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Hit Snooze on your Biological Clock

DISCUSSION STARTERS

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ABSTRACT

Ovarian reserve can be defined as the quality and quantity of oocytes in the ovaries. Ovarian reserve directly correlates with fertility. Ageing causes a natural decline in fertility, with ovaries having performed their full function by menopause, leaving females unable to conceive. Recent studies by Sfakianoudis et al. have explored the use of injected platelet rich plasma (PRP) to boost ovarian reserve and combat infertility. While this is currently a novel concept, the results are encouraging and PRP could well be introduced as a viable fertility treatment.

INTRODUCTION

It is widely understood that as women females age, their oocyte quantity and quality (ovarian reserve) decreases. Ageing oocytes are the main limiting factor for successful spontaneous conceptions as well asand assisted conceptions. They are also more susceptible to errors in cell division and DNA synthesis, such that subsequent conceptions are at an increased risk of aneuploidy and congenital defects (1). When women females reach menopause, their ovaries consist of very few follicles, leading to infertility ving them unable to conceive; a state known as infertility (2). Ovarian reserve can be measured by the serum Anti-Mullerian Hormone (AMH) and follicle stimulating hormone (FSH). Decreased ovarian reserve, (with DOR) is associated with low AMH and high FSH (3).

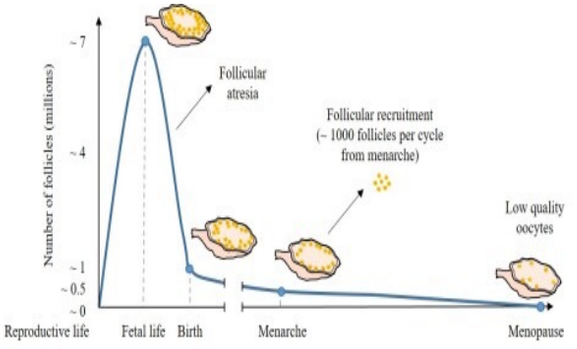

Figure 1: A timeline of follicular decay as a result of ageing. Modified and adapted with permission from Polonio AM et al. (2).

Infertility can be defined as failing to conceive after 1 year of unprotected sexual intercourse. While Ffor many, this is expected to occur at around 50 years of age, with menopause, as illustrated in figure 1. However, in around 1% of women, ovarian reserve starts to decline earlier, leading to premature ovarian insufficiency (POI) (2). A diagnosis of POI carries with it numerous health, psychological and reproductive implications and until recently, it was considered to be untreatable without using a donoregg donors (4). However, a recent scientific breakthrough proposed the intraovarian use of platelet rich plasma (PRP) for ovarian rejuvenation in patients with previous failed in vitro fertilisation (IVF) attempts (3). Since then, experimental studies have been conducted to evaluate the use of PRP in patients with POI or DOR.

PRP is infused non-surgically and is formed from the patient's centrifuged blood, comprising of high concentrations of platelets incorporated with hormones, macrophages, neutrophils, stem cell chemo-attractants, cytokines and various growth factors. The platelets are then activated to release assorted biologically active proteins (4). Combined, these encourage the repair and regeneration of tissues, enriching the ovarian tissue with vital factors for neoangiogenesis (formation of new blood vessels), resulting in reactivation of previously dysfunctional ovaries. Furthermore, there is evidence that PRP promotes the growth of endometrial tissue in patients with thin endometrial tissueum, therefore increasing the chance of successful implantation (3).

In a 2018 trial conducted by Sfakianoudis et al., roughly 5ml of PRP, per ovary, was infused directly into the ovaries of three patients (aged 37, 37, 40) with DOR. , by means ofThis was done using a transvaginal ultrasound-guided multifocal intramedullary injection. Following their first menstrual cycle after the PRP infusion, the patients' FSH and AMH levels were recorded to assess the effectiveness of the injections. All three patients were monitored by ultrasound scans, and follicle growth was assessed every two days until a follicle reached >16mm. Subsequently, human chorionic gonadotropin (hCG) was used to trigger ovulation and all mature follicles were inseminated using intracytoplasmic sperm injection (ICSI). The resulting embryos were cultured until blastocysts were observed. On day 5, the embryos were transferred to the patients, and the implantation success was monitored with hCG tests after ten days (3).

The findings were promising, advocating for the use of PRP in patients with previous failed IVF attempts, potentially with DOR. The average decrease in FSH levels of all three patients was 67.33% within the first three months of treatment. Likewise, the average increase in AMH levels was 75.18%. All three patients became pregnant within 6 months of the infusion, with no complications seen in any of the pregnancies. At the time of the report being written, one pregnancy had already resulted in the birth of a healthy baby boy (3).

While the study conducted by Sfakianoudis et al. was on a small scale, Cakiroglu et al. carried out a trial with similar aims on a larger significantly larger scale, incorporating 311 patients aged 24-40 with POI. The study found that PRP infusions resulted in an increase in AMH, but no significant change in FSH was observed. 23 of these women achieved spontaneous pregnancy within two cycles of PRP treatment. In the remaining 288 women, 82 developed embryos. Out of the 311 women, 25 achieved live birth, while another 25 decided to preserve their embryos. While the results seem less convincing than those of Sfakianoudis et al., it is interesting to note that women females with POI rarely achieve spontaneous pregnancy (4).

AMH levels in both studies increased with the use of PRP, supporting the use of PRP as a fertility treatment. However, whilst the FSH levels decreased in the study from Sfakianoudis et al., there were no changes in FSH levels found in the study by Cakiroglu et al (3,4). There could be several possible reasons for this contrast in FSH levels. PRP is injected directly into the ovaries of patients with POI, resulting in the regeneration of ovarian tissue. Therefore, it is likely that the effects of PRP would depend on the number and quality of the remaining follicles in the patient's ovaries. This number varies between patients, thus the extent of patient response to PRP will vary, resulting in differing FSH levels. Furthermore, Cakiroglu et al. found that patients who had one or more antral follicles present at the time of PRP injection were likely to respond better to PRP treatment than those with no antral follicles. Therefore, their response would vary based on which stage of their cycle the patients were in during time of treatment, contributing to the varying FSH levels (4).

The aforementioned studies have limitations. Sfakianoudis et al. conducted this series in a very small cohort of three patients. Although the results of this study were encouraging, large-scale research with a larger sample size would be more conclusive. Additionally, there was a reported difficulty in following up patients, so it was not possible to take repeated FSH and AMH measurements (3). The lack of serial FSH and AMH measurements could affect the validity of the research. The study conducted by Cakiroglu et al. focussed on ovarian reserve and IVF parameters, however in this study, some women conceived spontaneously and others decided to cyopreserve embryos for future use thus, the rates of successful embryo transfer could not be measured accurately. The study also did not incorporate an independent control group and therefore, patient outcomes were analysed in parallel to their pre-treatment state. As such, we are unable to decipher whether results of the study could be influenced by external factors. Due to the nature of the study, the cohort was not randomised and as such, selection bias remains.

The costs of this procedure should also be considered carefully. A 2013 figure estimates that the NHS spends around £68 million annually on IVF treatment. NICE recommends that couples who fulfil the criteria for IVF should be offered up to three cycles. However, NHS funding for IVF is managed by clinical commissioning groups (CCGs), and figures from 2017 reveal that only 27/200 CCGs in England fulfilled this. Therefore, the majority (59%) of IVF treatments are conducted privately. Here, one IVF cycle costs on average £3348, excluding 'add-ons'. The price varies hugely in different clinics and couples are required to pay for blood tests and supplementary medications on top of this (5). PRP would likely be considered an 'add-on' treatment to IVF, therefore introducing PRP as a standard treatment would increase the existing cost burden of IVF on the NHS. Thus, it is vital that before PRP is utilised in NHS patients, its effectiveness is confirmed by robust clinical trials.

Until now, it has not been widely possible for women with POI to have children with their own eggs (4). However, through the work of Sfakianoudis et al. and others who have explored PRP as a fertility treatment, it is very feasible that egg donors will no longer be the only treatment for POIrequired for patients with POI to conceive. An online search for clinical trials assessing the use of PRP reveals multiple ongoing studies of this nature (information from clinicaltrials.gov). Several of these take on a patient-blinded approach, with some employing a control group undergoing saline irrigation as a placebo. Yet, it is important to consider the ethical concerns that could arise with wide scale implementation of this fertility treatment.

PRP is essentially a means of turning back time on a biological clock. IVF is currently practised with an age limit within the NHS, therefore is it possible that this age limit will have to be revised? As it is still very much a new and innovative technique, discussions need to take place about who should have access to PRP. While the two studies considered did not report any potential risks, the results of new, large scalelarge-scale trials need to be conducted considered to ensure the safety of PRP. Nevertheless, the overall posistive findings are hugely encouraging, advocating for the use of PRP in fertility treatment. Perhaps, we will find that the strict age limits for IVF may no longer be necessary in future practice.

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