

Follicular activation in premature ovarian insufficiency (POI)

Sonia Herraiz¹ and Nuria Pellicer^{1,2}

April 2021

¹IVI Foundation-IIS La Fe, Valencia, Spain. ²IVIRMA Valencia, Valencia, Spain

Achieve ovarian reactivation and rescue is one of the challenges of Reproductive Medicine. Given the low birth rates and the delayed age of childbearing due to profound socioeconomic changes in modern society, infertility became a health problem affecting approximately 15% of women at reproductive age. Both quantity and quality of the oocytes from aged patients are seriously impaired [1] although diminished ovarian reserve (DOR) is not only associated with age. Premature ovarian insufficiency (POI) is a major cause of infertility in women, affecting 1% of the population, that associates very low pregnancy rates [2]. It is characterized by amenorrhea, hypoestrogenism, and elevated gonadotropin levels leading to a complete ovarian failure in women younger than 40 years of age. To date, there has not been yet described a useful strategy to improve IVF outcomes in this poor prognosis subgroup of patients, being in most cases oocyte donation their only practical option to achieve desired motherhood as their ovaries lack from antral gonadotrophin-stimulable follicles. Nevertheless, residual primordial follicles, that could potentially contribute to increase the final yield of competent oocytes, are frequently found in ovarian biopsies [3] from idiopathic POI women. In fact, competent oocytes could be retrieved following the activation of these remaining follicles by several approaches, providing an appropriate growth-supporting ovarian niche [4].

In vitro activation (IVA)

In the last decade, reactivation of these follicles has been achieved by a combination of IVA, with the PTEN inhibitors and Akt stimulating molecules, and ovarian fragmentation in a number of case series and cohort studies reporting diverse degrees of success in women with DOR and POI [4, 5]. More recently, this technique has been refined without the PTEN inhibitors or Akt stimulating molecules in an effort to reduce the number of surgical interventions and to avoid tissue cryopreservation. This drug free approach based on the mechanical tissue fragmentation to suppress the Hippo signaling pathway allows dormant follicle activation and growth, pregnancies and live births [6-9].

Stem cell ovarian transplant

Clinically, this follicular reactivation could also be the underlying mechanism of several reports of fertility recover and spontaneous pregnancies in patients with POI due to cancer treatments after receiving a bone marrow transplant. In fact, we recently described that bone marrow derived stem cell infusion promotes human and mouse follicular growth by increasing ovarian vascularization, stromal cell proliferation, and reducing cell death [10]. Other stem cell types such as mesenchymal, adipose, and hematopoietic origins have also been proved to restore ovarian function in POI mice models. Based on that, a prospective pilot study in 20 poor responder women was developed to evaluate the effects of autologous stem cell ovarian transplant (ASCOT) on ovarian function[11]. ASCOT improved AMH and AFC in 81.3% of women, increased follicle growth and oocyte yield enabling spontaneous pregnancies in poor prognosis women previously limited to egg donation.

In the context of ovarian tissue, stem cell paracrine actions should be evaluated for their capacity to activate the pre-existing quiescent follicles through a broad variety of soluble growth factors involved in follicular growth, angiogenesis, viability, and ovarian response to COS. In fact, ASCOT optimized the growth of existing follicles, mediated the presence of specific stem cell secreted factors such as FGF-2 and THSP-1 within aphaeresis.

Platelet-rich plasma (PRP)

Another approach also based on the paracrine signaling has been recently proposed to restore ovarian function in POI women. PRP is a concentrate composed by growth factors contained within platelets, which promote tissue healing, angiogenesis and cell growth. Intraovarian injection of PRP promoted an increase in AMH and a decrease in FSH, sufficient to permit oocyte retrieval. To date it

has been tested in different populations of patients including poor responders, POI, and perimenopausal women with positive results for the recovery of ovarian function, pregnancies, and live births, especially for poor responders (46.6% pregnancy rate). For POI, the largest cohort was reported by Cakiroglu et al. [12] with a total of 36 out of 311 women pregnant after PRP (11.5%) although 25 additional patients had cryopreserved embryos for transfer. Similar pregnancy rates (10%, 3/30 women) were reported by Sfakianoudis et al. [13], for POI.

Within the advantages of PRP stands out the fact that it is more readily applicable to clinical practice although further research is required to understand mechanisms and establish which group of patients could be really benefited from PRP [14].

Conclusions

Despite encouraging early studies using all the above-mentioned techniques, the variety of study designs, inclusion criteria and outcomes make it difficult to interpret the real efficiency of ovarian reactivation and which specific subgroup of the DOR population would benefit most from each specific technique. Moreover, the efficacy of these interventions has not yet been tested in randomized controlled trials including non-intervention control groups. This is of paramount relevance as POI spontaneous pregnancy rates across studies ranges from 3.5 % to 15.3%, and resumption of ovarian function can occur in 25% of patients, known as fluctuating FSH or intermittent POI, during the first year after the diagnose [3].

References

1. Evers, J.L., *Female subfertility*. Lancet, 2002. **360**(9327): p. 151-9.
2. van Kasteren, Y.M. and J. Schoemaker, *Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy*. Hum Reprod Update, 1999. **5**(5): p. 483-92.
3. Bachelot, A., et al., *Long-term outcome of ovarian function in women with intermittent premature ovarian insufficiency*. Clin Endocrinol (Oxf), 2017. **86**(2): p. 223-228.
4. Kawamura, K., et al., *Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment*. Proceedings of the National Academy of Sciences of the United States of America, 2013. **110**(43): p. 17474-9.
5. Zhai, J., et al., *In Vitro Activation of Follicles and Fresh Tissue Auto-transplantation in Primary Ovarian Insufficiency Patients*. J Clin Endocrinol Metab, 2016. **101**(11): p. 4405-4412.
6. Tanaka, Y., A.J. Hsueh, and K. Kawamura, *Surgical approaches of drug-free in vitro activation and laparoscopic ovarian incision to treat patients with ovarian infertility*. Fertil Steril, 2020. **114**(6): p. 1355-1357.
7. Kawamura, K., B. Ishizuka, and A.J.W. Hsueh, *Drug-free in-vitro activation of follicles for infertility treatment in poor ovarian response patients with decreased ovarian reserve*. Reprod Biomed Online, 2020. **40**(2): p. 245-253.
8. Ferreri, J., et al., *Drug-free in-vitro activation of follicles and fresh tissue autotransplantation as a therapeutic option in patients with primary ovarian insufficiency*. Reprod Biomed Online, 2020. **40**(2): p. 254-260.
9. Lunding, S.A., et al., *Biopsying, fragmentation and autotransplantation of fresh ovarian cortical tissue in infertile women with diminished ovarian reserve*. Hum Reprod, 2019. **34**(10): p. 1924-1936.
10. Herraiz, S., et al., *Fertility rescue and ovarian follicle growth promotion by bone marrow stem cell infusion*. Fertil Steril, 2018. **109**(5): p. 908-918 e2.
11. Herraiz, S., et al., *Autologous stem cell ovarian transplantation to increase reproductive potential in patients who are poor responders*. Fertil Steril, 2018. **110**(3): p. 496-505.e1.
12. Cakiroglu, Y., et al., *Effects of intraovarian injection of autologous platelet rich plasma on ovarian reserve and IVF outcome parameters in women with primary ovarian insufficiency*. Aging (Albany NY), 2020. **12**(11): p. 10211-10222.
13. Sfakianoudis, K., 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).
14. Atkinson, L., F. Martin, and R.G. Sturmey, *Intraovarian injection of platelet-rich plasma in assisted reproduction: too much too soon?* Hum Reprod, 2021. **36**(7): p. 1737-1750.