infusion of mouse amniotic fluid MSCs improves ovarian function by reducing atresia, maintaining development of surviving follicles and restoring estrous cyclicity, allowing short-term fertility recovery and generation of offspring [32]. Amniotic epithelial cell (AEC) and amniotic mesenchymal cells (AMSCs) can also be easily isolated from amniotic membranes and discarded after delivery, allowing recovery of clinically relevant cell values. Both human AECs and AMSCs have been successfully tested in rodents with different grades of chemotherapy-induced ovarian damage ranging from DOR to established POF [33]. Recovery of hormone production, differentiation into granulosa cells and restoration of folliculogenesis after infusion of hAECs are reported [34], although hAMSCs show further benefits [33].

Umbilical cord blood has been considered a feasible source of MSCs, with promising results for several degenerative diseases outside the reproductive system [35,36]. When transplanted into ovaries, umbilical cord blood MSCs protect follicular cells against apoptosis [37], promoting follicle development and estradiol secretion. These findings have been confirmed in both chemotherapy-treated [38–40] and naturally aged perimenopausal rat ovaries [41] and seem to be mediated by an indirect effect on the ovarian epithelium and niche via expression of key regulators for apoptosis and folliculogenesis, such as cytokeratin 8/18, transforming growth factor β (TGF-β) and proliferating cell nuclear antigen [40].

Human menstrual blood-derived endometrial stem cells (MenSCs) have been recently proposed

as a therapeutic tool for ovarian disorders [25,27,42,43] based on their multipotency, proliferation rate and reduced immunogenicity, as well as the feasibility of noninvasive collection [44]. MenSCs promote similar positive effects on folliculogenesis, hormone production and apoptosis to that described for amniotic and umbilical cord blood MSCs. Further, MenSCs can differentiate into granulosa cells [27] and can partially restore long-term fertility.

Nevertheless, the absence of an autologous source for these MSCs should be considered a limitation to their application for cell therapy in already aged and POI patients without previously cryopreserved umbilical cord blood or amniotic membranes or in the absence of menses, such as women with POI. On the basis of these issues, other autologous cell sources have been tested, such as adipose tissue [45] and bone marrow. In fact, adipose MSCs [46,47] reduce ovarian apoptosis and recover ovulation in a chemoablated mouse model by inducing POF-related gene expression and secretion of paracrine cytokines [47]. However, ovarian effects seem to be weaker than observed for amniotic-derived MSCs [48].

In the bone marrow, MSCs represent less than 1% of mononuclear cells but can be isolated and cultured based on their adherence [49]. When assayed in chemotherapy-induced POF models [24,43,50–54], bone marrow-MSCs engraft and proliferate over long times in the ovarian stroma [43], protecting germ cells from apoptosis [54] and recovering ovarian function by increasing the number of growing follicles and litter size compared to noncell-treated mice [24,52]. Although MSC-based therapy solves the concern of an autologous cell source, it still requires several culture and isolation techniques [55] to reach relevant cell numbers [56]. Cells can lose their specific regenerative properties after in-vitro culture [57] and can accumulate epigenetic modifications or chromosomal aberrations [58]. To avoid this, reproductive medicine research uses protocols developed for the treatment of hematological malignancies to increase proliferation and stem cell mobilization from bone marrow to peripheral blood by using cytokines such as granulocyte colony-stimulating factor (G-CSF) [59], allowing noninvasive collection of appropriate stem cell numbers from bone marrow and avoiding invasive collection by iliac crest aspiration [60].

Bone marrow-derived stem cells (BMDSCs) represent a heterogeneous group of mononuclear cells with multidifferentiation potential that includes several hematopoietic, mesenchymal and endothelial stem/progenitor cells [61,62]. These multiple regenerative effects on the ovarian stroma have been observed by intravenous infusion of the whole population of human BMDSCs into two different mouse models for DOR and POF, where BMDSCs recover long-term fertility by increasing local ovarian vascularization, increasing follicular and stromal cell proliferation and reducing apoptosis [22▪]. This unique study using human ovarian tissues from POR patients demonstrated for the first time that BMDSCs can engraft close to human follicles and vessels, promoting follicle development and ovarian niche regeneration and vascularization. Importantly, these functions are crucial to maintain follicle growth and maturation cycle [63]. Further work demonstrates the 'homing' ability of BMDSCs into ovarian tissue [43], showing that direct ovarian injection [52] is not needed to induce positive ovarian effects [22▪,33,64]. This finding is of paramount relevance to design less invasive approaches for clinical practice.

Overall, animal studies suggest that stem cell-based therapies could be a suitable option to increase reproductive potential of aging women and women with DOR, POR and POI, in which the ovarian niche cannot maintain growth of their residual follicular pool. In these instances, autologous BMDSCs may be a feasible cell source to recover ovarian function.

HUMAN STUDIES

To date, studies have attempted to regenerate the damaged ovarian niche by offering an appropriate environment to women with impaired ovarian reserves. Many researchers have been attracted by autologous stem cells derived from different tissues [22▪,65,66▪▪,67–69]. Other researchers have focused their attention on different approaches, such as platelet-rich-plasma [70], based on the suggested regenerative mechanism for adult stem cells via paracrine secretion of soluble factors (cytokines, chemokines and growth factors) [71] that could also be implicated in the activation of primordial follicles in impaired ovaries. In fact, some of these stem cell-secreted soluble growth factors have already been related to follicular growth, normal ovarian function and ovarian response to COS. Folliculogenesis involves not only pituitary gonadotrophins (luteinizing hormone and FSH), but also multiple paracrine and autocrine factors produced in the ovary, including prostaglandins, steroid hormones and several families of growth factors, such as insulin-like growth factor-1, TGF-β, epidermal growth factor and fibroblast growth factor (FGF). For instance, FGF-2 acts on granulosa cells to promote cell proliferation and inhibit apoptosis [72–74] and has been related to positive ovarian response to stem cell therapy [75▪].

Several factors influence the proposed ovarian regenerative therapies (Table 1) [65,66▪▪,69,75▪]. One is the stem cell administration technique — although animal studies show that direct ovarian infusion is not required, human stem cells have been infused into one or both ovaries by various methods, such as direct injection via laparoscopy, transvaginal ultrasound-guided injection [65,66▪▪,70], intra-arterial catheterization of the ovarian artery [22▪] or a combination of techniques [69]. Further research is needed to determine the most effective approach, although less invasive methods are needed for both stem cell collection and instillation.

Stem cell source also appears to be an important factor. Several spontaneous pregnancies indicate that BMDSCs can recover ovarian function in patients with POI because of cancer treatment [76–80]. On the basis of this evidence, our group has used BMDSCs to reactivate the ovarian niche, showing activated human follicle growth in mouse and xenografted human ovarian tissues [22▪]. Further, we used BMDSCs to reactivate and rescue human follicles in a prospective pilot study [22▪].

In addition, a published study [75▪] performed autologous cell ovarian transplantation (ASCOT) in 17 POR women (<40 years old) according to European Society of Human Reproduction and Embryology criteria [81], with a total 24 previous in-vitro fertilization cycles as POR (3–5 years infertility). First, stem cells were mobilized from bone marrow to peripheral blood by subcutaneous administration of G-CSF. Then, BMDSCs, including both haematopoietic and mesenchymal stromal cells, were isolated by apheresis and infused by intra-arterial catheter into one ovarian artery. Ovarian reserve biomarkers [antral follicle count (AFC) and antimullerian hormone (AMH)] improved in up to 81.3% patients, which positively correlated with the presence of circulating growth factors FGF-2 and thrombospondin 1. The increase in AFC was statistically significant on day 15, although both AFC and AMH increased during the first 4 weeks after ASCOT. ASCOT treatment achieved five pregnancies (three

Table 1. Human studies involving bone marrow stem cell treatment for premature ovarian insufficiency-poor ovarian responder and perimenopausal patients

Regenerative factor	Study population	Administration method	Main findings	Limitations	Reference
BM-MSC	10 women with idiopathic POI (<40 years old)	BM-MSCs into both ovaries via laparoscopy	Resumption of menses in 20% patients after 3 months 10% treatment POR One pregnancy and a live birth in one patient showing endometrial regeneration	POR similar to that reported for POI patients without treatment	Edessy *et al.* [65]
BM-MSC	1 perimenopausal woman (45-year old)	BM-MSCs into both ovaries via laparoscopy	AFC and AMH increased 8 weeks after treatment 1 live birth	POR similar to that reported for POI patients without treatment	Gupta *et al.* [66▪▪]
BM-MSC	30 patients with POF (18–40 years old)	Direct laparoscopic infusion into the ovarian stroma and catheterism into the ovarian artery of one side	86.7% POF patients improved hormone profile 4 week after treatment 60% showed ovulation 3 patients underwent IVF 1 spontaneous pregnancy	AFC not reported or compared between ovaries. IVF outcomes were not reported	Gabr *et al.* [69]
BM-MSC	33 patients with idiopathic/other POF/POI and low ovarian reserves	BM-MSCs into both ovaries via laparoscopy	Not yet reported	Still ongoing	Al-Hendy *et al.*, (NCT02696889)
BMDSC	15 POR patients (<40 years old)	One ovarian artery by intraarterial catheterism	81.3% POR improved AFC and AMH 2 weeks after the treatment 33.3% treatment pregnancy rate 5 pregnancies and 3 live births	16% euploidy rate because of advanced maternal age was not ameliorated	Herraiz *et al.*, [75▪]

AFC, antral follicle count; AMH, antimullerian hormone; BMDSCs, bone marrow-derived stem cells; BM-MSCs, bone marrow mesenchymal stem cells; IVF, in-vitro fertilization; POF, premature ovarian failure; POI, premature ovarian insufficiency; POR, poor ovarian responder.

spontaneous) and three live births, whereas cycles before ASCOT achieved no pregnancies in 15 POR who completed the study. However, age-associated aneuploidies were not ameliorated (16% euploidy rate). The ASCOT technique's 33.3% treatment pregnancy rate suggests that invasive cell collection, selection/culture procedures and direct infusion into the ovarian stroma are not required to restore fertility. In fact, AFC also improved in the noninfused ovary, suggesting positive effects of circulating BMDSCs during mobilization.

All other human studies have involved cell culture and use of the bone marrow-MSC fraction collected by iliac crest aspiration. By this approach, Gupta *et al.* [66▪▪] reported a baby born to a 45-year-old premenopausal woman after autologous bone marrow-MSC therapy. In this study, bone marrow was aspirated from the posterior iliac crest, and MSCs were instilled into both ovaries by laparoscopy. After 8 weeks, ovarian reserve markers AFC and AMH improved, so an IVF cycle was initiated. A healthy baby was born 11 months after treatment months, although this study only reports one case.

Similarly, Edessy *et al.* [65] injected autologous bone marrow-MSCs from bone of 10 women with idiopathic POI (<40 years old) into both ovaries via laparoscopy. Injection induced resumption of menses in two patients (20%), with one pregnancy and a live birth in one patient (10% treatment pregnancy rate). Similar results were reported by Gabr *et al.* [69] in 30 patients with POF (18–40 years old) transplanted with autologous bone marrow-MSCs. In addition, this study also implies that G-CSF mobilizes cells [75▪], although Gabr *et al.* [69] aspirated cells from the iliac crest and infused them using a combination of two methods (direct laparoscopic infusion into the ovarian stroma and catheter into the ovarian artery) into the same ovary. Four weeks after cell infusion, 86.7% of POI patients showed an ameliorated hormone profile, which was maintained for up to 2 years. Three patients underwent IVF cycles and one patient had a spontaneous pregnancy (3.3% treatment pregnancy rate). A similar study is being developed by El Andaloussi *et al.* [64] (NCT02696889) using autologous MSCs from the iliac crest laparoscopically infused into the ovaries of 33 patients with idiopathic and other types of POF/POI and low ovarian reserves. This study is based on the authors' previous work in animal models [82].

In contrast, Pantos *et al.* [70] introduced a different technique without the direct use of stem cells to reactivate folliculogenesis in perimenopausal women. In this study, the ovaries of eight perimenopausal women of advanced maternal age (41–49 years old) were infused with platelet-rich plasma by transvaginal ultrasound-guided injection. Treatment resulted in the restoration of menses, with the presence of ovarian follicles that allowed oocyte retrieval after IVF treatment in all patients and cryopreservation of 1.50 ± 0.71 embryos. However, a limitation of the study is that it only included eight women and did not document their previous ovarian reserves.

CONCLUSION

This new field of investigation currently indicates that BMDSCs could be an alternative in ovary regeneration and follicular development for women who are POR or have POI. Nevertheless, despite promising reports of bone marrow-MSCs in POI patients, these results should be carefully evaluated and POI patients should be well diagnosed, as resumption of ovarian function has been reported in 23% of untreated POI patients, known as intermittent POI or fluctuating FSH, during their first year of amenorrhea [83]. To date, the ASCOT approach involving the whole BMDSC population seems to be a good approach to treat women who are POR, with a 33.3% treatment pregnancy rate. This treatment should also be investigated in POI patients, where autologous MSCs have resulted in three reported pregnancies in a total of 41 POI patients included in the three published studies to date [65,66▪▪,69].

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Conflicts of interest

S.H. reports personal fees from Ovascience outside the submitted work. The remaining authors declare no conflicts.

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- ▪ of special interest
- ▪▪ of outstanding interest

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