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Case Report

Bone marrow-derived stem cell and platelet-rich plasma therapy for ovarian rejuvenation: natural pregnancy after ovarian failure and review of the literature

Zaher Merhi[1,2,3]

[1]Reproductive Endocrinology and Infertility, Rejuvenating Fertility Center, New York, NY, USA; [2]Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Albert Einstein College of Medicine, Bronx, NY, USA; [3]Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Maimonides Medical Center, Brooklyn, NY, USA

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Abstract: Diminished ovarian reserve (DOR) and premature ovarian insufficiency (POI) remain among the most difficult challenges in reproductive medicine, for which oocyte donation has historically been the only realistic path to biological parenthood. Autologous cell-based approaches such as bone marrow-derived stem cell (BMDSC) administration following granulocyte colony-stimulating factor (G-CSF)-mediated mobilization, and platelet-rich plasma (PRP) supplementation together, have been proposed to reactivate quiescent primordial follicles and restore ovarian function. We report here a new case of a spontaneous pregnancy following combined G-CSF-mobilized BMDSC and PRP therapy combination in a woman with idiopathic POI and synthesize this case alongside nineteen published human studies. Ovarian reserve markers—antral follicle count (AFC) and anti-Müllerian hormone (AMH)—improved in most treated women, and pregnancies, including spontaneous conceptions and live births, occurred even in women with previously exhausted reproductive potential. The two studies collecting stem cells by G-CSF-mediated mobilization, rather than direct bone marrow aspiration, enrolled a combined 160 women and accounted for the majority of reported pregnancies. Proposed mechanisms center on paracrine secretion of angiogenic, follicle-supportive factors such as fibroblast growth factor-2 (FGF-2) and thrombospondin-1 (TSP-1). Safety profiles so far have been favorable, though the evidence remains limited by small, heterogeneous, largely uncontrolled cohorts and short follow-up. We discuss the mechanistic rationale and evidence gaps that must be addressed before this approach can be validated as an alternative to oocyte donation.

Keywords: Ovarian rejuvenation, bone marrow-derived stem cells, platelet-rich plasma, diminished ovarian reserve, premature ovarian insufficiency

1 Introduction

Diminished ovarian reserve (DOR), poor ovarian response (POR), and premature ovarian insufficiency (POI) together account for a substantial share of infertility encountered in assisted reproduction clinics, with poor responders alone estimated to represent up to 24% of women undergoing in vitro fertilization (IVF) [1, 2]. Because the pool of gonadotropin-responsive antral follicles is severely reduced in these conditions, conventional controlled ovarian stimulation protocols and their many modifications have largely failed to meaningfully improve oocyte yield or live birth rates [1, 3]. For decades, oocyte donation has been presented as the only realistic route to pregnancy for many of these women, despite the psychological burden and regulatory restrictions that accompany it, and despite the fact that it forecloses the possibility of a genetically related child [1-3].

This clinical impasse has motivated a search for interventions capable of reactivating the small residual pool of quiescent primordial follicles (approximately 1,000) that persists even in ovaries that are severely depleted or menopausal [1, 3, 4]. Observations that spontaneous pregnancies occasionally follow bone marrow transplantation performed for unrelated hematologic indications first suggested that bone marrow-derived cells might carry a capacity to

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rescue ovarian function [3-5], providing the clinical rationale for translating cell-based ovarian rejuvenation directly into human practice [1, 3, 4].

Here, we report a new previously undescribed case of spontaneous pregnancy following combined granulocyte colony-stimulating factor (G-CSF)-mobilized bone marrow-derived stem cell (BMDSC) and platelet-rich plasma (PRP) combination therapy in a woman with idiopathic POI. Additionally, our literature search draws on six core source publications: a prospective pilot study of autologous stem cell ovarian transplantation (ASCOT) in poor responders [1]; a large retrospective cohort describing a combined G-CSF mobilization and intraovarian PRP protocol ("Stem Cell Regenera") [5]; a case report describing a live birth following laparoscopic BMDSC instillation in a 45-year-old perimenopausal woman [4]; a mixed interventional series applying BMDSC and PRP to both ovarian and endometrial indications [2]; a current-opinion review by Herraiz et al. that synthesizes the wider human BMDSC literature, including several additional prospective series and an ongoing controlled trial not otherwise captured in the first four sources [3]; and a broader review by Ulin, Al-Hendy, and colleagues covering novel POI treatments, which contributes further BMDSC data and substantially expands the PRP evidence base, including the largest PRP cohort published to date [6].

A targeted literature search restricted to human clinical evidence identified five additional BMDSC studies not captured by these six sources: a pilot study combining autologous BMDSC with PRP in poor responders [7], a non-randomized controlled trial of autologous BMDSC transplantation in young women with DOR [8], a case report describing spontaneous conceptions following BMDSC therapy [9], a case study describing a spontaneous pregnancy and live birth following combined BMDSC-based therapy in a woman with idiopathic POI [10], and a case series describing spontaneous and clinical pregnancies, including a live birth, in women with severe DOR treated with combined BMDSC and PRP [11].

Together, these publications allow an integrated picture of the mechanistic rationale of non-invasive stem cell collection (compared to the invasive bone marrow biopsy), the full range of human studies conducted to date, and the strengths and limitations of the current evidence base. No meta-analytic or inferential statistical methods were applied in preparing this review; percentages, counts, and pooled totals presented throughout (e.g., the combined pregnancy counts by collection route in Section 4.8) are simple descriptive summations of figures reported in the original source publications, not the result of new statistical testing.

2 Case report: spontaneous pregnancy following G-CSF-mobilized bone marrow stem cell and PRP therapy

A 29-year-old woman presented with idiopathic POI, diagnosed after she developed secondary amenorrhea and vasomotor symptoms following discontinuation of oral contraceptive pills (OCP) at age 26; she was subsequently maintained on hormone replacement therapy (HRT). Baseline evaluation, obtained while on HRT, showed an AMH of 0.02 ng/mL and a follicle-stimulating hormone (FSH) of 50 mIU/mL. A genetic work-up for POI was unremarkable. Transvaginal ultrasound at initial evaluation demonstrated ovaries of adequate size but with no follicular activity—appearing quiescent rather than atrophic.

The patient underwent sequential ovarian regenerative treatment. An initial intraovarian PRP injection was performed, at which point HRT was discontinued; ultrasound at that visit again showed ovaries of adequate size but with quiescent follicular activity. Several months later and due to no-response to the regular PRP intraovarian administration, she underwent a combined procedure in which autologous BMDSC, mobilized into peripheral blood with G-CSF (filgrastim/Neupogen), were combined with PRP and delivered to the ovaries. The first stage of the treatment was four-day mobilization with G-CSF injection with a SC dose of 10 μg/kg/d. On the fifth day, blood draw was performed followed by centrifugation at 5,000×g. The bottom layer that contains the red blood cells and the upper layer containing platelet-poor plasma were discarded and the middle layer was collected in a 10 mL syringe for administration (total amount of 6 mL). This layer is supposed to be containing the stem cells and the PRP. The second stage of treatment involved injecting BMDSC-PRP combination into the ovarian cortical area (3 mL per

ovary) under ultrasound-guided process like that of an oocyte puncture, on the fifth day.

Following this procedure, she completed a two-week course of OCP before transitioning to natural-cycle monitoring with serial bloodwork and transvaginal ultrasound, without any ovarian stimulation medication. The patient ovulated spontaneously approximately six weeks after the procedure. On natural-cycle monitoring, serum estradiol and progesterone rose in a pattern consistent with ovulation and early luteal support (estradiol rising from 54 to 170 pg/mL and progesterone from 2.3 to 15.9 ng/mL over the following two weeks). A serum human chorionic gonadotropin (hCG) level obtained after the expected implantation window returned positive at 164 mIU/mL, rising to 366 mIU/mL 48 hours later—a more-than-twofold rise over 48 hours, consistent with an early, appropriately developing pregnancy. She was started on supplemental oral estradiol and progesterone daily; at the time of this writing the pregnancy is ongoing and a fetal heart rate at 140 beats per minute was noted on her ultrasound. The pregnancy is at the end of the first trimester and transitioning to the second trimester smoothly with no complications.

This conception occurred spontaneously, without ovarian stimulation medication, in a natural monitored cycle following combined G-CSF-mobilized BMDSC and PRP therapy—consistent with the paracrine, follicle-reactivating mechanism proposed for this collection route (see Section 4.8 below), and adding a further data point to the still-small number of pregnancies reported in the literature following G-CSF-mobilized peripheral blood collection specifically, as distinct from direct bone marrow aspiration. As with any single case, a causal relationship between treatment and conception cannot be established; spontaneous conception, while uncommon in women with an AMH this low, cannot be excluded, and this case should be interpreted with the same caution applied to the anecdotal reports discussed in Section 4.6.

3 Mechanisms of action in human ovarian tissue

As of today, none of the clinical studies claim that transplanted bone marrow cells differentiate directly into oocytes. Rather, the prevailing hypothesis is a paracrine one: circulating and locally delivered stem cells secrete cytokines, chemokines, and growth factors that restore a supportive ovarian niche, permitting follicles that were previously dormant or growth-arrested to resume development [1-3, 5]. The two factors FGF-2 and TSP-1 were specifically measured in the ASCOT pilot study (discussed below in details) and were found in higher concentration in the apheresis product of women who subsequently showed an improvement in AFC or AMH; FGF-2 in particular is known to act on granulosa cells to promote proliferation and inhibit apoptosis, and has been associated with, though not established as a cause of, a positive ovarian response to stem cell therapy [1, 3]. Both FGF-2 and TSP-1 are stored in and released from platelet alpha-granules; because the apheresis product analyzed by Herraiz et al. is not platelet-depleted, platelet-derived release, rather than a specific product of the mobilized CD133+ hematopoietic fraction, is a plausible source of this signal and should be considered alongside a direct stem-cell origin. Anagani et al. similarly emphasize angiogenesis, anti-apoptotic, anti-fibrotic, and immunomodulatory paracrine actions of mesenchymal stem cells (MSC) and hematopoietic stem cells, alongside PRP-derived growth factors including insulin-like growth factor (IGF)-1 and vascular endothelial growth factor (VEGF) [2].

A second recurring theme is that ovarian aging and DOR may reflect deterioration of the follicular niche and its vascular supply rather than an absolute absence of follicles capable of growth [1, 3-5]. Poor responders are known to have reduced ovarian stromal blood flow, and growing follicles require an adequate vascular network to progress; restoring local angiogenesis is therefore proposed as a plausible route by which stem cell- or PRP-derived factors could rescue follicular development even in ovaries with very low AFC [1, 3]. This niche-centered framework underlies the shared clinical strategy across all studies reviewed: mobilize or harvest autologous stem cells, then deliver them (or PRP enriched with their secreted factors) directly to the ovary or systemically, by intra-arterial catheterization, intraovarian injection under laparoscopic or transvaginal ultrasound guidance, or intravenous infusion.

Mechanistic work on the BMDSC secretome specifically supports a cell-free, factor-mediated model of action. Park et al. showed that con-

ditioned medium from human BMDSCs enhances proliferation of human ovarian microvascular endothelial cells and upregulates approximately 42 angiogenesis-related genes, including transforming growth factor-alpha (TGF-α), epidermal growth factor (EGF), VEGF-A, and angiopoietin-2 (ANGPT2), several of which converge on the PI3K/Akt (phosphoinositide 3-kinase/protein kinase B) signaling pathway that also governs primordial follicle activation [6, 12]. This secretome-focused evidence strengthens the rationale, discussed further below, for exploring cell-free or PRP-based alternatives that reproduce the paracrine benefit of stem cell transplantation without the logistical and regulatory burden of cell harvesting and delivery [6].

4 Review of clinical evidence

4.1 Autologous stem cell ovarian transplantation (ASCOT) in poor responders

Herraiz et al. conducted a prospective observational pilot study in 17 women meeting European Society of Human Reproduction and Embryology (ESHRE) poor-responder criteria, of whom 15 completed follow-up after one withdrawal for a procedural vascular event [1]. Peripheral blood stem cells were mobilized with five days of G-CSF and collected by apheresis; a CD133-enriched fraction was then delivered directly into one ovarian artery via intra-arterial catheterization, with the contralateral ovary serving as an internal control [1]. Total AFC rose significantly by day 15 post-treatment, and using a composite definition of response (an AFC increase of three or more follicles and/or two consecutive increases in AMH), 81.3% of women showed an improvement in ovarian reserve within the first four weeks [1]. Paired comparison of stimulation cycles before and after ASCOT showed increased AFC, more oocytes retrieved, and a marked reduction in cycle cancellation (from 29.2% to 14.2%) [1]. Ultimately, five pregnancies were achieved among the 15 women, three of them spontaneous, yielding three live births and a treatment pregnancy rate of 33.3% [1]. Embryo euploidy rates, however, remained low (16.1%), consistent with the advanced reproductive age of the cohort and confirming that this therapy improves oocyte quantity rather than age-related aneuploidy [1, 3].

4.2 The stem cell regenera protocol: a large real-world cohort

Santamaria et al. reported a retrospective, real-world analysis of 145 women with POR, DOR, or POI treated between January 2023 and December 2024 [5]. The protocol combined a tailored, symptom- and leukocyte count-adjusted four-day course of G-CSF with intraovarian injection of stem-cell-factor-enriched PRP administered transvaginally to both ovaries [5]. Using a similar activation definition to the ASCOT trial, 68.28% of women achieved oocyte activation [5]. Among activated women, 7.07% conceived spontaneously and a further 14.14% became pregnant after IVF, whereas no pregnancies occurred among non-activated women [5]. CD34+ cell mobilization was successful in all participants, and G-CSF was well tolerated, with no severe adverse events [5]. As the largest cohort reviewed here, this study offers the most robust real-world estimate of activation and pregnancy rates, while acknowledging that its retrospective, uncontrolled design limits causal inference [5].

4.3 Live birth following laparoscopic BMDSC instillation in a perimenopausal woman

Gupta et al. described a single case of a 45-year-old perimenopausal woman with an AFC of one and an AMH of 0.4 ng/mL who declined donor oocyte treatment [4]. Bone marrow was aspirated from the posterior iliac crest, processed with a closed automated separation system, and instilled laparoscopically into both ovaries at multiple sites [4]. By eight weeks, AFC had risen to two follicles in each ovary and AMH had approximately doubled to 0.9 ng/mL; a subsequent stimulation cycle yielded three oocytes and a single Grade A embryo, which after frozen transfer resulted in a healthy live birth roughly eleven months after treatment [3, 4]. The authors present this as the first reported live birth following autologous BMDSC ovarian therapy in a woman of this age, extending prior published experience—which had been confined to women under 40 with POI—into the perimenopausal range [4].

4.4 Combined ovarian and endometrial regeneration with BMDSC and PRP

Anagani et al. evaluated a broader, heterogeneous cohort of 37 women aged 18-56 years

with thin endometrium, POI, DOR, secondary amenorrhea, hypothalamic hypogonadism, or menopause, receiving combined BMDSC and PRP instilled into the endometrium, the ovaries, or both, depending on indication [2]. Endometrial thickness improved in all treated patients, and FSH declined significantly in the ovarian treatment group overall and specifically in POI and menopausal subgroups, in which 100% showed improvement [2]. Three clinical pregnancies were reported among treated women, together with resumption of spontaneous menses in one amenorrheic patient and symptomatic improvement in two menopausal women [2]. This study is unique among those reviewed in combining endometrial and ovarian indications within a single protocol and in extending treatment to menopausal women, though its heterogeneous population and lack of a comparator group make its findings primarily hypothesis-generating [2].

4.5 Additional BMDSC series identified in the current-opinion review

Herraiz et al.'s 2019 current-opinion review tabulates several additional human BMDSC studies that predate or run parallel to the ASCOT trial and are not otherwise captured above [3]. Edessy et al. treated ten women under 40 years old with idiopathic POI, injecting autologous BMDSCs (collected by iliac crest aspiration) into both ovaries via laparoscopy; menses resumed in 20% of patients within three months, and one patient achieved a pregnancy and live birth, corresponding to a 10% treatment pregnancy rate [3, 13]. Gabr et al. treated 30 women aged 18-40 with POI using a combined approach—direct laparoscopic infusion into the ovarian stroma together with catheterization of the ovarian artery on the same side—and reported an improved hormone profile in 86.7% of patients at four weeks, sustained for up to two years, with 60% showing ovulation; three patients underwent IVF and one achieved a spontaneous pregnancy (3.3% treatment pregnancy rate), though AFC and full IVF outcomes were not systematically reported [3, 14]. A further prospective trial by Al-Hendy and colleagues (registered as ROSE-1 [Rejuvenation Of premature ovarian failure with Stem cells], NCT02696889) was ongoing at the time of the current-opinion review, enrolling 33 women with idiopathic and other types of POI for laparoscopic bilateral intraovarian infusion of autologous BMDSCs; a preliminary case had resumed menses roughly six months post-injection with improvement in menopausal symptoms, but full trial results were not yet available [3, 15]. A subsequent report from the same University of Illinois at Chicago/University of Chicago research group, Igboeli et al., published two case reports of women with POI who received a laparoscopic intraovarian injection of autologous bone marrow nucleated cell concentrate into one ovary; both women showed an increase in baseline estrogen and amelioration of menopausal symptoms, and both experienced a single episode of menstrual bleeding around seven months after treatment, though neither achieved a pregnancy [6, 16]. Given the overlapping investigator group and cell source, this case report may represent early clinical experience from the same program registered as ROSE-1, though the two publications report different patient numbers and the relationship between them is not stated explicitly in either source; readers should treat the ROSE-1 trial as still substantively unreported pending a full peer-reviewed trial publication. Taken together, these earlier MSC-based series achieved substantially lower treatment pregnancy rates (0-10%) than the ASCOT protocol's 33.3%, which Herraiz et al. suggest may indicate that the more invasive cell culture and stromal-infusion procedures used in these studies are not necessary to restore fertility, and that whole, uncultured BMDSC populations delivered via a less invasive route may be equally or more effective [3].

4.6 Additional BMDSC studies identified through a targeted literature search

To ensure this review reflects the most current human evidence, we conducted a targeted literature search restricted to clinical studies of autologous BMDSC therapy in women, which identified five additional studies not captured by the review articles above. Tandulwadkar and Karthick conducted a pilot study combining autologous BMDSC with PRP in 20 women meeting POSEIDON Group 3 or 4 poor-responder criteria, instilling both preparations directly into the ovaries; treatment produced statistically significant increases in AFC, the number of metaphase II oocytes retrieved, and the number of Grade A and Grade B embryos obtained on subsequent stimulation, although the increase in AMH did not reach statistical sig-

nificance [7]. Singh et al. reported the Trial of Autologous Marrow-derived Stem Cell Ovarian Transplantation (TAMSCOT), a non-randomized controlled trial conducted at the All India Institute of Medical Sciences that enrolled 42 infertile women under 35 years of age with DOR, of whom 22 elected to undergo bilateral transvaginal intraovarian BMDSC transplantation and 20 served as an untreated comparator group; 68% of treated women (15/22) showed an improvement in AMH and AFC, with significant increases relative to baseline sustained through six months of follow-up and no treatment-related complications observed [8]. Additionally, Tandulwadkar et al. described two women with decreased ovarian reserve, treated at the same Indian center, who conceived spontaneously following autologous BMDSC therapy after prior unsuccessful fertility treatment, reported as the first such spontaneous conceptions described in the Indian literature [9]. Naimat et al. described a further single case of a 32-year-old woman with idiopathic POI, diagnosed at age 28 with FSH 44 mIU/mL, LH 15 mIU/mL, and undetectable AMH (0.01 ng/mL) after two failed IVF cycles, who underwent laparoscopic instillation of autologous bone marrow-derived mononuclear cells obtained by iliac crest aspiration and double-spin separation, 2 mL injected into each ovary plus 1 mL into the endometrial cavity, together with adjunctive tadalafil, dexamethasone, and myoinositol, intravaginal radiofrequency at three months, a PRP injection at three months, and a second BMDSC injection at six months [10]. FSH normalized to 9 mIU/mL and menses resumed by seven months post-treatment, and the patient conceived spontaneously at nine months, delivering a healthy 3.5 kg male infant by cesarean section at 38 weeks [10]. Alzogaray et al. described a case series of three women with severe DOR and repeated IVF failure, treated at a single IVF center with combined intraovarian PRP injection and autologous BMDSC administration; the report describes the occurrence of a spontaneous pregnancy, a clinical pregnancy, and a live birth among the group, though the published abstract does not specify which outcome occurred in which patient or provide detailed hormonal or procedural data [11]. These additional studies reinforce the pattern seen across the broader BMDSC literature—consistent improvement in AFC and AMH in a majority of treated women—and the TAMSCOT trial in particular is notable as the only study reviewed here, apart from ASCOT's within-patient design, that enrolled a concurrent comparator group [1, 7-9]. Two of these five studies (the Naimat et al. case study and the Alzogaray et al. case series) additionally illustrate that pregnancies, including live births, continue to be reported anecdotally with combined BMDSC/PRP protocols, even outside formal cohort designs [10, 11].

4.7 Platelet-rich plasma (PRP) alone, without stem cell transplantation

A distinct approach reported by Pantos et al. dispensed with stem cell transplantation altogether, instead injecting autologous platelet-rich plasma directly into the ovaries of eight perimenopausal women of advanced maternal age (41-49 years) via transvaginal ultrasound guidance [3, 17]. Treatment restored menses and was associated with the presence of ovarian follicles sufficient to permit oocyte retrieval after IVF stimulation in all eight patients, with cryopreservation of on average 1.5 embryos per patient [3, 17]. This small series suggests that PRP-derived growth factors alone, without cellular transplantation, may be sufficient to reactivate folliculogenesis in some women, consistent with the paracrine mechanism proposed for cell-based approaches; however, the study is limited by its very small size and the absence of documented baseline ovarian reserve for comparison [3, 17].

The Ulin/Al-Hendy review substantially broadens this PRP evidence base beyond the Pantos et al. series [6]. Sills et al. reported the first documented case of blastocyst formation following intraovarian PRP injection, treating four patients with calcium gluconate-activated autologous PRP under ultrasound guidance and achieving blastocyst formation for cryopreservation in all patients, with one clinical pregnancy at nine weeks [6, 18]. Sfakianoudis et al. described a case series of three poor responders who conceived after a similar transvaginal PRP protocol [6, 19]. Hsu et al. reported a live birth of twins in a woman with POI who received PRP combined with low-dose gonadotropin, with spontaneous resumption of menses on days 25 and 48 after treatment [6, 20]. Petryk et al. treated 38 women with low ovarian reserve using a laparoscopic-assisted, high-dose PRP protocol (platelet concentration

approximately 1×10^6/μL) and reported ten pregnancies, four of them spontaneous, resulting in six live births - among the higher treatment pregnancy rates (26%) reported for any PRP or stem cell protocol reviewed here [6, 21].

By far the largest body of PRP evidence comes from Cakiroglu et al., who treated 510 women with POI using transvaginal ultrasound-guided intraovarian injection of 2-4 mL of autologous PRP [6, 22]. Following treatment, AFC and serum AMH increased while serum FSH decreased; 3.9% of the full cohort (approximately 20 women) conceived spontaneously, and of 477 patients who proceeded to IVF, 23 achieved a pregnancy, for a combined estimated pregnancy rate on the order of 8% across the entire treated population [6, 22]. Although still an uncontrolled, real-world cohort rather than a randomized trial, this study is more than three times larger than the direct-aspiration BMDSC literature combined, and its consistency with the smaller PRP series and with the BMDSC studies—improved AFC and AMH, reduced FSH, and pregnancies occurring in a meaningful minority of treated women—lends convergent support to the paracrine, niche-restorative mechanism proposed throughout this review [6, 22].

4.8 Collection route as a design variable: G-CSF-mobilized peripheral blood versus direct bone marrow aspiration

The 13 BMDSC studies reviewed above can be divided by how the stem cell product was obtained. Most rely on direct BM aspiration from the iliac crest under local or general anesthesia, followed by laparoscopic, transvaginal, or (in Gabr et al.'s combined protocol) ovarian-artery delivery of the aspirate or its processed mononuclear or mesenchymal fraction [2, 4, 7-11, 13-16]. Two studies instead used G-CSF (e.g., filgrastim/Neupogen) to mobilize hematopoietic stem and progenitor cells out of the marrow and into peripheral circulation, where they were collected from a blood draw or apheresis rather than a marrow aspiration procedure: Herraiz et al.'s ASCOT trial (4 days of G-CSF, apheresis collection, a CD133-enriched fraction delivered by ovarian artery catheterization) [1] and Santamaria et al.'s Stem Cell Regenera protocol (a tailored four-day G-CSF course, with stem-cell-factor-enriched PRP prepared from the mobilized peripheral blood and injected intraovarian transvaginally) [5].

An important caveat to this proposed collection-route distinction is cellular composition. G-CSF mobilizes predominantly hematopoietic stem and progenitor cells (CD34+, and in ASCOT a CD133+-enriched subset) into peripheral blood; bona fide mesenchymal stromal cells, which are thought to mediate much of the paracrine, niche-restorative activity attributed to direct BM aspirates, are present in peripheral blood only in trace numbers even after G-CSF mobilization. Neither Herraiz et al. nor Santamaria et al. report flow-cytometric characterization confirming a mesenchymal stromal component in their apheresis or peripheral-blood products [1, 5]. The rationale for the G-CSF-mobilization route therefore cannot rest on delivering mesenchymal stromal cells to the ovary; a more defensible interpretation is that the active constituents are the hematopoietic progenitor cells, monocytes, and platelets co-collected in the same product, all of which are established secretors of angiogenic and immunomodulatory factors independent of any mesenchymal stromal cell content. This mechanistic distinction between the two collection routes has not been directly investigated in any of the studies reviewed here and should be regarded as an open question rather than an established explanation for the observed clinical effect.

These two G-CSF-based studies are notable both for their scale and their outcomes. Together they enrolled 160 women (n=15 analyzed in ASCOT, n=145 in Stem Cell Regenera)—comparable in total size to the entire direct-aspiration literature combined and reported 26 pregnancies: 5 in ASCOT (3 of them spontaneous, yielding 3 live births) and 21 among Santamaria et al.'s activated subgroup (7 spontaneous conceptions and 14 IVF-mediated pregnancies) [1, 5]. By contrast, the direct-aspiration studies that have reported conception outcomes to date describe at least 9 confirmed pregnancies in total across smaller, more heterogeneous cohorts (1 in Gupta et al., 3 in Anagani et al., 1 in Edessy et al., 1 in Gabr et al., 2 in Tandulwadkar et al.'s Ray of Hope series, and 1 in Naimat et al.), plus an unspecified but small number described in Alzogaray et al.'s three-patient case series, while several of the

larger direct-aspiration trials—TAMSCOT, ROSE-1, and Tandulwadkar and Karthick's BMDSC-plus-PRP pilot—have not yet reported conception or live birth data at all [2, 4, 7-11, 13, 14].

This raises the possibility that G-CSF-mediated mobilization of peripheral blood stem cells—avoiding a marrow aspiration procedure altogether—could be both a less invasive and a more reproducibly effective collection strategy than direct BM harvesting, consistent with the paracrine, secretome-driven mechanism proposed throughout this review (Section 3), in which therapeutic benefit is thought to derive from circulating or locally delivered growth factors rather than from engraftment of the aspirated marrow cells themselves. However, this comparison should be interpreted cautiously: the two collection routes were not tested head-to-head, are confounded by differing patient populations (poor responders in ASCOT versus a heterogeneous POR/DOR/POI population in Stem Cell Regenera, versus more uniformly POI cohorts in several of the direct-aspiration studies), differing pregnancy definitions and denominators, and by the fact that several direct-aspiration trials with pending conception data could ultimately report comparable results once fully published. A direct, prospectively controlled comparison of G-CSF-mobilized peripheral blood collection versus direct BM aspiration—ideally within a single trial design, would be needed to confirm whether collection route itself, rather than population selection or protocol intensity, drives the apparent difference in reported pregnancy outcomes.

5 Comparative summary of study design and outcomes

Table 1 summarizes the design, populations, interventions, and principal outcomes of all twenty human studies and reports discussed above: a new de-identified case report presented in Section 2, four original clinical reports (Sections 4.1-4.4), four additional BMDSC studies identified through the Herraiz et al. 2019 current-opinion review (Section 4.5), five additional BMDSC studies identified through a targeted literature search of the human clinical evidence (Section 4.6), and six further entries - one BMDSC case report and five PRP series or cohorts, including the 510-patient Cakiroglu et al. cohort - identified through the Ulin/Al-Hendy 2021 review (Section 4.7).

Several patterns emerge from this expanded comparison. First, delivery route varied considerably—intra-arterial catheterization [1], transvaginal ultrasound-guided intraovarian injection [5, 8, 17-20, 22], and laparoscopic intraovarian instillation [2, 4, 13-16, 21]—yet all approaches were associated with improvement in reserve or hormonal markers in a majority of treated women. Second, treatment pregnancy rates varied widely across studies, from 0% in the Igboeli et al. case reports to 33.3% in the ASCOT trial, with the two largest cohorts (Santamaria et al., n=145, and Cakiroglu et al., n=510) each showing a combined pregnancy rate in roughly the 8-21% range [1, 5, 6, 16, 22], a spread that likely reflects differences in patient selection, cell/PRP preparation, and delivery route rather than a single dominant variable. The Naimat et al. case study (1/1) and the Alzogaray et al. case series (pregnancies reported among 3 patients) reinforce this signal anecdotally, though single cases and very small series are too underpowered to yield a meaningful population-level treatment pregnancy rate [10, 11]. Third, of the twenty studies and reports, only the ASCOT trial and the TAMSCOT trial incorporated any comparator—the untreated contralateral ovary in ASCOT, and a non-randomized untreated control group in TAMSCOT—and none used a randomized, sham-controlled design [1, 8]. Fourth, the ongoing Al-Hendy ROSE-1 trial remains the only study in this table explicitly registered as a controlled prospective trial, though the related Igboeli et al. case reports suggest at least preliminary clinical experience from the same program is beginning to emerge in the peer-reviewed literature [3, 6, 15, 16]. Fifth, the Cakiroglu et al. cohort is, by patient count, more than three times larger than the direct-aspiration BMDSC literature combined, and its results—improved AFC and AMH, reduced FSH, and pregnancies in a meaningful minority of women—are broadly concordant with the smaller BMDSC and PRP series, offering the most robust single data point in favor of a real, if modest, treatment effect [6, 22].

6 Safety

The safety profile reported across the studies reviewed is reassuring, though systematically assessed only in the two G-CSF-based protocols [1, 5]. In the ASCOT pilot study, one patient

Table 1. Comparison of human studies of autologous stem cell- and/or PRP-based ovarian therapy

Study (Ref.)	Design/n	Population	Intervention	Key ovarian-reserve outcome	Pregnancy outcome	Safety
Herraiz et al., 2018 [1] (ASCOT)	Prospective pilot, n=17 (15 analyzed)	Poor responders, <40y (ESHRE/Bologna criteria)	G-CSF mobilization + apheresis; BMDSC delivered by intra-arterial ovarian catheterization (1 ovary treated, contralateral as control)	AFC increased significantly at day 15; reserve improved (AFC and/or AMH) in 81.3%; correlated with FGF-2 and TSP-1	5/15 pregnancies (33.3% PR); 3 live births; 3/5 spontaneous	1 venous spasm (withdrawn); 1 G-CSF headache; otherwise well tolerated
Santamaria et al., 2025 [5] (Stem Cell Regenera)	Retrospective, real-world, n=145	POR, DOR, and POI (heterogeneous)	Tailored G-CSF mobilization + intraovarian injection of stem-cell-factor-enriched PRP (transvaginal, both ovaries)	Oocyte activation (AFC + 3 and/or AMH + 20%) in 68.28%	7.07% spontaneous gestation; 14.14% pregnancy after IVF; none in non-activated women	No severe adverse effects; mild-moderate G-CSF symptoms, self-limited
Gupta et al., 2018 [4]/[3] (case report)	Single case, n=1	45-year-old perimenopausal woman, AFC=1, AMH 0.4 ng/mL	Bone-marrow aspiration; BMDSC isolated (Sepax); laparoscopic bilateral intraovarian instillation	AFC rose to 2 follicles/ovary; AMH rose to 0.9 ng/mL by 8 weeks	Live birth of healthy baby (~11 months after treatment)	None reported
Anagani et al., 2021 [2]	Non-randomized interventional, n=37 (ovarian subset)	Mixed: POF, DOR, thin endometrium, secondary amenorrhea, hypothalamic hypogonadism, menopause	Laparoscopic intraovarian BMDSC + PRP (± hysteroscopic endometrial instillation); adjunct medications	FSH improved in 89.7% (32.9→10.7 IU/L); ovarian blood flow improved in 19%	3 clinical pregnancies (2 POF, 1 secondary infertility); 1 delivery, 2 ongoing	None reported
Edessy et al., 2016 [13] (cited in [3])	Prospective, n=10	Idiopathic POI, <40 years old	Autologous BM-MSC (iliac crest aspiration) into both ovaries via laparoscopy	Resumption of menses in 20% of patients within 3 months	1 pregnancy and 1 live birth (10% treatment PR)	Not detailed; no major complications reported
Gabr et al., 2016 [14] (cited in [3]) [conference abstract; not peer-reviewed]	Prospective, n=30	POF, 18-40 years old	Autologous BM-MSC via combined direct laparoscopic ovarian-stroma infusion + ovarian artery catheterization (same ovary)	86.7% showed improved hormone profile at 4 weeks, sustained to 2 years; 60% showed ovulation	3 patients underwent IVF; 1 spontaneous pregnancy (3.3% treatment PR)	AFC and IVF outcomes not systematically reported
Al-Hendy et al. (ROSE-1, NCT02696889) [15] (cited in [3])	Ongoing prospective trial, n=33	Idiopathic and other POF/POI with low ovarian reserve	Autologous BM-MSC (iliac crest) laparoscopically infused into both ovaries	Not yet fully reported at time of Herraiz et al. 2019 review; preliminary case: resumed menses ~6 months post-injection with improved menopausal symptoms	Not yet reported	Not yet reported
Pantos et al., 2016 [17] (cited in [3]) [conference abstract; not peer-reviewed]	Small prospective series, n=8	Perimenopausal women, advanced maternal age (41-49 years)	Autologous platelet-rich plasma (no stem cells) via transvaginal ultrasound-guided intraovarian injection	Restoration of menses; follicles present allowing oocyte retrieval in all patients	Oocyte retrieval and cryopreservation of 1.50 ± 0.71 embryos per patient after IVF in all patients	No adverse effects reported; baseline ovarian reserve not documented (limitation)
Tandulwadkar & Karthick, 2020 [7]	Prospective pilot, n=20	POSEIDON Group 3/4 poor responders	Combined autologous BMDSC + PRP, intraovarian instillation	Significant increases in AFC, MII oocytes, and Grade A/B embryos on subsequent stimulation; AMH increase not statistically significant	Not the primary endpoint; not systematically reported in source summary	No adverse events reported
Singh et al., 2021 [8] (TAMSCOT) [conference abstract; not peer-reviewed]	Non-randomized controlled trial, n=42 (22 treated, 20 untreated comparators)	Infertile women <35y with DOR (AFC<5, AMH<1.2 ng/mL and/or FSH>8 IU/L)	Autologous BM-MSC (iliac crest aspiration); bilateral transvaginal intraovarian transplantation	68% (15/22) improved AMH/AFC; significant increase vs. baseline at 1 and 6 months, sustained to 10-month follow-up	Not yet reported at time of publication (conception follow-up ongoing)	No complications reported
Tandulwadkar et al., 2022 [9] (Ray of Hope)	Case report, n=2	Women with decreased ovarian reserve	Autologous BMDSC ovarian therapy	Not detailed in source summary	2 spontaneous conceptions (first reported in this Indian cohort)	No adverse events reported
Naimat et al., 2022 [10] [preprint; not peer-reviewed]	Case study, n=1	32-year-old woman, idiopathic POF (dx age 28)	Autologous BM mononuclear cells (iliac crest, double-spin) 2cc/ovary + 1cc endometrial cavity, laparoscopic; adjunct tadalafil, dexamethasone, myoinositol, radiofrequency, PRP at 3 mo, repeat BMDSC at 6 mo	FSH normalized 44→9 mIU/mL by 7 months; menses resumed at 7 months	Spontaneous conception at 9 months; live birth (3.5 kg male) by cesarean at 38 weeks	Not detailed in source summary

Alzogaray et al., 2024 [11] [preprint; not peer-reviewed]	Case series, n=3	Severe DOR, repeated IVF failure	Intraovarian autologous PRP + autologous BM-derived MSCs	Not detailed in source summary	Spontaneous pregnancy, clinical pregnancy, and live birth reported among the 3 patients (not individually attributed)	Not detailed in source summary
Igboeli et al., 2020 [16] (cited in [6])	2 case reports	POI/POF women with menopausal symptoms	Autologous BM-MSC (bone marrow nucleated cell concentrate) injected into one ovary via laparoscopy	Increased baseline estrogen; amelioration of menopausal symptoms; both patients had 1 episode of menstrual bleeding at 7 months	No pregnancy reported	No adverse effects reported
Sills et al./Sfakianoudis et al./Hsu et al., 2018-2020 [18-20] (cited in [6])	Small case series/reports, n=4/n=3/n=1	POR and POI/POF	Autologous PRP (calcium gluconate-activated in [18]; combined with gonadotropin in [20]) via transvaginal ultrasound-guided intraovarian injection	Blastocyst formation achieved in all patients [18]; restored menstruation and hormone profile improvement in [19, 20]	1 pregnancy (~9-week) [18]; 3 pregnancies [19]; 1 twin live birth [20]	No severe adverse effects reported across the three series
Petryk et al., 2020 [21] (cited in [6])	Prospective series, n=38	Women with low ovarian reserve	Laparoscopic-assisted high-dose autologous PRP (1×10^6/μL) intraovarian injection	Not detailed in source summary	10 pregnancies (4 spontaneous, 6 live births)	Not detailed; no major complications reported
Cakiroglu et al., 2020 [22] (cited in [6])	Largest PRP cohort to date, n=510	Women with POI	Autologous PRP (2-4 mL) via transvaginal ultrasound-guided intraovarian injection	AFC and serum AMH increased; serum FSH decreased	3.9% spontaneous conception (~20/510); 23/477 pregnancies after IVF (~4.8%); ~43 total pregnancies (~8.4% of cohort)	No severe adverse effects reported in this large cohort
Present case (this report)	Case report, n=1	Woman in her late 20s, idiopathic POI, AMH 0.02 ng/mL	G-CSF-mobilized autologous BMDSC + PRP delivered to ovaries; OCP lead-in then natural-cycle monitoring, no stimulation	Ovaries quiescent pre-treatment; spontaneous ovulation ~6 weeks post-procedure with appropriate E2/P4 rise	Spontaneous conception; hCG 164→366 mIU/mL over 48 h; pregnancy ongoing	No adverse events reported

Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; BMDSC, bone marrow-derived stem cell; DOR, diminished ovarian reserve; FSH, follicle-stimulating hormone; G-CSF, granulocyte colony-stimulating factor; IVF, in vitro fertilization; MSC, mesenchymal stem cell; POF, premature ovarian failure; POI, premature ovarian insufficiency; POR, poor ovarian response; PR, pregnancy rate; PRP, platelet-rich plasma. Entries marked [conference abstract] or [preprint] have not undergone full peer review and should be weighted accordingly.

experienced a venous spasm during intra-arterial infusion that required withdrawal from the study, and one patient developed a headache during G-CSF administration that resolved with paracetamol; no other adverse events were reported [1]. In the larger Stem Cell Regenera cohort, G-CSF mobilization was successful in all 145 participants, and adverse effects were predominantly mild and self-limited, with no severe complications [5]. None of the remaining studies—the case report, the mixed endometrial/ovarian series, the additional MSC series, the five studies identified through the targeted literature search, or any of the PRP studies including the 510-patient Cakiroglu et al. cohort—described procedural or treatment-related adverse events [2-4, 6-11, 13, 14, 16-22]. The absence of reported serious adverse events even in the largest PRP cohort to date is a meaningful, if uncontrolled, safety signal [22]. Herraiz et al. additionally note a theoretical concern regarding ovarian granulosa cell tumor formation with any intervention that stimulates ovarian stromal proliferation, though no such cases have been reported to date [3, 4]. Collectively, these data support bone marrow mobilization and intraovarian cell or PRP delivery as procedures with a low apparent short-term risk profile, though larger, prospectively monitored series with longer follow-up will be needed to confirm this impression.

7 Limitations of the current evidence base

Taken together, the studies reviewed share a set of limitations that temper enthusiasm for their clinical implications. All but two are observational or single-arm; only the ASCOT study incorporates a within-patient comparator (the untreated contralateral ovary), which is itself imperfect given the possibility of systemic paracrine effects reaching both ovaries, and only the TAMSCOT trial includes a separate, albeit non-randomized and non-blinded, untreated comparator group [1, 8]. Sample sizes range from a single case to 510 patients, and most of the additional MSC and small PRP series enrolled fewer than 40 women [3, 4, 13, 14, 16, 18-21]. The five studies identified through the targeted literature search share these constraints: the BMDSC-plus-PRP pilot enrolled only 20 women without a comparator group, the Ray of Hope case report describes only two patients, the Naimat et al. case study and the Alzogaray et al. case series report outcomes in a single patient and three patients respectively with no comparator group, and even the TAMSCOT trial's comparator group was drawn from women who declined the intervention rather than being randomized, introducing potential selection bias [7-11]. The new case reported in Section 2 shares these same constraints in an even more pronounced form: it is a single, uncontrolled observation with no comparator and, as with any single case, causality between treatment and conception cannot be established. Only the Cakiroglu et al. PRP cohort approaches a scale that would support subgroup analysis, and even it remains an uncontrolled, single-arm, real-world series [22]. Definitions of a positive ovarian response varied across studies (a fixed AFC and/or AMH increase in some [1, 5], resumption of menses or hormone profile improvement in others [3, 13, 14, 22]), complicating direct comparison of response rates. Follow-up periods were relatively short in most reports—weeks to a few months—so that cumulative live birth rates and the durability of any ovarian reserve improvement remain incompletely characterized [1, 2, 5]. Patient populations were also heterogeneous, particularly in the series that combined POR, DOR, POI, and menopausal women within a single analysis [2, 5]. Embryo euploidy rates remained low in the one study that reported them, underscoring that even successful follicular activation does not overcome the oocyte quality constraints imposed by advanced maternal age [1]. Several of the additional studies identified through the review sources are reported only in abstract or conference form (e.g., the Pantos et al. PRP series and the TAMSCOT trial) or remain incomplete at the time of publication (the Al-Hendy ROSE-1 trial), meaning their findings should be regarded as preliminary pending full peer-reviewed reporting [3, 8, 15, 17]. Finally, PRP protocols themselves are not standardized across studies - injection volume, platelet concentration, activation method, and unilateral versus bilateral delivery all varied - so that even the reassuring aggregate signal from the Cakiroglu et al. cohort cannot yet be attributed to a single, reproducible PRP formulation or technique [6, 18-22].

8 Future directions

Several steps appear necessary before autologous stem cell-based ovarian rejuvenation can

move from promising pilot data toward an accepted clinical alternative to oocyte donation. Adequately powered randomized controlled trials, ideally with sham-procedure or placebo-PRP comparator arms, are needed to distinguish true biological effect from spontaneous fluctuation in ovarian reserve markers; the ongoing Al-Hendy ROSE-1 trial and a randomized successor to the TAMSCOT protocol may provide important steps in this direction once complete [1, 3, 5, 8, 15]. Standardization of the definition of a positive ovarian response, and of pre-treatment diagnostic criteria, would allow more direct comparison across studies and centers [5]. Given that the two G-CSF-mobilized peripheral blood collection studies reviewed here (ASCOT and Stem Cell Regenera) reported a substantially higher combined pregnancy count than the direct bone marrow aspiration studies despite comparable total enrollment (Section 4.8), a prospective head-to-head comparison of collection route—G-CSF-mobilized peripheral blood versus direct iliac crest aspiration—within a single trial design should be prioritized, to determine whether the less invasive, apheresis-based approach can be adopted as the preferred collection method without sacrificing efficacy. Further mechanistic work correlating specific paracrine factors—FGF-2, TSP-1, the BMDSC secretome's angiogenesis-related genes, and others—with clinical response could help identify predictive biomarkers and possibly permit cell-free, factor-enriched plasma therapies (such as the PRP-only approaches of Pantos et al. and Cakiroglu et al.) as a less invasive alternative to cellular transplantation, since the large PRP-only cohort achieved outcomes broadly comparable to the smaller cell-based series without the logistical burden of stem cell harvesting [1-3, 6, 17, 22]. Longer follow-up is required to determine the durability of any reserve improvement and to establish cumulative, rather than per-cycle, live birth rates. Standardization of PRP preparation (platelet concentration, activation method, injection volume, unilateral versus bilateral delivery) would also allow the promising Cakiroglu et al. signal to be replicated and refined [6, 22]. Finally, larger and more homogeneous cohorts, stratified by diagnosis (POR versus DOR versus POI versus menopause), would help clarify which subpopulations are most likely to benefit; the TAMSCOT trial's exclusive focus on a DOR population under 35 years offers a useful template for this kind of diagnosis-stratified design [5, 8].

9 Conclusion

The evidence reviewed here, ranging from one prospective pilot trial and a large real-world BMDSC cohort to smaller BMDSC series (some conference abstracts or preprints not yet fully peer-reviewed) and an expanding PRP literature culminating in a 510-patient cohort, suggests that autologous BMDSC and/or PRP-based ovarian therapy can improve AFC, AMH, and hormonal profiles in most treated women with POR, DOR, or POI, and can be associated with spontaneous and IVF-mediated pregnancies, including live births. Proposed mechanisms center on paracrine restoration of a vascularized ovarian niche rather than oocyte regeneration; correlations between factors such as FGF-2 and TSP-1 and clinical response are associative, not causal, and their cellular source remains unresolved. Safety has been favorable throughout, but the evidence is largely uncontrolled, heterogeneous, and variable in pregnancy rate (0-33%). Collection route (G-CSF mobilization versus direct aspiration) warrants prospective comparison. This therapy remains investigational, not a validated alternative to oocyte donation.

Disclosure of conflict of interest

None.

Address correspondence to: Zaher Merhi, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Albert Einstein College of Medicine and Maimonides Medical Center and Rejuvenating Fertility Center, 315 West 57th Street, Suite 208, New York, NY 10019, USA. Tel: 203-557-9696; ORCID: 0000-0002-7952-1428; E-mail: zaher.merhi@rfcfertility.com

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