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Review article

Recent progress in the treatment of women with diminished ovarian reserve

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ABSTRACT

Diminished ovarian reserve (DOR) refers to a decrease in the number and/or quality of oocytes in the ovary, accompanied by a decline in reproductive potential, which is generally related to advanced age or ovarian disease. In in vitro fertilization (IVF) clinical practice, managing patients with DOR remains one of the most challenging tasks. In recent years, increased research on improving ovarian function has provided us with new insights into treating patients with DOR. Many therapeutic options have been proposed to improve the ovarian function of patients with DOR, yet they are not widely utilized in clinical practice because of limited evidence of safety and effectiveness. In this review, we focus on the mechanisms from animal models and clinical trials that have been applied to the treatment of DOR in recent years, intending to improve IVF outcomes in patients with DOR. Furthermore, new insights and perspectives on the molecular and cellular regulation of follicular development and ovarian reserve are emphasized to provide more clues for research on the treatment of DOR.

Diminished ovarian reserve (DOR) is defined as a decrease in the number and/or quality of oocytes in the ovary, accompanied by decline in the level of anti-Müllerian hormone (AMH), a decrease in the number of antral follicles, and an increase in the level of follicle-stimulating hormone (FSH).[1,2] The American Society of Reproductive Medicine (ASRM) put forward an expert consensus in 2020 that DOR has no diagnostic criteria, but it is mainly manifested in the decline in the quality and quantity of oocytes and the decline in reproductive potential.

A number of risk factors for DOR have been reported in the literature, including advanced age (over 35 years old), family history of early menopause, genetic factors (45, X chromosome mosaicism, FMR1 gene mutation, etc.), diseases that may cause ovarian damage (endometriosis, pelvic tuberculosis, pelvic infection, etc.) or history of ovarian surgery, chemotherapy for ovarian-related diseases, pelvic radiotherapy and autoimmune diseases, smoking, and environmental factors.[3–5] In particular, several terminologies such as primary ovarian insufficiency (POI), poor ovarian response (POR), and other common diseases in reproductive medicine are all closely related to DOR.[6]

DOR is characterized by decreased fertility and poor fertility outcomes even when assisted reproductive techniques (ARTs) are used.[7,8] Improving the clinical outcome of patients with DOR is still one of the most challenging tasks in in vitro fertilization (IVF) clinical practice.[9] Therefore, while continuously improving IVF treatment strategies, researchers have also extensively tried to identify specific medication to improve ovarian functions in patients with DOR to obtain better treatment results. Researchers have obtained preliminary results showing increased pregnancy outcomes in ART treatment. This review focuses on the findings from recent studies and aims to present a more comprehensive view of the treatment of DOR.

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1. Human stem cells

Over the last ten years, extensive research has been carried out on stem cell therapy for improving ovarian function. Human amniotic mesenchymal stem cells (hAMSCs) have been shown to be able to improve ovarian function in multiple studies. For instance, Liu et al. have provided evidence showing an improved ovarian function of POF (premature ovarian failure) mice through hAMSC transplantation. Such a beneficial effect is related to an improved intraovarian microenvironment because of the promotion of follicular development and an increase in granulosa cell proliferation and secretion in the mouse ovary.[10] Additionally, the secretion level of EGF and HGF from hAMSCs was higher than other growth factors which can improve the proliferation rate and more effectively inhibit the apoptosis rate of granulosa cells.[11] Human umbilical cord-derived mesenchymal stem cells (hUCMSCs) have been shown to improve ovarian function through secreting several paracrine factors, such as HGF, vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1).[12] Similarly, human amniotic fluid mesenchymal stem cells (hAFMSCs) are reported to be helpful in the treatment of ovarian physiologic aging (OPA) by means of resisting DNA damage.[13] Human bone marrow-derived stem cells (BMDSCs) produce higher numbers of preovulatory follicles, metaphase II oocytes, and 2-cell embryos in mice with chemotherapy-induced ovarian damage. Meanwhile, stem cells promote ovarian vascularization and cell proliferation and reduced apoptosis during the treatment, indicating that promoting ovarian angiogenesis is crucial for improving follicular development.[14] The effects of bone marrow-derived stem cells on ovarian function in patients with DOR has been confirmed by a prospective observational pilot study. The ovarian function improves in 81.3% of DOR patients with an increase in antral follicle count of three or more follicles and/or two consecutive increases in AMH levels as success criteria after autologous stem cell ovarian transplantation (ASCOT). Meanwhile, the improvement is accompanied by a higher concentration of fibroblast growth factor-2 and thrombospondin. In addition, ASCOT increases the number of stimulable antral follicles and oocytes; however, the embryo euploidy rate was low (16.1%) during controlled ovarian stimulation.[15]

Exosomes derived from different stem cells also seem to be related to ovarian functions. Human adipose stem cell-derived exosome (hADSC-exo) transplantation significantly exerts better therapeutic effects on mouse ovarian function. Furthermore, hADSC-exos also significantly promoted the proliferation rate and inhibited the apoptosis of granulosa cells via the SMAD-dependent signaling pathway.[16] Similarly, animal studies using a rat model show that bone marrow mesenchymal stem cell-derived exosomes prevent ovarian follicular atresia via the delivery of miR-144–5p in chemotherapy-induced ovarian failure.[17] The exosomes derived from human umbilical cord mesenchymal stem cells (HucMSC-exos) are reported to stimulate primordial follicles by activating the phosphatidylinositol 3-kinase (PI3K)/mTOR signaling pathway in oocytes. Furthermore, HucMSC-exos stimulates primordial follicles by delivering functional microRNAs, such as miR-146a-5p or miR-21–5p. In addition, HucMSC-exos are capable of increasing oocyte production and enhance oocyte quality in elderly female mice.[18] The effects of stem cells and their exosomes on inhibiting ovarian damage and alleviating age-related decline in fertility indicate that stem cells exert paracrine effects.

Researchers began to explore the better strategy to improve ovarian function with stem cells given that the stem cell therapy is effective. A study comparing two methods (intravenous injection or IV vs. in situ ovarian microinjection or MI) reveals that hUCMSCs IV is more effective to restore ovarian function with a lower rate of ovarian granulosa cell apoptosis accompanied by higher levels of SOD (superoxide dismutase) and Bcl2 and higher efficiency in regular cycle recovery (25–37.5% with IV treatment vs. 12.5–25% with MI treatment).[19] Nevertheless, the in-depth analysis of the stem cell and identification of key molecules need further exploration to provide a new paradigm basis for cell-free treatment strategies.

2. Dehydroepiandrosterone (DHEA)

DHEA, a C19 androgenic steroid, has a pro-inflammatory immune function against cortisol. Researchers have reported a series of potential mechanisms by which DHEA modulates ovarian function, including improving follicular steroidogenesis, increasing IGF-1 (insulin-like growth factor (IGF)-1) acting as a prehormone for follicular testosterone, reducing aneuploidy, and increasing AMH levels and antral follicle count.[20,21] Also, Kuan-Hao Tsui et al. found that DHEA can restore starvation-induced reactive oxygen species (ROS) production and mitochondrial membrane potential imbalance via upregulation of cytochrome *c* and downregulation of BAX in mitochondria.[22]

DHEA has been used in the treatment of patients with DOR during IVF in recent years.[23] A retrospective cohort study showed that DHEA supplementation increased oocyte and embryo yields, as well as cumulative pregnancy rates in patients with DOR.[24] However, a meta-analysis evaluated the effect of DHEA therapy in patients with DOR. The results showed that clinical pregnancy rates were increased significantly in patients who were pretreated with DHEA. In contrast, no differences were found in the number of oocytes retrieved, the cancellation rate of IVF cycles, or the miscarriage rate. Furthermore, the difference in the clinical pregnancy rate disappeared when the data were restricted to RCTs.[25] Taken together, DHEA might have a beneficial effect in patients with DOR, but the method of DHEA treatment and its in-depth mechanism still need further research to confirm these effects.

3. Growth hormone (GH)

GH has been used as an adjuvant in the treatment of infertility for more than 25 years.[26] It was initially used for patients with GH deficiency, but recent studies found that GH and GH/IGF axes might improve ovarian function.[27] GH and IGF modulate key signal pathways, such as the MAPK/ERK, Jak/STAT, and PI3K/Akt signaling pathway along with the subsequent effects on cell division and steroidogenesis related to ovarian function.[28] Medium- and high-dose recombinant human GH (rhGH) significantly increase the level of antral follicles but not AMH in aged mice. In addition, several parameters, including retrieved oocytes, MII-stage oocyte rate, ATP levels, mitochondrial membrane potential, and frequencies of homogeneous mitochondrial distribution, increase after rhGH treatment.[29] Clinical studies also present a higher number of grade 1 embryos (70.7% vs. 50.6%) and levels of estradiol and progesterone on the day of HCG administration in patients receiving GH. The rates of cumulative clinical pregnancy were higher in patients who received GH, yet the clinical pregnancy rates were not significantly different.[30,31] However, a meta-analysis analyzing GH application for patients with POR during their IVF treatment showed that there was no evidence for an increased live birth rate for a woman who received GH.[26] In this regard, the role of GH treatment for patients with DOR awaits further investigation and clarification.

4. Melatonin

Melatonin is an indoleamine produced by all cells.[32] It has potent antioxidant activity and can directly scavenge free radicals without relying on receptors, acting as ROS.[33] Previous studies discovered that melatonin promote oocyte maturation, fertilization and embryonic development by protecting oocytes and other follicle cells from oxidative damage. In this regard, melatonin eliminates free radicals and reduces oxidative stress in ovarian follicles, thereby protecting oocytes and granulosa cells.[34,35] In addition, PAR (poly adp-ribose) expression and AIF nuclear translocation are significantly higher in cumulus GCs (granulosa cells) of DOR patients, indicating PARP1-dependent cell death may be associated with DOR. However, melatonin treatment effectively inhibits polyADP-ribosylation (PARylation) and blocks translocation of AIF into the nucleus, thereby reducing the risk of apoptosis in GCs.[36] A double-blinded, placebo-controlled clinical trial has been conducted to

verify the effectiveness of melatonin. The results showed that patients who received melatonin had higher serum estradiol levels on the triggering day and increased numbers of good-quality oocytes and embryos. However, there were no differences in clinical pregnancy rate or other ART outcomes.[37] Therefore, the effectiveness of melatonin in the treatment of DOR still needs more clinical trials to confirm.

5. Traditional Chinese medicines

So far, many studies have worked on the influence of pivotal ingredients in Chinese herbal medicine on ovarian function, especially its important role in the treatment of DOR. Polysaccharides of *Fructus corni* (PFC) were reported to be antiaging molecules, and ovarian function was protected after PFC treatment, which was assessed by sex hormone levels and follicular development. Furthermore, treatment with PFC upregulated Bcl-2 and downregulated Bax and cleaved-caspase-3, suggesting that PFC inhibited apoptosis of granulosa cells in the ovaries of aging mice.[38] Yifuning is a traditional Chinese medicine recipe that can significantly prevent ovarian failure in aging mice, which has been shown to maintain estrous cycling, reproductive organ weights, and serum sex hormone levels. Yifuning has been shown to reduce age-induced p19, p53, p21, and Rb activity, and DNA damage by inhibiting the expression of 8-OHDG and p53 in the ovaries.[39] In addition, the Kuntai capsule improves damaged ovarian function via antioxidant and antiapoptosis effects.[40] A meta-analysis study comparing the effectiveness of cotreatment with Kuntai capsule and climen for patients with POF shows that cotreatment is more effective than climen alone.[41] Although traditional Chinese medicine might have a favorable effect on ovarian function, further exploring its specific mechanism is still necessary to improve its application for clinical treatment.

6. Other therapeutic options

Although age-related ovarian failure cannot be reversed, many researchers are still committed to discovering effective methods to improve or preserve ovarian function. In recent years, various molecules have been found to improve ovarian function or delay ovarian aging, but the specific mechanisms are still unclear.

Rapamycin has been reported to be detrimental to follicular development and ovulation with long-term treatment. However, shortening the administration time of rapamycin to 2 weeks causes a rebound in fertility and prolongs the reproductive lifespan in aging females, which appears after short-term ovarian dysfunction. The improvement of ovarian function is accompanied by increased oocyte numbers, higher quality of oocytes, higher levels of Gdf 9 and Bmp15 and higher mitochondrial activity.[42]

A prospective observational cohort study has shown that intraovarian platelet-rich plasma (PRP) infusion significantly improves the hormonal profile and ovarian reserve status , as well as improves pregnancy outcomes in intracytoplasmic sperm injection (ICSI) cycles in POR participants. A similar effect on improving ovarian function can be observed in perimenopausal and premature ovarian insufficiency participants.[43] Similarly, a study including 38 women (31–45 years old) with low ovarian reserves and who had at least two unsuccessful attempts to receive their oocytes through IVF shows laparoscopically assisted treatment administration of 0.7 ml 1×10^6 PRP into the ovary is capable to improving ovarian function based on the improvement in the levels of FSH, luteinizing hormone (LH), estradiol, and AMH, as well as the pregnancy rate.[44]

Curcumin (CRC) is a constituent of the traditional medicine known as turmeric, and capsaicin (CPS) is the active ingredient of chili peppers.[45,46] CRC and CPS also have a beneficial effect on ovarian function in a cyclophosphamide-induced POF model. A significant reduction in serum levels of FSH and LH and an increase in AMH can be observed after treatment with CRC and CPS. Moreover, malonaldehyde levels are significantly reduced, glutathione levels and superoxide dismutase activity are significantly increased, and histopathological damages, such as atresia in ovarian follicles, vascular congestion, and hemorrhage around the corpus luteum, are all attenuated by the treatment with CRC and CPS.[47]

The immunopotentiator chitosan oligosaccharide (COS) is the only basic amino oligosaccharide among natural sugars.[48] Multiple studies have discovered its unique role in restoring ovarian function. With increased doses of COS, the total number of follicles and every stage of follicles show progressive tendencies. Neutral red experiments revealed that the phagocytosis ability of peritoneal macrophages becomes stronger. Additionally, the levels of dynamic germ stem cell markers have a positive correlation with the levels of immune factors.[49] In the study performed by Huang et al. COS significantly increases the organ index of the ovary and immune organs, the levels of estradiol and AMH and protein expression levels of IL-2 and TNF-α in the ovary. Additionally, COS reduces the rate of follicular atresia, hence significantly promotes the proliferation of ovarian germ stem cells (OGSCs), and protects ovarian function.[50]

7. Conclusion

Numerous therapeutic options developed to improve the ovarian function of women with DOR are gradually being utilized in clinical treatment thus far. Moreover, according to clinical studies, DOR caused by ovarian aging or ovarian diseases can be reversed or prevented efficiently by current methods to a certain degree, which brings us more motivation to explore the mechanism of regulating and preserving ovarian function.

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Declaration of competing interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

References

1. Cohen J, Chabbert-Buffet N, Darai E. Diminished ovarian reserve, premature ovarian failure, poor ovarian responder–a plea for universal definitions. *J Assist Reprod Genet*. 2015;32(12):1709–1712. https://doi.org/10.1007/s10815-015-0595-y.
2. Alborzi S, Madadi G, Samsami A, et al. Decreased ovarian reserve: any new hope? *Minerva Ginecol*. 2015;67(2):149–167.
3. Rasool S, Shah D. Fertility with early reduction of ovarian reserve: the last straw that breaks the Camel's back. *Fertil Res Pract*. 2017;3:15. https://doi.org/10.1186/s40738-017-0041-1.
4. Haydardedeoglu B, Zeyneloglu HB. The impact of endometriosis on fertility. *Womens Health (Lond)*. 2015;11(5):619–623. https://doi.org/10.2217/whe.15.48.
5. Bunyaeva E, Kirillova A, Khabas G, et al. Feasibility of in vitro maturation of oocytes collected from patients with malignant ovarian tumors undergoing fertility preservation. *Int J Gynecol Cancer*. 2021;31(3):475–479. https://doi.org/10.1136/ijgc-2020-001754.
6. Fàbregues F, Ferreri J, Méndez M, et al. In vitro follicular activation and stem cell therapy as a novel treatment strategies in diminished ovarian reserve and primary ovarian insufficiency. *Front Endocrinol (Lausanne)*. 2020;11:617704. https://doi.org/10.3389/fendo.2020.617704.
7. Bishop LA, Richter KS, Patounakis G, et al. Diminished ovarian reserve as measured by means of baseline follicle-stimulating hormone and antral follicle count is not associated with pregnancy loss in younger in vitro fertilization patients. *Fertil Steril*. 2017;108(6):980–987. https://doi.org/10.1016/j.fertnstert.2017.09.011.
8. Chang Y, Li J, Li X, et al. Egg quality and pregnancy outcome in young infertile women with diminished ovarian reserve. *Med Sci Mon Int Med J Exp Clin Res*. 2018;24:7279–7284. https://doi.org/10.12659/msm.910410.
9. Wald Kaitlyn A, Shahine Lora K, Lamb Julie D, et al. High incidence of diminished ovarian reserve in young unexplained recurrent pregnancy loss patients. *[J] .Gynecol Endocrinol*. 2020;36:1079–1081.
10. Liu R, Zhang X, Fan Z, et al. Human amniotic mesenchymal stem cells improve the follicular microenvironment to recover ovarian function in premature ovarian failure

mice. *Stem Cell Res Ther*. 2019;10(1):299. https://doi.org/10.1186/s13287-019-1315-9.
11. Ding C, Zou Q, Wang F, et al. Human amniotic mesenchymal stem cells improve ovarian function in natural aging through secreting hepatocyte growth factor and epidermal growth factor. *Stem Cell Res Ther*. 2018;9(1):55. https://doi.org/10.1186/s13287-018-0781-9.
12. Li J, Mao Q, He J, et al. Human umbilical cord mesenchymal stem cells improve the reserve function of perimenopausal ovary via a paracrine mechanism. *Stem Cell Res Ther*. 2017;8(1):55. https://doi.org/10.1186/s13287-017-0514-5.
13. Huang B, Ding C, Zou Q, et al. Human amniotic fluid mesenchymal stem cells improve ovarian function during physiological aging by resisting DNA damage. *Front Pharmacol*. 2020;11:272. https://doi.org/10.3389/fphar.2020.00272.
14. Herraiz S, Buigues A, Díaz-García C, et al. Fertility rescue and ovarian follicle growth promotion by bone marrow stem cell infusion. *Fertil Steril*. 2018;109(5):908–918. https://doi.org/10.1016/j.fertnstert.2018.01.004. e2.
15. Herraiz S, Romeu M, Buigues A, et al. Autologous stem cell ovarian transplantation to increase reproductive potential in patients who are poor responders. *Fertil Steril*. 2018;110(3):496–505. https://doi.org/10.1016/j.fertnstert.2018.04.025. e1.
16. Huang B, Lu J, Ding C, et al. Exosomes derived from human adipose mesenchymal stem cells improve ovary function of premature ovarian insufficiency by targeting SMAD. *Stem Cell Res Ther*. 2018;9(1):216. https://doi.org/10.1186/s13287-018-0953-7.
17. Yang M, Lin L, Sha C, et al. Bone marrow mesenchymal stem cell-derived exosomal miR-144-5p improves rat ovarian function after chemotherapy-induced ovarian failure by targeting PTEN. *Lab Invest*. 2020;100(3):342–352. https://doi.org/10.1038/s41374-019-0321-y.
18. Yang W, Zhang J, Xu B, et al. HucMSC-derived exosomes mitigate the age-related retardation of fertility in female mice. *Mol Ther*. 2020;28(4):1200–1213. https://doi.org/10.1016/j.ymthe.2020.02.003.
19. Zhang J, Xiong J, Fang L, et al. The protective effects of human umbilical cord mesenchymal stem cells on damaged ovarian function: a comparative study. *Biosci Trends*. 2016;10(4):265–276. https://doi.org/10.5582/bst.2016.01125.
20. Hassa H, Aydin Y, Ozatik O, et al. Effects of dehydroepiandrosterone (DHEA) on follicular dynamics in a diminished ovarian reserve in vivo model. *Syst Biol Reprod Med*. 2015;61(3):117–121. https://doi.org/10.3109/19396368.2015.1011353.
21. Fouany MR, Sharara FI. Is there a role for DHEA supplementation in women with diminished ovarian reserve? *J Assist Reprod Genet*. 2013;30(9):1239–1244. https://doi.org/10.1007/s10815-013-0018-x.
22. Tsui KH, Wang PH, Lin LT, et al. DHEA protects mitochondria against dual modes of apoptosis and necroptosis in human granulosa HO23 cells. *Reproduction*. 2017;154(2):101–110. https://doi.org/10.1530/rep-17-0016.
23. Ozcil MD. Dehydroepiandrosterone supplementation improves ovarian reserve and pregnancy rates in poor responders. *Eur Rev Med Pharmacol Sci*. 2020;24(17):9104–9111. https://doi.org/10.26355/eurrev_202009_22856.
24. Chen SN, Tsui KH, Wang PH, et al. Dehydroepiandrosterone supplementation improves the outcomes of in vitro fertilization cycles in older patients with diminished ovarian reserve. *Front Endocrinol (Lausanne)*. 2019;10:800. https://doi.org/10.3389/fendo.2019.00800.
25. Qin JC, Fan L, Qin AP. The effect of dehydroepiandrosterone (DHEA) supplementation on women with diminished ovarian reserve (DOR) in IVF cycle: evidence from a meta-analysis. *J Gynecol Obstet Hum Reprod*. 2017;46(1):1–7. https://doi.org/10.1016/j.jgyn.2016.01.002.
26. Hart RJ. Use of growth hormone in the IVF treatment of women with ooor ovarian reserve. *Front Endocrinol (Lausanne)*. 2019;10:500. https://doi.org/10.3389/fendo.2019.00500.
27. Silva JR, Figueiredo JR, van den Hurk R. Involvement of growth hormone (GH) and insulin-like growth factor (IGF) system in ovarian folliculogenesis. *Theriogenology*. 2009;71(8):1193–1208. https://doi.org/10.1016/j.theriogenology.2008.12.015.
28. Ipsa E, Cruzat VF, Kagize JN, et al. Growth hormone and insulin-like growth factor Action in reproductive tissues. *Front Endocrinol (Lausanne)*. 2019;10:777. https://doi.org/10.3389/fendo.2019.00777.
29. Hou HY, Wang X, Yu Q, et al. Evidence that growth hormone can improve mitochondrial function in oocytes from aged mice. *Reproduction*. 2018;157(4):345–358. https://doi.org/10.1530/rep-18-0529.
30. Dogan S, Cicek OSY, Demir M, et al. The effect of growth hormone adjuvant therapy on assisted reproductive technologies outcomes in patients with diminished ovarian reserve or poor ovarian response. *J Gynecol Obstet Hum Reprod*. 2021;50(2):101982. https://doi.org/10.1016/j.jogoh.2020.101982.
31. Chen Y, Tao L, Lin Y, et al. Outcomes of in vitro fertilization-embryo transfer in women with diminished ovarian reserve after growth hormone pretreatment. *Gynecol Endocrinol*. 2020;36(11):955–958. https://doi.org/10.1080/09513590.2020.1737005.
32. Zhao D, Yu Y, Shen Y, et al. Melatonin synthesis and function: evolutionary history in animals and plants. *Front Endocrinol (Lausanne)*. 2019;10:249. https://doi.org/10.3389/fendo.2019.00249.
33. Tamura H, Takasaki A, Taketani T, et al. Melatonin as a free radical scavenger in the ovarian follicle. *Endocr J*. 2013;60(1):1–13. https://doi.org/10.1507/endocrj.ej12-0263.
34. Tamura H, Jozaki M, Tanabe M, et al. Importance of melatonin in assisted reproductive technology and ovarian aging. *Int J Mol Sci*. 2020;21(3). https://doi.org/10.3390/ijms21031135.
35. Lin T, Lee JE, Kang JW, et al. Melatonin supplementation during prolonged in vitro maturation improves the quality and development of poor-quality porcine oocytes via anti-oxidative and anti-apoptotic effects. *Mol Reprod Dev*. 2018;85(8-9):665–681. https://doi.org/10.1002/mrd.23052.
36. Batnasan E, Xie S, Zhang Q, et al. Observation of parthanatos involvement in diminished ovarian reserve patients and melatonin's protective function through inhibiting ADP-Ribose (PAR) expression and preventing AIF translocation into the nucleus. *Reprod Sci*. 2020;27(1):75–86. https://doi.org/10.1007/s43032-019-00005-8.
37. Jahromi BN, Sadeghi S, Alipour S, et al. Effect of melatonin on the outcome of assisted reproductive technique cycles in women with diminished ovarian reserve: a double-blinded randomized clinical trial. *Iran J Med Sci*. 2017;42(1):73–78.
38. Wang Y, Wu JZ, Li Y, et al. Polysaccharides of fructus corni improve ovarian function in mice with aging-associated perimenopause symptoms. *Evid Based Complement Alternat Med*. 2019;2019:2089586. https://doi.org/10.1155/2019/2089586.
39. Liang L, Zhang XH, Ji B, et al. Yifuning postpones ovarian aging through antioxidant mechanisms and suppression of the Rb/p53 signal transduction pathway. *Mol Med Rep*. 2016;14(1):888–896. https://doi.org/10.3892/mmr.2016.5322.
40. Zhang J, Fang L, Shi L, et al. Protective effects and mechanisms investigation of Kuntai capsule on the ovarian function of a novel model with accelerated aging ovaries. *J Ethnopharmacol*. 2017;195:173–181. https://doi.org/10.1016/j.jep.2016.11.014.
41. Ma Q, Tan Y, Mo G. Effectiveness of cotreatment with Kuntai capsule and climen for premature ovarian failure: a meta-analysis. *Evid Based Complement Alternat Med*. 2020;2020:4367359. https://doi.org/10.1155/2020/4367359.
42. Dou X, Sun Y, Li J, et al. Short-term rapamycin treatment increases ovarian lifespan in young and middle-aged female mice. *Aging Cell. Aug*. 2017;16(4):825–836. https://doi.org/10.1111/acel.12617.
43. Sfakianoudis K, Simopoulou M, Grigoriadis S, et al. Reactivating ovarian function through autologous platelet-rich plasma intraovarian infusion: pilot data on premature ovarian insufficiency, perimenopausal, menopausal, and poor responder women. *J Clin Med*. 2020;9(6). https://doi.org/10.3390/jcm9061809.
44. Petryk N, Petryk M. Ovarian rejuvenation through platelet-rich autologous plasma (PRP)-a chance to have a baby without donor eggs, improving the life quality of women suffering from early menopause without synthetic hormonal treatment. *Reprod Sci*. 2020;27(11):1975–1982. https://doi.org/10.1007/s43032-020-00266-8.
45. Nelson KM, Dahlin JL, Bisson J, et al. The Essential medicinal chemistry of curcumin. *J Med Chem*. 2017;60(5):1620–1637. https://doi.org/10.1021/acs.jmedchem.6b00975.
46. Sharma SK, Vij AS, Sharma M. Mechanisms and clinical uses of capsaicin. *Eur J Pharmacol*. 2013;720(1-3):55–62. https://doi.org/10.1016/j.ejphar.2013.10.053.
47. Melekoglu R, Ciftci O, Eraslan S, et al. Beneficial effects of curcumin and capsaicin on cyclophosphamide-induced premature ovarian failure in a rat model. *J Ovarian Res*. 2018;11(1):33. https://doi.org/10.1186/s13048-018-0409-9.
48. Zhuo D, Li X, Guan F. Biological roles of aberrantly expressed glycosphingolipids and related enzymes in human cancer development and progression. *Front Physiol*. 2018;9:466. https://doi.org/10.3389/fphys.2018.00466.
49. Li XY, Cao X, Liu XY, et al. [Effects of COS on promoting the pathological ovarian aging mice ovarian function by regulating immune function]. *Zhongguo Ying Yong Sheng Li Xue Za Zhi*. 2017;33(2):97–102. https://doi.org/10.12047/j.cnki.5457.2017.025.
50. Huang Y, Ye H, Zhu F, et al. The role of Chito-oligosaccharide in regulating ovarian germ stem cells function and restoring ovarian function in chemotherapy mice. *Reprod Biol Endocrinol*. 2021;19(1):14. https://doi.org/10.1186/s12958-021-00699-z.