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Original Research Article

Role of autologous bone marrow derived stem cells and platelet rich plasma for endometrial regeneration and repair and ovarian rejuvenation

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ABSTRACT

Background: Stem cells are undifferentiated cells with a potential for self- renewal and differentiation into multiple mature cell types. PRP is blood plasma that has been enriched with platelets and multiple growth factors that can stimulate cellular processes and activate multi-potent stem cells to generate new, younger tissue and new blood vessels relevant to ovarian rejuvenation and endometrial regeneration.
Methods: This study was to evaluate the effectiveness of ABMDSC and PRP application in patients with thin endometrium refractory to treatment, premature ovarian failure, infertility and menopause. 37 symptomatic women between age group 18 years to 56 years were selected for ABMDSC and PRP instillation in endometrium and/ or ovaries. PRP was instilled in endometrium in 8 patients, in ovaries in 5 patients and in both endometrium and ovaries in 24 patients.
Results: There was significant improvement in endometrial thickness, along with improved blood flow to both endometrium and ovaries. FSH levels decreased and ovarian volume increased. There were three confirmed pregnancies with one delivery. Menopausal symptoms decreased in 2 patients and spontaneous resumption of menses was seen in 1 patient of POF.
Conclusions: Stem cell therapy serves as a game changer with their unique properties, offering solutions for scores of women suffering from POF, poor oocyte quality, endometrial degeneration/ damage or menopausal symptoms.

Keywords: Bone marrow-derived stem cell, Platelet rich plasma, Premature ovarian failure, Thin endometrium

INTRODUCTION

Current research has supported the knowledge that approximately 1000 quiescent residual primordial follicles remain in the ovaries at menopause. This is in contrast to the earlier concept that human ovaries are born with a finite number of ova, that determined her reproductive lifespan, the number depleting entirely during menopause.

Stem cells are undifferentiated cells with the ability for self-renewal producing exact copies of themselves by continuous division and to advance into specialized cells by differentiation. PRP is autologous blood plasma enriched with platelets containing several growth factors and cytokines. The growth factors released by the PRP also activates multiple stem cells instrumental in angiogenesis and formation of denovo younger tissue.

Premature Ovarian Failure (POF) is defined as hypergonadotropic ovarian insufficiency, affecting approximately 1% of women below the age of 40.[1] Aged women with decreased ovarian reserve (DOR) are typically referred to as poor responders and make up 9%–24% of patients seeking infertility therapy.[2] Till date no therapeutic intervention has proven effective in restoring fertility in patients with POF. Oocyte donation, although a practical option, is limited in utility with psychological burden, legal restrictions and negating the choice of a biological offspring.

Ovarian rejuvenation is a procedure of creating new ova in the damaged or aged gonads. This discovery of so-called "ovarian stem cells" is the basis for ovarian rejuvenation techniques. Competent oocytes could be retrieved after the activation of dormant primordial follicles in patients with DOR and POF. Ovarian rejuvenation doesn't just restore a woman's fertility, it can also alleviate some of the side effects associated with low estrogen, POF and menopause. The method of rejuvenation also benefits women with thinned out refractory endometrium and intrauterine adhesions.

Objective

Non-Randomized, Interventional study to evaluate the effectiveness of ABMDSC and PRP application for Endometrial Regeneration and Repair in patients with thin endometrial lining or intrauterine scarring and ovarian rejuvenation in POF and DOR.

Aim of the study were to measure the change in endometrial lining thickness, to measure blood flow to zone 3 of endometrium, to determine the rate of return/normalization of menses in patients with Asherman's Syndrome, to determine improvement in ovarian intrastromal blood flow, to assess improvement in FSH levels toward normal ranges and to determine clinical pregnancy rate.

METHODS

The study was conducted at Medicover woman and child hospital from January 2019 to January 2020. 37 symptomatic women between age group 18 Years to 56 Years were selected for ABMDSC and PRP instillation in endometrium and/ or ovaries. (Figure 1) Of the 37 women, 12 were suffering from POF, 23 had primary or secondary infertility with 7 patients having DOR, 8 with thin endometrium, 3 with secondary amenorrhea, 2 Hypothalamic hypogonadism and 2 menopausal (MP). Diagnosis was made in all patients based on a detailed history, clinical examination, laboratory tests and ultrasound pelvis doppler. Hormones like FSH, LH, AMH were measured before procedure or on 2nd day of menstrual cycle. Endometrial thickness was measured at the thickest part at the longitudinal axis of the uterus by an experienced ultrasonographer. The thickness was measured thrice to confirm thin endometrium, and the average from 3 measurements were recorded. Endometrial layering and Zone 3 blood flow was also measured. Ovarian intrastromal blood flow and ovarian volume was measured. A proper informed consentwas takenexplaining the pros and cons of this procedure. ABMDSC therapy is a voluntary procedure with temporary and variable results was explained prior to procedure. Pre anaesthesia fitness was taken. Results were analysed using Excel and SPSS software.

Inclusion criteria

For endometrium

Persistent thin lining <6 mm in previous IVF or FET cycle, moderate-to-severe Asherman's syndrome, severe oligomenorrhea/amenorrhea.

For ovaries

Primary or secondary amenorrhea at least for 3 months, infertile women having DOR and low AMH levels, diagnosis of DOR defined as: AMH ≤0.42 ng/ML & FSH ≥12 IU/L,diagnosis of POF with FSH levels ≥ 30 IU/L, normal karyotype 46, XX, presence of at least one ovary

Exclusion criteria

Age≤18 years old, pregnancy or lactation, history of, or evidence of malignancy, Hb≤8 g/dl, platelets≤150,000/mm^3, anticoagulation therapy, any contraindication to laparoscopic surgery and / general anesthesia, medical conditions that are contraindicated in pregnancy, any significant comorbidity or psychiatric disorder.

Procedure

Bonemarrow aspiration was done from posterior iliac crest under local anesthesia maintaining strict asepsis by the orthopedician. Aspiration was done using 13 G Jamshidi needle and 20 ml syringe prewashed with heparin. 40 ml of bone marrow was aspirated, centrifuged and the buffy coat/ MNC fraction was collected from the defined layer at the interface. 4-5 ml BMDSC was separated using centrifugation and sedimentation. A sterile bandage was applied to the site when the collection ends. PRP was prepared from 20- 40 ml of patient's venous blood. After centrifugation 2- 4 ml of PRP was obtained. Activation of PRP was done by 0.1 ml of calcium gluconate just before administration. Considering the small size of ovaries which were not well approachable with the vaginal route and were difficult to fix for instillation, we preferred laparoscopic instillation of ABMDSC in ovaries. Under GA three port laparoscopy with 5mm telescope was done to see uterus, tubes, ovaries, adhesions and to rule out any other disease. Intraovarian instillation of about 1-2 ml of ABMDSC and 1ml PRP was done at cranial and caudal ends of ovary directing towards ovarian and

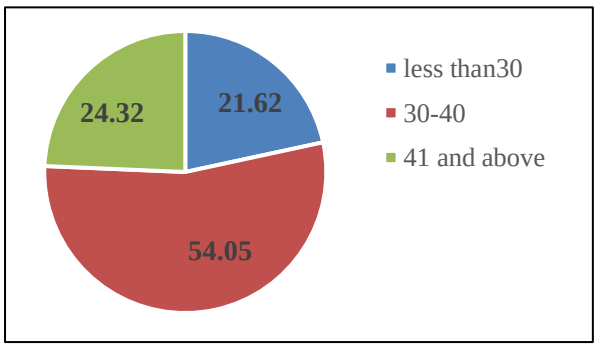
infundibulopelvic ligament bilaterally. Hysteroscopy was done to see uterine cavity, endometrium, adhesions and to rule out any other disease.[12-15] subendometrial holes were made and 1ml each of ABMDSC's and PRP was infused into the uterine cavity immediately with IUI catheter. Patient was monitored for 6 hours and discharged. Post procedure medications were given to improve blood supply to endometrium and ovaries like sildenafil, DHEAS, ecosprin, estradiol, dexamethasone, ARG-9, vitamin E, and Inj Bharglob.

Follow-up procedure

AMH, FSH, LH levels were measured at monthly intervals in women who do not menstruate, and during the 2nd day of menstrual flow in menstruating women for a period of 3 months. Decreasing FSH, LH levels provides objective evidence that ovarian rejuvenation is happening. Ultrasound measurements were done on15 and 30 days post procedure for endometrial thickness, endometrial blood flow to zone 3, ovarian volume and ovarian intrastromal blood flow. Following the ABMDSC protocol, infertile subjects were instructed to resume normal unprotected sexual intercourse as soon as possible and to continue for 12 months with monitoring of pregnancy test or until clinical pregnancy was confirmed.

RESULTS

In our study, we evaluated improvement in endometrial lining thickness, blood flow to zone 3 of endometrium, blood flow in ovarian Doppler and FSH levels for 1-3 months. No adverse effects were noted. All patients were evaluated at four time points: T1 (beginning of study), T2 (2weeks), T3 (1 month), T4 (3 months).



Figures 1: Age groups.

ABMDSC and PRP was instilled in endometrium in 8 patients, in ovaries in 5 patients and in both endometrium and ovaries in 24 patients (Figure. 2).

Endometrial thickness (ET) increased in 31/31 patients (100%) (Table 1), Improvement in Endometrial Thickness (Day 15)]. 8/8 patients (100%) of thin endometrium showed improvement towards normal range.

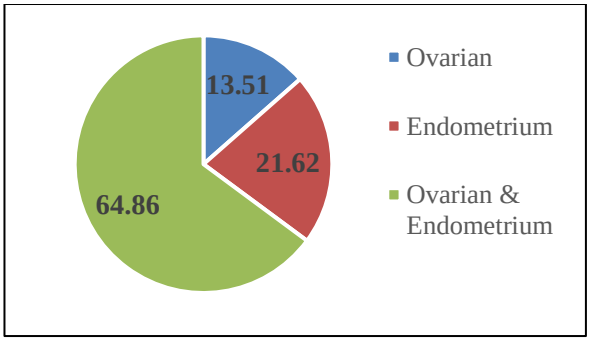


Figure 2: ABMDSC and PRP instillation.

Table 1: Improvement in endometrial thickness (Day 15).

Improvement in endometrial thickness	Frequency	Percent
Improved	31	100
Total	31	100

Comparison of initial ET and ET on day 15 showed P-Value of 0.000 which indicates significant improvement (Paired sample test 1).

Blood flow to zone 3 of endometrium improved in 23/33 patients (69.70%) (Table 2), Improvement in Endometrial Blood flow (Day 15). There was no improvement in 10 patients, out of which 3 patients had grade 3 Asherman's and 2 patient had positive endometrial TB.7/8 patients of thin endometrium showed improvement in blood flow.

Table 2: Improvement in endometrial blood flow (Day 15).

Improvement in endometrial blood flow	Frequency	Percent
Improvement	23	69.70
No improvement	10	30.3
Total	33	100

Comparison of initial endometrial blood Flow and blood flow on Day 15 showed P-Value of 0.000 which indicates significant improvement (Paired sample test).

16/37 patients had normal ovarian blood flow pre procedure. Post procedure ovarian intrastromal blood flow improved in 20/ 37 patients (Table 3).

Table 3: Improvement in ovarian blood flow (day 30).

Improvement in ovarian blood flow	Frequency	Percent
Improvement	4	19.05
No Improvement	17	80.95
Total	21	100

FSH levels improved in 26/29 cases (89.66%) with no improvement in 3/29 cases (Table 4), FSH improvement (Day 30) with mean FSH of 32.86 before study to 10.73 at end of 30days (Table 5), Mean FSH values before and after procedure. FSH levels improved in 12/12 POF patients and 2/2 MP patients (Table 6, FSH improvements in POF and MP patients (Day 30).

Table 4: FSH improvement (Day 30).

Improvement in FSH Patients	Frequency	Percent
Improvement	26	89.66
No improvement	3	10.34
Total	29	100

Table 5: Mean FSH values before and after procedure.

	Mean	N	Std. deviation
FSH –Before	32.8686	29	28.62151
FSH - After	10.7359	29	9.41591

Table 6: FSH improvements in POF and MP patients (Day 30).

	Total patients	Improvement	Percent
POF	12	12	100
MP	2	2	100

Table 7: Paired samples statistics.

		Mean	N	Std. deviation	Std. error mean
Pair 1	ETB	5.5811	37	1.84810	0.30383
	ETA	7.7162	37	1.45173	0.23866
Pair 2	BFB	1.2162	37	.62960	0.10351
	BFA	2.5135	37	.86992	0.14301
Pair 3	FSHB	32.8686	29	28.62151	5.31488
	FSHA	10.7359	29	9.41591	1.74849

ETB – Endometrial Thickness Before; ETA – Endometrial thickness after (Day 15); BFB – Blood flow before; BFA – Blood flow after (Day15); FSHB – FSH before; FSHA – FSH after (Day 30)

Table 8: Paired sample tests.

		Paired differences		t	df	Sig. (2-tailed)
		Mean	Std. Deviation			
Pair 1	ETB - ETA	-2.13514	1.52027	-8.543	36	0.000
Pair 2	BFB - BFA	-1.29730	.96796	-8.152	36	0.000
Pair 3	FSHB - FSHA	22.13276	23.69853	5.029	28	0.000

Table 9: Paired samples statistics.

		Mean	N	Std. deviation
Pair 4	TEB	4.2250	8	0.70660
	TEA	7.7250	8	1.34244
Pair 5	FSHB	61.3867	12	20.94519
	FSHA	17.0600	12	11.31338

TEB-Thin endometrium before; TEA - Thin endometrium after (Day 15); FSHB - FSH before in POF patients; FSHA - FSH after (Day 30).

Comparison of ET in thin endometrium before and after 15 days showed P-value of 0.000 which indicates significant improvement. (Paired sample test).[4]

Pair 1

Comparison of initial endometrial thickness and endometrial thickness on Day 15. P-value is 0.000 which indicates that there is significant improvement in ET after 15 days at 5% level of significance.

Pair 2

Comparison of initial blood flow and blood flow on Day 15. P-value is 0.000 which indicates that there is significant improvement in BF after 15 days at 5% level of significance.

Pair-3

Comparison of Initial SFSH and SFSH on day 15. P-value is 0.000 which indicates that there is significant improvement in SFSH after 15 days at 5% level of significance. Comparison of FSH levels in POF patients before and after 30 days showed P-Value of 0.000 which indicates significant improvement (Paired sample test) Table 5. Not much increase in AMH was observed as it denotes the ovarian reserve and not the present functional status of ovary. It is the author's opinion that ovarian reserve which is predetermined doesn't change much but the hormonal changes created by ovarian rejuvenation shows it's effect.

Table 10: Paired samples statistics.

		Paired differences	t	df	Sig. (2-tailed)	
		Mean	**Std. deviation**			
Pair 4	TEB - TEA	-3.50000	0.72309	-13.691	7	0.000
Pair 5	FSHB - FSHA	44.32667	19.53551	7.860	11	0.000

Pair 4

Comparison of ET in Thin Endometrium before and after 15 days.

P-Value is 0.000 which indicates that there is significant improvement in thin endometrium after15 days at 5% level of significance.

Pair 5

Comparison of FSH levels in POF patients before and after 30 days.

P-value is 0.000 which indicates that there is significant improvement in FSH levels of POF patients after one month (30 days) at 5% level of significance.

5 patients are undergoing ovulation induction and 3 pregnancies were achieved out of which 2 patients had POF and 1 had secondary infertility. One patient conceived with IVF and had an uneventful delivery and 2 have ongoing pregnancy with one being a twin gestation.

Spontaneous resumption of menses was seen in 1 patient of secondary amenorrhea and 2 MP patients have decreased post-menopausal symptoms.

DISCUSSION

Regenerative medicine involves delivering specific types of cells or cell products to diseased tissues or organs to restore function. This can be done through Stem cells or by using cell products, such as growth factors or PRP. Stem cells are undifferentiated cells that have potential for self- renewal and differentiate into specific functioning self-sustain cells. They are classified into embryonic stem cells, adult stem cells and induced pluripotent stem cells.

Bone marrow stromal cells were initially described by Owen and Friedenstein in 1988. They not only commit to osteoblasts, adipocytes, and chondroblasts, but also differentiate into granulosa, endometrial and endothelial cells.[3] Adult stem cells are often isolated from bone marrow, blood, adipose tissue, liver and skin.[4] However, as a natural consequence of aging, their quantity and quality decreases with the age affecting their regenerative potential, growth, and divisions.[4]

Germline stem cells (GSCs) are a unique cell population committed to producing gametes for the propagation of the species.[5] Johnson et al postulated that, If GSCs were present in adult female ovaries, the occurrence of menopause is not due to the exhaustion of a fixed supply of oocytes but instead is a result of GSC and somatic cell aging, thus losing their capacity to regenerate and differentiate.[6] White et al identified rare population of mitotically active germ cells from reproductive aged human ovaries Germ line SCs capable of forming oocyte like structures.[7] Singh et al showed that autologous implantation of Embryonic SCs can lead to endometrial regeneration.[8]

Recent research suggests that diminished ovarian reserve is a result of the aging of the niche rather than a defect in the germ cells. Stem cell niches are located in specific anatomic microenvironment that allows for stem cells self-renewal and maintenance of their undifferentiated potential.[4] SCs have a rapid proliferation ability, achieving a thousand fold expansion of cell number in a two- to three- week period. Several mechanisms have been proposed to achieve tissue regeneration by adult stem cell therapy. The possible mechanisms include promoting angiogenesis, differentiating into functional cells, anti-inflammation, immunomodulation, antiapoptosis, antifibrosis and a paracrine mechanism.[3] Although the molecular autocrine/paracrine mechanisms that control primordial follicle activation remain unknown, it is believed that the local environment (niche) plays a fundamental role.[2] The effects are dependent on the ability of adult stem cells to produce a variety of cytokines, chemokines, and growth factors including vascular endothelial growth factor, insulin-like growth factor, and hepatocyte growth factor.[2,3] FGF-2, expressed in early human follicles, is a key player in estrogen production associated with the improved follicular development. THSP-1 has been recognized as a mediator of ovarian angiogenesis and folliculogenesis.[9]

BMDSC's induce endometrial proliferation by engrafting around endometrial vessels of the traumatized endometrium and secreting specific growth factors, such as thrombospondin-1 and insulin-like growth factor-1, promote angiogenesis and tissue repair and inhibit fibrosis.[3]

Several studies have shown beneficial effects of BMDSC's treatment in chemotherapy-induced ovarian failure animal models. In 2013, Abd-Allah et al. used bone marrow stromal cells from male rabbits to treat

cyclophosphamide-induced ovarian failure and discovered that the ovarian functional reserve and number of follicles were improved.[10] Badawy et al, showed that bone marrow stromal cells were able to restore ovaries damaged by chemotherapy in mice. Furthermore, the animals regained their fertility.[11] In humans, Implantation of ABMDSC's to treat endometrial injury restored menstruation in five out of six cases.[3] Additionally, bone marrow stromal cells restored functional endometrium in patients with Asherman syndrome and improved the reproductive outcomes.[3]

In 2013, Kawamura in Japan and his collaborators showed a new way of IVA (In Vitro Activation) approach to treat infertility of POF patients by fragmenting ovaries followed by in vitro treatment of ovarian fragments with Akt stimulators and autografting. They successfully promoted follicle growth, retrieved mature oocytes, and performed in vitro fertilization. Following embryo transfer, a healthy baby was delivered.[12] Edessy et al in 2014 evaluated the therapeutic potential of ABMDSC's transplantation in 10 patients with POF. The results revealed resumption of menstruation in 1 case after 3 months and 2 cases showed focal secretory changes after having atrophic endometrium.[1]

In the ROSE-1 study started in February 2016 at University of Illinois, Chicago, participants were designed to determine the efficacy of BMDSC therapy on ovarian function recovery in subjects with idiopathic and other types of POF.[1,33] Their first patient resumed menses after 6 months post stem cell injection and she also reported amelioration of her post-menopausal symptoms including a decrease in hot flashes frequency and severity, decreased vaginal dryness and improved sleeping patterns.[1]

Herraiz et al introduced the beneficial effects of autologous stem cell ovarian transplant (ASCOT) on ovarian reserve and IVF outcomes for 15 women, who were poor responders and with very bad prognosis. Using this approach, 5 pregnancies were achieved and 3 healthy babies were born.[2] Ovarian function improved in 81.3% of women with 33.3% pregnancy rate The positive AFC response in women who are poor responders was detected mainly during the first 4 weeks after treatment, suggesting that the secondary follicles at the time of treatment were likely the main beneficiaries of ASCOT.[2] Rapid growth of secondary follicles to produce preovulatory follicles in a few weeks has been reported by Kawamura et al.in patients with POI.[2]

According to these results, BMDSC's seem to have the ability to revive prematurely failed ovaries both in their hormonal and follicular development abilities.

PRP is an autologous concentration of human platelets to supra-physiologic levels. The actual mechanisms of action of PRP are extensive because of the release of a myriad of bioactive factors. Growth Factors cause the growth of new blood vessels, connective and nerve tissues by the activation of Stem Cells that are normally found in all parts of the human body. PRP was first developed in the 1970s and first used in Italy in 1987 in an open heart surgery procedure.[13] Autologous blood products including platelets were first popularized in the 1990s in oral and plastic surgery.[14]

For the first time, Chang reported the efficacy of intrauterine infusion of PRP for endometrial growth in 5 women with thin endometrium. Normal pregnancy was reported in 4 women.[15] In a study by Nazari et al, 10 patients who had a history of cancelled FET cycles due to inadequate endometrial growth underwent PRP. Endometrial thickness increased in 48 h after the first PRP and reached more than 7 mm after the second PRP in all patients. Five patients became pregnant and in four of them the pregnancy progressed normally.[16] 20 women with a history of recurrent implantation failure were recruited in a study of PRP by Zadehmodarres et.al participants were pregnant with one early miscarriage and one molar pregnancy.[17,18] Dr Konstantinos Pantos in an experimental study of PRP showed that out of 27 menopausal women, 12 managed to ovulate and 3 out of 6 became pregnant.[18] The Inovium Ovarian Rejuvenation Treatment with PRP was done by Eric S. Sills in 60 women aged 45-64 years experiencing menopause, perimenopause, and POF. According to them over 75% had overall hormone levels return to normal with 9 successful pregnancies.[19]

Zhang et al. compared placebo, Menstrual blood MB-MSC transplantation, PRP transplantation, and combined MB-MSC and PRP transplantation in the treatment of a rat model of intrauterine adhesion. They found that combining MB-MSCs with PRP was more effective than either treatment alone in improving endometrial proliferation, angiogenesis, and morphological recovery.[20]

ABMDSCT and PRP is considered to be a safe, natural treatment because, rather than using a synthetic substance, it uses cells and growth factors from patient's own blood making it safe from possibility of allergic reactions, risk of transmission of blood borne infections as hepatitis and HIV and risk of rejection during autotransplantation. BMDSC's are easily isolated and obtain high yield. They are free of both ethical concerns and teratoma formation. No documented cases of carcinogenesis, hyperplasia or tumor growth were associated with use of autologous PRP. The primary risks and discomforts are related to the bone marrow withdrawl where there is a slight pinch to insert the needle for collection and there is a potential for bruising at the site, bleeding, pain or infection.

While the clinical evidence is still in its preliminary stages and the ovarian ABMDSC's and PRP application is still a very new practice, the existing evidence points to incredible outcomes in patients even in menopausal

stages. The benefit of this procedure is the possibility of achieving pregnancy with one's own eggs, which had not been possible prior to this procedure. Many clinicians feel that PRP therapy is safe given its autologous nature and long-term usage without any reported major complications.

CONCLUSION

One reason stem cells generate intense scientific and clinical interest is the hope that understanding their unique properties may lead to new treatments for a variety of degenerative illnesses. It serves as a game changer, offering solutions for scores of women suffering from POF, poor oocyte quality, endometrial degeneration/ damage or menopausal symptoms.

Although the field of stem cell biology has grown rapidly, considerable confusion with limited understanding of stem cell biology and their differentiation mechanisms exists. Although the ovary as a target for stem cell therapy is relatively new, it has shown favourable results when applied to other organs which assures its safety and validity. ABMDSC's transplantation would prove a new paradigm of treatment with the convenience of sample collection, plentiful resources and avoidance of ethical and legal barriers to name a few.

Akin to novel therapies, the consistency of outcomes, possible risks and collection of large-scale data is required for it to be further implemented. The aim of this review is to stimulate and sensitise the readers to carry out well designed, statistically meaningful, large scale multicentric population based trials to achieve its validation in the modern gynaecological practice.

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REFERENCES

1. Rejuvenation of Premature Ovarian Failure with Stem Cells (ROSE-1), University of Illinois at Chicago, 2016, Available at https://clinicaltrials.gov/ct2/show/NCT02696889. Accessed on 30 August 2020.
2. Herraiz S, Romeu M. Autologous stem cell ovarian transplantation to increase reproductive potential in patients who are poor responders. Fertn Stert. 2018;110(3):496-505.
3. Zhao Y, Chen S. Using mesenchymal stem cells to treat female infertility: an update on female reproductive diseases. Fertn Stert. 2019:9071720.
4. Łos MJ, Skubis A, Ghavami S. Stem cells and biomaterials for regenerative medicine. Stem Cells. 2019;2:5-16.
5. Dunlop CE, Telfer EE, Anderson RA. Ovarian germline stem cells. Stem Cell Res Therapy. 2014;5:98.
6. Johnson J, Canning J, Kaneko T, Pru JK, Tilly JL, Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature. 2004;428:145-50.
7. White YA, Woods DC, Takai Y, Ishihara O, Seki H, Tilly JL. Oocyte formation by mitotically active germ cells purified from ovaries of reproductive-age women. Nat Med. 2012;18:413-21.
8. Singh N, Mohanty S, Seth T, Shankar M, Dharmendra S, Bhaskaran S. Autologous stem cell transplantation in refractory Asherman's syndrome: a novel cell based therapy. J Human Reproductive Sci. 2014;7(2):93-8.
9. Christianson M, Segars J. Unleashing the potential of stem cells to help poor responders American Society for Reproductive Medicine. 2018;110(3):410-11.
10. Abd-Allah SH, Shalaby SH, Pasha HF. Mechanistic action of mesenchymal stem cell injection in the treatment of chemically induced ovarian failure in rabbits, Cytotherapy. 2013;15(1):64-75.
11. Badawy A, Sobh MA, Ahdy M, Abdelhafez MS. Bone marrow mesenchymal stem cell repair of cyclophosphamide-induced ovarian insufficiency in a mouse model. Int J Women's Health. 2017;9:441-7.
12. Kawamura K. Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment. Proc Natl Acad Sci. 2013;110(43):17474-9.
13. Ferrari M, Zia S, Valbonesi M, Henriquet F, Venere G, Spagnolo S, et al. A new technique for hemodilution, preparation of autologous platelet-rich plasma and intraoperative blood salvage in cardiac surgery, Int J Artif Organs. 1987;10(1):47-50.
14. Arshdeep, Kumaran MS. Platelet-rich plasma in dermatology: boon or a bane? Indian J Dermatol Venereol Leprol. 2014;80:5-14.
15. Chang Y, Li J, Chen Y, Wei L, Yang X, Shi Y, et al. Autologous platelet-rich plasma promotes endometrial growth and improves pregnancy outcome during in vitro fertilization. Int J Clin Exp Med. 2015;8:1286-90.
16. Nazari L, Salehpour S, Hoseini S, Zadehmodarres S, Ajori L. Effects of autologous platelet-rich plasma on implantation and pregnancy in repeated implantation failure: A pilot study. Int J Reprod Biomed. 2016;14(10):625-8.
17. Zadehmodarres S, Salehpour S, Saharkhiz N, Nazari L. Treatment of thin endometrium with autologous platelet-rich plasma: a pilot study. JBRA Assist Reprod. 2017;21(1):54-6.
18. Reversing menopause: new technique claims to 'rejuvenate' ovaries. Available at https://globalnews.ca/news/2846089/reversing-menopause-new-technique-claims-to-rejuvenate-ovaries/. Accessed on 29 August 2020.
19. Sills ES. Platelet-rich plasma (PRP) infusions and biomarkers of ovarian rejuvenation and aging,

inovium ovarian rejuvenation trials. Available at https://clinicaltrials.gov/ct2/show/NCT03178695. Accessed on 29 August 2020.
20. Zhang S, Li P, Yuan Z, Tan J. Platelet-rich plasma improves therapeutic effects of menstrual blood-derived stromal cells in rat model of intrauterine adhesion. Stem Cell Res Therapy. 2019;10:1.

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