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EFFICACY AND SAFETY OF OVARIAN STEM CELL TRANSPLANTATION IN PATIENTS WITH PRIMARY OVARIAN INSUFFICIENCY AND POOR OVARIAN RESPONSE: A SYSTEMATIC REVIEW

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Abstract: **Objective**. To perform a systematic review to evaluate the efficacy and safety of mesenchymal stem cell transplantation in the treatment of patients with reduced ovarian function or poor response to infertility treatment. **Methods.** Studies published over the last 10 years (from January 2012 to June 2022) were analyzed by systematic review using the PubMed, Cochrane Library, Scopus and National Library of Medicine (ClinicalTrials.gov) databases as references. Materials and methods included the checklist determined by the PRISMA Statement, 2020. The risk of bias of the studies was inferred by two independent reviewers and evaluated using the Risk of Bias (RoB) 2.0 tool provided by the Cochrane Library. This systematic review was registered in the Prospero platform with the identification number CRD42022354259. **Results.** Fifteen studies that met the selection criteria were within the scope of this review. The analyzed studies involved publications from the last ten years that evaluated ovarian stem cell transplantation in patients with decreased ovarian function or poor ovarian response and were found in the selected databases. **Conclusion.** From this review of the studies that met the inclusion criteria, we can conclude that there is a lack of randomized studies with a high number of patients. Furthermore, it was observed that no study evaluated the safety of the proposed long-term therapy. However, through the analysis of the obtained results, it can be concluded that ovarian stem cell transplantation seems to be promising for this group of patients who, in turn, do not have any established treatment.
Keywords. Female infertility; Primary ovarian insufficiency; Ovarian reserve; Poor responder; Cell therapy; Transplantation; Mesenchymal stem cells.

INTRODUCTION

Infertility affects approximately 12% of the population (VANDER BORGHT; WYNS, 2018). Increased age is known to cause a decrease in egg quantity and quality beginning at the age of 35 years until the occurrence of complete failure at menopause between the ages of 45 and 55 years (AHMED *et al.*, 2019).

In some cases, ovarian failure occurs early, and the woman presents an absence of ovarian follicular activity before 40 years of age. This condition is known as premature ovarian failure (POF) and is characterized by amenorrhea (absence of menstruation) and hormonal changes, particularly elevations in follicle-stimulating hormone (FSH) and decreases in estradiol (E2) and anti-Müllerian hormone (AMH). Because ovulation no longer occurs, in vitro fertilization (IVF) with donated eggs is indicated for such patients who wish to become pregnant (CHRISTIN-MAITRE *et al.*, 2021).

Patients undergoing IVF who have a poor response to ovarian stimulation, with poor development of ovarian follicles and low egg uptake, are referred to as low responders or poor responders (PR). The most commonly used criteria for this diagnosis are the Bologna criteria. Accordingly, patients who meet at least two of the following criteria are classified as low responders: age over 40 years; response to conventional ovarian stimulation in a previous cycle of IVF with three or fewer oocytes collected; or test results indicating low ovarian reserve, such as antral follicle count (AFC) < 5 to 7 and AMH < 0.5-1.1 ng/ml (FERRARETTI *et al.*, 2011).

Approximately 9 to 24% of patients undergoing IVF are considered low responders (KYROU *et al.*, 2009), and several factors have increased this rate. Currently, women are seeking to become pregnant later in life (EVERS, 2002), and there is an increasing number of cancer survivors who

have undergone cancer treatments, such as whose chemotherapy or radiotherapy, that have deleterious effects on ovarian function (LARSEN *et al.*, 2003).

The pregnancy rates of treatment for PR, either with ovarian stimulation with high doses of gonadotropins (ZHANG *et al.*, 2020) or with the combination of adjuvant drugs or hormones such as dehydroepiandrosterone (DHEA) (ZHANG et al., 2016), testosterone (NOVENTA *et al.*, 2019) or growth hormone (GH) (LI *et al.*, 2017) are poor. The most effective (or only) therapy to help these patients become pregnant is IVF with egg donation; however, there are several obstacles with this treatment, such as the low availability of donated eggs, the resistance of couples to the treatment and the fact that it is not allowed in many countries (BRACEWELL-MILNES *et al.*, 2016).

In this context, therapy with autologous mesenchymal stem cell (MSC) transplantation (AMSCT) involving (MSCs) from different origins may become a promising treatment for both POF patients and PR. It is believed that after menopause, follicles remain in the ovaries in small numbers (<1,000) (MACKLON; FAUSER, 1999). These quiescent follicle niches can be activated by mesenchymal stem cells (MSCs) (KAWAMURA *et al.*, 2013). It is assumed that cytokines, which are growth factors produced by MSCs, stimulate angiogenesis and decrease apoptosis and the ovarian response to gonadotropic stimulation (CERVELLÓ *et al.*, 2015; PRICE, 2016a).

Animal studies have shown restoration of ovarian function in rats with chemotherapeutic POF by the transplantation of stem cells derived from human placenta (ZHANG *et al.*, 2018) or the umbilical cord (LV et al., 2021; YANG *et al.*, 2019).

Some clinical trials have been conducted in patients with POF and in PR using AMSCT (MASHAYEKHI *et al.*, 2021), (HERRAIZ *et al.*, 2018a), (ZAFARDOUST *et al.*, 2020).

Because there are no systematic reviews in the literature covering the treatment of both POF patients and PR with AMSCT, we decided to conduct the present study to evaluate the efficacy and safety of stem cell transplantation in patients with reduced or absent ovarian function.

METHODOLOGY

The main question of the present review was as follows: "What is the efficacy and safety of AMSCT in with POF patients and PR?" For execution, the computer tool to support the Systematic Review - *State of the art through Systematic Review* (StArt) was used. The protocol described below complied with the standards determined by the PRISMA *Statement*, 2020 (PAGE *et al.*, 2021a), (PAGE *et al.*, 2021b). This systematic review was registered on the Prospero platform under the identification number CRD42022354259. It is declared that there was no conflict of interest in the design of this study.

Planning. The following keywords and search strings were selected: *("Female infertility" AND "Cell therapy") OR ("Female infertility" AND Transplantation) OR ("Female infertility" AND "Mesenchymal Stem Cells") OR ("Primary Ovarian Insufficiency") " AND "Cell therapy") OR ("Primary Ovarian Insufficiency" AND Transplantation) OR ("Primary Ovarian Insufficiency" AND "Mesenchymal Stem Cells") OR ("Ovarian reserve" AND "Cell therapy") OR ("Ovarian reserve" AND Transplantation) OR ("Ovarian reserve" AND "Mesenchymal Stem Cells") OR ("Poor responder" AND "Cell therapy") OR ("Poor responder" AND Transplantation) OR ("Poor responder" AND "Mesenchymal Stem Cells")*. The databases searched were *PubMed*, *Scopus*, *Cochrane* and *Clinical Trials*, and publications in English published between January 2012 and June 2022 were selected.

Execution. We found (n=3628) publications analyzed by two independent researchers to select the articles relevant to the proposed objective.

Selection and Extraction. The selection of studies was performed in two stages for evaluation of the titles and abstracts of the previously selected articles and exclusion of duplicates (n = 693), as well as by reading the full text of the articles extracted after the first selection (n = 284). Articles were excluded articles if they met any of the following criteria: (i) animal study, (ii) therapies other than AMSCT in patients with decreased ovarian function, (iii) lack of the full-text article, or (iv) study designs other than a clinical trial. Articles that evaluated the efficacy and safety of using stem cells in the management of POF patients or PR (n=7) were included. Clinical trials in progress were verified (n=7). The risk of bias of the selected studies was assessed by two independent reviewers using the RoB 2.0 tool provided by *Cochrane* (STERNE *et al.*, 2019).

Summary and Results. The data are summarized and organized into two tables according to the study design, the degree of ovarian failure, the source of the stem cells, the route of administration and dose applied, the type of intervention and follow-up, limitations, risk of bias and the outcomes of each. The results were analyzed in the form of discussion and conclusion.

The methodology used, containing the set of steps to conduct the present study, is summarized in the form of a flowchart (Figure 1).

RESULTS

In this regard, the clinical trials were published and analyzed according to the degree of ovarian failure, the source of the stem cells, the dose and route of administration, the follow-up and the results. No significant side effects were observed among the studies evaluated. Table 1 shows the results of the published clinical studies.

In addition, there are ongoing studies to evaluate pregnancy rates, recovery of ovarian function, occurrence of side effects and ovarian volume after treatment with AMSCT. Thus, Table 2 summarizes the results of clinical trials in progress.

DISCUSSION

Five clinical articles on POF were found. The studies with more patients were those of YAN *et al.* (2020) and TINJIĆ *et al.* (2021) with 61 and 50 patients, respectively. The study by IGBOELI *et al.* (2020) was a report of two cases.

The MSCs had different origins, namely, adipose tissue, bone marrow and umbilical cord, and different amounts were used. In most studies, they were cultured, identified and quantified by staining with specific antibodies against surface antigens and subjected to flow cytometry. The collagen *scaffold* associated with stem cells was used in a group of patients in the study by DING *et al.* (2018).

Inoculation of the stem cells for transplantation was performed by uni- or bilateral transvaginal ultrasound (TVUS). Laparoscopic transplantation was performed in some studies (IGBOELI *et al.*, 2020; MASHAYEKHI *et al.*, 2021). TINJIĆ *et al.* (2021) In particular, there was previous removal of ovarian tissue by video laparoscopy, which was subjected in vitro to inhibition of the HIPPO genes, which affect follicular growth, plus activation of genes of the AKT group, which stimulate follicular development by autologous growth factors. Subsequently, activated ovarian tissue and MSCs were transplanted by TVUS bilaterally.

Patients in all studies were followed for up to one year, with the exception of those in the study by YAN *et al.* (2020), whose follow-up

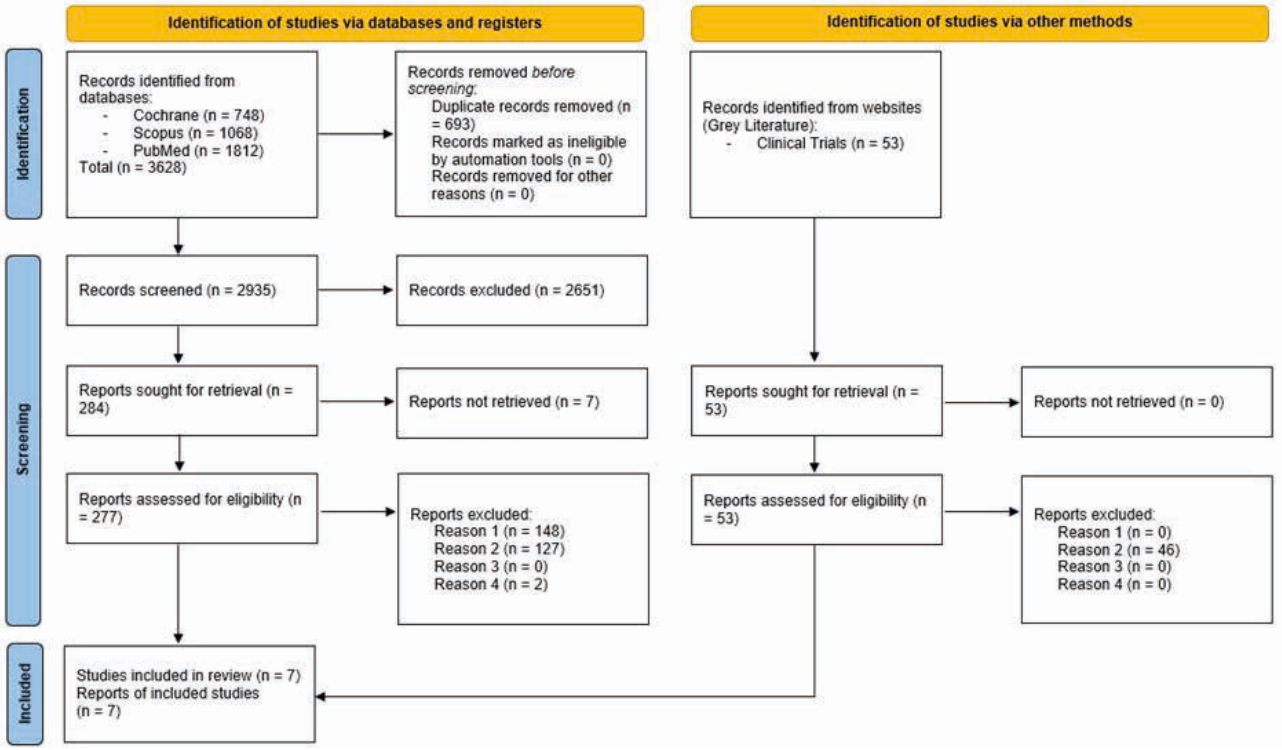

Figure 1: PRISMA 2020 flowchart for systematic reviews.

*Reasons: (1) Used a non-human experimental model; (2) Included therapies other than AMSCT in patients with POF or PR; (3) Impossibility of finding the full article; or (4) Study design other than a clinical trials.

**Source: the authors.

(Authors, year)	Study design	Degree of ovarian insufficiency	Stem cell source	Route of administration and dose applied	Follow-up	Limitations	Risk of bias according to the authors	Result
(DING et al., 2018)	RCT (n = 14, with 6 in UC-MSC arm and 8 in col/UC-MSC arm)	POF	Umbilical cord-derived MSCs associated or not with collagen matrix (col/UC-MSC and UC-MSC)	Unilateral intraovarian injection of SC UC-MSC or col/UC-MSC guided by TV-US, at a dose of $5x10^4$ cells/cm^2 in 0.5 ml of solution.	12 months (weekly for 3 months and fortnightly thereafter)	Lack of studies to define MSC doses and collagen matrix preparation techniques to be used.	Low risk of bias	Decreased serum FSH levels ($P<0.01$) and increased serum estradiol levels ($P<0.05$) in both groups. Increased ovarian volume (UC-MSC $P<0.05$) and follicular activity in both groups; occurrence of two natural pregnancies (one in each group). No side effects related to bleeding, pain or inflammation. Promising treatment for POF.

(HERRAIZ et al., 2018b)	RCT (n=17)	PR	Bone marrow-derived SC (previously mobilized by G-CSF at a dose of 10 µg/kg/d for 5 d)	Autologous SC ovarian transplantation via unilateral ovarian artery catheterization (at a dose of $50x10^6$ cells), with the other ovary considered as control	Every 48 hours for 2 weeks; thereafter, every 7 days for 4 weeks and thereafter, every month for 5 months.	Lack of more studies with a larger homogenous population; lack of definition of the ideal follow-up time and strategy.	Low risk of bias	Increase in antral follicle count ($P<0.05$) and AMH levels in some isolated cases, indicating improvement in ovarian reserve; occurrence of five pregnancies among 15 patients, three of them being spontaneous pregnancies; no information in the study regarding side effects; treatment can optimize the mobilization of the existing ovarian reserve.
(YAN et al., 2020)	non-RCT (n=61)	POF	Umbilical cord-derived SCs	TVUS-guided bilateral ovarian transplantation of SCs	6 months	Lack of definition of the duration of the proposed treatment and validation of the proposed doses through new studies.	Moderate risk of bias	Increased follicular growth and the number of oocytes collected, indicating improvement in ovarian function; occurrence of four pregnancies (one natural pregnancy; 3 pregnancies among 15 patients who underwent IVF); absence of side effects.
(IGBOELI et al., 2020)	Case report (n=2)	POF	Bone marrow-derived mesenchymal SCs	Unilateral autologous transplantation by intraovarian injection of SCs (4 ml of solution with ~$5x10^8$ cells) via laparoscopy.	12 months	New studies are needed to evaluate the approach used in this case report.	High risk of bias	Increase in ovarian volume, increase in serum E2 levels, return of menstruation, improvement of climacteric symptoms in both cases; decreased FSH and LH in one case; no occurrence of pregnancy was recorded; absence of side effects.

(ZAFARDOUST et al., 2020)	RCT (n= 31, with 15 cases and 16 controls)	PR	Mesenchymal SCs derived from menstrual blood	TVUS-guided unilateral autologous ovarian transplantation of SCs (at a dose of 20 million cells/ml)	Up to 12 months	Small population, need for large-scale RCTs to deepen results.	Low risk of bias	Increase in antral follicle count, number of oocytes, fertilization rate and number of viable embryos. Occurrence of 7 pregnancies, 4 of which were natural pregnancies in the case group within the first three months of follow-up; absence of side effects.
(MASHAYEKHI et al., 2021)	non-RCT phase I (n=9)	POF	SC derived from adipose tissue	Autologous SC ovarian transplantation (at doses of $5x10^6$, $10x10^6$ and $15x10^6$ cells in 2 ml solution)	12 months	Further studies with more patients are needed to define the therapeutic strategy.	Moderate risk of bias	Decreased FSH levels and resumption of menstruation; no occurrence of pregnancy was recorded; there were no side effects related to bacteremia, sepsis, PID, anaphylactic shock, hematoma, abscess, or neoplasms in 12 months.
(TINJIĆ et al., 2021)	Longitudinal, prospective, observational study (N=50)	POF ("Ovarian dysfunction")	Bone marrow-derived SCs	Bilateral autologous ovarian transplantation of ~2.2 ml of SC-rich concentrated solution, guided by TV-US	12 months	More studies are needed to maintain the viability of SCs in the long term.	Low risk of bias	Decreased FSH and LH levels, increased E2, decreased progesterone; activation of dormant follicles and development of mature oocytes; occurrence of 3 cases of pregnancy.

*Legend: RCT = randomized clinical trial; non-RCT = nonrandomized clinical trial; SC = stem cell; UC-MSC = mesenchymal stem cell derived from the umbilical cord; PID = pelvic inflammatory disease; LH = luteinizing hormone.

Table 1: Published clinical trials.

(Principal investigator, year of onset). Status, NCT	Design	Degree of ovarian insufficiency	Stem cell source and interventions	Route of administration and dose applied; therapeutic strategy	Date of the last update posted; follow-up	Location, Responsible Persons and Collaborators	Outcomes to be evaluated
(SU, F. 2012) Status unknown, NCT 01742533	Phase I/II RCTs N=40	POF	Umbilical cord-derived MSCs	Ovarian transplantation of SCs associated or not with hormone replacement therapy	December 2012; follow-up 12 months	Shenzhen People's Hospital – Shenzhen, Guangdong, China; Shenzhen Beike Bio-Technology Co., Ltd.	Serum FSH levels (compared to the hormone replacement therapy group), ovarian and uterine ultrasound characteristics (including size and blood flow), modified Kupperman index score and the incidence of serious and nonserious adverse events.
(MIRZADEH, E. S. 2015) Status unknown, NCT 02603744	Phase I/II RCTs N=9	POF	Adipose tissue-derived MSCs	Intraovarian injection of SCs, divided into 3 groups according to the dose of SCs (5, 10 and 15 million)	April 2017; follow-up to 12 months	Royan Institute - Tehran, Islamic Republic of Iran	To evaluate possible adverse effects (occurrence of ovarian masses and abscesses), serum FSH and AMH levels, antral follicle count and volume, menstrual recurrence and pregnancy rate.
(DAI, J. 2015) Study Complete, NCT 02644447	Phase I/II RCTs N=23	POF	Umbilical cord-derived SCs	Autologous transplantation via bilateral intraovarian transvaginal injection of SCs (10 million SCs), associated or not with collagen matrices	January 2020; follow-up up to 6 months and 2 weeks after embryo implantation	The Affiliated Nanjing Drum Tower Hospital of Nanjing, Chinese Academy of Sciences - Nanjing, Jiangsu, China	Safety and tolerance regarding side effects, antral follicle count, serum levels of E2, FSH and AMH; pregnancy rates.
(WANG, H. 2016) Status unknown, NCT 03033277	Phase I/II RCTs N=320	POF	Umbilical cord-derived SCs	Intraovarian transplantation of SCs versus placebo, guided by VT-US. There is no specification of the dose used.	January 2017; follow-up 4-12 months	The Third Affiliated Hospital of Guangzhou Medical University, Chinese Academy of Sciences - Beijing, China	Number of mature follicles, serum FSH, E2 and AMH levels, antral follicle count, ovarian volume and pregnancy rates.
(HERRAIZ, S.; PELLICER, A. 2018) Status unknown, NCT 03535480	Phase IV RCT N=20	POF	Bone marrow-derived SCs activated or not by G-CSF	Ovarian artery catheterization for selective infusion of stem cells into the ovary.	May 2018; follow-up 6 to 24 months	University Hospital and La Fe Polytechnic, La Fe Institute of Sanitary Investigation - Valencia, Spain	Antral follicle count, time to return to menstruation, serum FSH and E2 levels, analysis of follicular development and ovarian reserve dynamics, ovarian response to gonadotropins, pregnancy rate, number of quality embryos, side effects.

(LIU, G. 2018) Study interrupted, NCT 03816852	Phase II RCT N=12	POF	Umbilical cord-derived MSCs	SC transplantation by intravenous infusion at concentrations of $9x10^7$, $6x10^7$ and $3x10^7$ cells in 30 ml of solution.	February 2022; follow-up 270 days	Henan Provincial People's Hospital - Zhengzhou, Henan, China; Sclnow Biotechnology Co., Ltd.	To evaluate the safety and efficacy of umbilical cord-derived mesenchymal SCs in the treatment of POF, menstrual disorders, Kupperman index score, serum FSH, estrogen and AMH levels, and follicular development.
(DING, L.; HAN, G. 2019) Recruiting, NCT 05308342	Inter-ventional study N=66	POF	Umbilical cord-derived MSCs	TV-US-guided SC intraovarian transplantation (at dose of $10x10^6$ or $5x10^6$ if unilateral injection), associated or not with hormone replacement therapy.	March 2022; follow-up 9-12 months	The Affiliated Drum Towel Hospital of Nanjing, Nanjing University - Nanjing, Jiangsu, China	To determine the safety and efficacy of umbilical cord-derived mesenchymal SCs in the treatment of POF; to evaluate the rate of development of ovarian follicles, changes in ovarian blood flow and pregnancy rates.

*Legend: NCT = Identifier number in the *National Library of Medicine* (NLM).

**Note: To date, in all clinical trials found in the gray literature, there were no limitations described.

Table 2: Clinical trials in progress.

time was 6 months.

No study reported significant adverse effects.

Regarding the parameters of the ovarian reserve, a decrease in FSH values was observed in the studies by DING *et al.* (2018), MASHAYEKHI *et al.* (2021) and TINJIĆ *et al.* (2021), as was estradiol elevation in three of the selected studies. Follicular reactivation causes estradiol production by the ovaries, and the negative feedback system decreases FSH production by the pituitary.

AMH levels were assessed by MASHAYEKHI *et al.* (2021) and IGBOELI *et al.* (2020) and did not change. This hormone reflects the number of active ovarian follicles present in the ovaries, which demonstrates that few ovarian follicles are reactivated.

The return of activity and increase in AFC by TVUS were observed by DING *et al.* (2018) and YAN *et al.* (2020). The AFC did not change in the studies by MASHAYEKHI *et al.* (2021) and IGBOELI *et al.* (2020). DING *et al.* (2018) observed an increase in the ovarian volume of ovaries that underwent stem cell transplantation.

The return of menstruation was observed in three studies (MASHAYEKHI *et al.*, 2021; YAN *et al.* 2020 and IGBOELI *et al.*, 2020). IGBOELI *et al.* (2020) observed improvement in menopausal symptoms, which occurs due to increased production of estradiol. Likewise, the return of menstruation results from the stimulation of the endometrium by estradiol and ovulation.

The occurrence of natural pregnancy was reported in the studies by DING *et al.* (2018) and YAN *et al.* (2020). In the trials in which the patients were stimulated for IVF, there were three pregnancies reported by YAN *et al.* (2020) and TINJIĆ *et al.* (2021). In the study by TINJIĆ *et al.* (2021), 64% of patients developed follicles, but aspirated oocytes were obtained from only 16% of the patients. The fertilization rate was 75%, and only 12% of the patients obtained embryos, which resulted in pregnancy in three patients (6% of the total). In the study by YAN *et al.* (2020), fifteen patients underwent IVF, three became pregnant, and there was one natural pregnancy later. The authors reported that there was no effect on the recovery of ovarian function in patients with more than three years of amenorrhea. If this is confirmed in other studies, this is an important finding that underscores the need for early diagnosis for effective treatment.

Although the pregnancy rate is considered low, which needs to be confirmed in studies with more patients, it is still an advance for those who can become pregnant only with donated eggs. TINJIĆ *et al.* (2021) blamed the advanced age of the patients and low oocyte quality (aneuploidy) for the low pregnancy rate. In the study by DING *et al.* (2018), there was a natural pregnancy with trisomy 21, but according to the authors, the genetic study of the origin of trisomy excludes the possibility that it was due to AMSCT.

Two studies evaluated the AMSCT in PR. In both trials, the patients had already undergone IVF treatment before AMSCT.

In the study by HERRAIZ *et al.* (2018b), MSCs derived from bone marrow were transplanted into a group of 17 patients without a control group. The MSCs were mobilized by G-CSF, collected by apheresis and transplanted into the ovary via TVUS. Patients who exhibited follicular activity underwent ovarian stimulation and IVF.

In the study by ZAFARDOUST *et al.* (2020), MSCs derived from menstrual blood were used. Fifteen patients in the treated group and 16 in the control group were evaluated. AMSCT was performed using TVUS. Follow-up was one year.

There were no significant differences in HAM in either group. In the study by HERRAIZ et al. (2018b), there was an

increase in CFA, which was not observed by ZAFARDOUST *et al.* (2020).

In both studies, AMSCT made IVF treatment more effective than the IVF cycles prior to AMSCT. Both had more oocytes collected and a higher embryo fertilization rate. The pregnancy rate in the study by HERRAIZ *et al.* (2018b) was 33% versus 0% in previous cycles. In the study by ZAFARDOUST *et al.* (2020), the pregnancy rate was 46%, and the live birth rate was 33%. In the control group of this study, the pregnancy rate was 12.5% and 6.3% of live births.

Only 5 embryos reached the blastocyst stage and were biopsied in the study by HERRAIZ *et al.* (2018b). All were euploid, corresponding to 16% of all embryos obtained. This shows that although AMSCT improved the number of embryos obtained, it did not affect euploidy status. However, among women whose pregnancy rate in previous cycles was 0% or close to it, there was a significant increase in the number of pregnancies in both studies, with rates above 33%. Some of these pregnancies occurred naturally.

Recovery of folliculogenesis would hardly occur due to MSC differentiation. The presence of spontaneous pregnancy in the first three months after AMSCT in the study by ZAFARDOUST *et al.* (2020) and the fact that AMH (which correlates with the number of ovarian follicles) did not change after treatment in several studies, discrediting this theory. Mesenchymal cells have little potential for differentiation into theca or granulosa cells. Furthermore, they are short-lived (XIAO *et al.*, 2014).

The presence of ovarian stem cells (OTC) located in the tunica albuginea of the ovary capable of originating niches for granulosa cells and germ cells was reported by some researchers (BHARTIYA; PATEL, 2018). The decline in senile ovarian activity is due to the degradation of niches of ovarian stem cells. The immune and vascular systems are involved in the formation of CTO niches (YE *et al.*, 2017). However, there is a debate in the literature about the existence of CTO (HORAN; WILLIAMS, 2017).

Menstrual mesenchymal cells and their culture medium decrease granulosa cell apoptosis and increase the number of follicles in mice with POF due to follicle repair mediated by angiogenesis-stimulating factor (FGF-2) (WANG *et al.*, 2017). Therefore, the recovery of ovarian function by MSCs probably occurs by the restoration of niches of the MSCs through the secretome of the transplanted MSCs (LAI *et al.*, 2015).

DING *et al.* (2018), in their study with collagen *scaffolds* and MSCs from the umbilical cord, showed increased phosphorylation of AKT9 (via PI3K-AKT), which may have activated the phosphorylation and displacement of FOXO3a from the nucleus to the cytoplasm and, consequently, the activation of primordial follicles into preovulatory follicles. FOXO3a maintains primordial follicles at rest, and its phosphorylation and transport from the nucleus to the cytoplasm initiates the process of folliculogenesis (JOHN *et al.*, 2008).

It is known that MSCs have other properties in addition to the ability to differentiate into other cells. They have angiogenic, antiapoptotic, immunoregulatory and anti-inflammatory effects, all of which are fundamental in the process of ovarian tissue restoration (XU *et al.*, 2016), (HE *et al.*, 2018).

HERRAIZ *et al.* (2018b) demonstrated a positive correlation of FGF-2 with follicular development, estrogen level and neovascularization of follicular niches. In fact, FGF-2 stimulates granulosa cell proliferation, decreases apoptosis and is involved in the development of primordial follicles into preovulatory follicles (PRICE, 2016b), (SKINNER, 2005). The deficient

vascularization of the ovaries of nonresponders should contribute to the deficient follicular response. In this sense, the increase in vascularization would contribute to a better response performance to ovarian stimulation.

Commonly, the studies described in this review had few patients, which reduces the statistical power. Randomized clinical trials initiated between 2012 and 2019 are being conducted and may present greater evidence on the efficacy and safety of autologous transplantation of stem cells originating from the umbilical cord, adipose tissue or bone marrow. They are described in Table 2.

CONCLUSIONS

AMSCT seems to be a safe and viable alternative for patients with poor response to IVF or early ovarian failure before egg donation. This is what can be inferred from the studies analyzed, which reported results showing the resumption of menstruation, improvement of ovarian reserve indices and the occurrence of pregnancy, although with low statistical power. Thus, large, randomized studies with a higher number of patients and long-term follow-up are needed to define the ideal number of cells to be transplanted, whether there is a need for repeated administration, and the standard interval for these additional treatments. Furthermore, it is necessary to know how long after menopause the treatment can be effective, as mesenchymal cells do not transform into new follicles but activate previously existing niches. Studies with infusion of growth factors for recovery of ovarian function will also be useful because, as the benefits occur through growth factors and cytokines present in the secretome of mesenchymal cells, the administration of these factors may be beneficial in the treatment of these patients.

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ANNEX

ABBREVIATION	DEFINITION
POF	Premature ovarian failure
FSH	Follicle-stimulating hormone
AMH	Anti-Müllerian hormone
IVF	In vitro fertilization
AFC	Antral follicle count
DHEA	Dehydroepiandrosterone
GH	Growth hormone
AMSCT	Autologous mesenchymal stem cell transplantation
MSCs	Mesenchymal stem cells
PR	Poor responders
StARt	State of the Art through Systematic Review
TVUS	Transvaginal ultrasound
OSCs	Ovarian stem cells
FGF2	Angiogenesis-stimulating factor
FOXO	Fibroblast growth factor
PI3K	Phosphatidylinositol-3-kinase enzyme
AKT9	Specific protein kinase
G-CSF	Plasma growth factor

Table 3. Abbreviations used.