



# Ovarian rejuvenation and folliculogenesis reactivation in peri-menopausal women after autologous platelet-rich plasma treatment

P-401

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## Background

- Platelet-rich plasma (PRP) constitutes a concentrated source of platelets, which is prepared by peripheral blood withdrawal after centrifugation. Platelets carry more than 800 proteins, such as cytokines, hormones and chemo-attractants of stem cells, macrophages and neutrophils, responsible for various post-translational modifications of nearly 1,500 bioactive factors<sup>1</sup>. The platelets also carry various growth factors, which are released after alpha granule activation by native or exogenous molecules, including thrombin, collagen, magnesium and calcium chloride.
- Numerous studies in various medical fields have demonstrated the beneficial effects of PRP on tissue regeneration, angiogenesis activation, inflammation control, anabolism increase as well as cell migration, differentiation and proliferation<sup>2-4</sup>.
- PRP treatment has been shown to improve vascularization and quality of an implant in an autologous ovarian transplantation<sup>5</sup>, while intrauterinely administered PRP has been shown to promote endometrial growth in cases with poor endometrial quality<sup>6</sup>. Finally, the study of an ischemia/reperfusion injury rat model has shown that PRP treatment diminishes the oxidative stress and the ovarian histopathology caused by the bilateral adnexal torsion, while it increases the peritoneal vascular endothelial growth factor<sup>7</sup>.
- In the current study, we sought to explore whether autologous ovarian PRP treatment could lead to ovarian rejuvenation and folliculogenesis reactivation in peri-menopausal women.

## Material & Methods

### Subjects

- Eight peri-menopausal women undergoing PRP treatment constituted the study population. All subjects, aged 45.13±4.42 years, had absence of menstrual cycle for 4.88±1.13 months.
- The FSH, LH, E<sub>2</sub> and AMH levels were determined before the PRP treatment and at monthly intervals after the PRP treatment in order to monitor the ovarian function. The presence of developing follicles was confirmed by ultrasound scan.

### Methods

- PRP was prepared using the RegenACR<sup>®</sup>-C Kit and was infused into the ovaries using a transvaginal ultrasound-guided injection.
- All patients underwent natural cycle IVF without any ovarian stimulation or GnRH antagonist supplementation.
- When a follicle of >16 mm was observed, ovulation triggering was achieved with 5000 IU of hCG and follicle aspiration was performed 32 hours later by the transvaginal route.
- The follicular size, the follicle and oocyte numbers were recorded during oocyte retrieval.

## Results

- The successful ovarian rejuvenation was confirmed by the menstrual cycle restoration **1-3** months after the ovarian PRP treatment.
- The subsequent oocyte retrievals were successful in all cases, resulting in **2.50±0.71 follicles** of **15.20±2.05 mm diameter**, **1.50±0.71 oocytes** and **1.50±0.71 MII oocytes**. All mature oocytes were inseminated by ICSI and the **1.50±0.71 resultant embryos** were cryopreserved at 2pn stage until transfer. To date, no embryo transfer has been performed.
- Taking into account the highly angiogenic ovarian structure and the critical role of various platelet derived factors for the vascular activation and stabilization, we could assume that PRP infusion probably enriched the dysfunctional, peri-menopausal ovarian tissue with the essential factors for angiogenesis and normal vascular function leading to tissue regeneration.
- Regarding the observed folliculogenesis, many peri-menopausal women may maintain a restricted amount of inactive primordial follicles, that could be activated by the PRP growth factors or the subsequent ovarian tissue regeneration and mature into preantral and antral follicles. Indeed, platelet-derived growth factors (PDGFs), regulating cell growth and division, have been shown to enhance blood vessel formation and growth. PDGFs have been localized in human oocytes and granulosa cells, while their receptors in granulosa cells, suggesting a potential association with primordial follicle activation.
- The recent detection of ovarian stem cells<sup>8</sup>, germline stem cells<sup>8</sup> and very small embryonic-like stem cells<sup>9</sup> in human ovarian surface epithelium as well as their ability to differentiate into oocytes under certain conditions, create new data for the origin of PRP-derived follicles. Therefore, the continual flow of hormones and growth factors, which may become temporarily available in the rejuvenated ovary of peri-menopausal women and premature ovarian failure (POF) patients by the PRP treatment, could give birth to 'new primary ovarian follicles' and subsequently to antral follicles.

## Conclusions

- Our data show, for the first time, the successful temporary ovarian activity restoration in peri-menopausal women after an autologous ovarian platelet-rich plasma treatment.
- After the verification of our preliminary results in larger population groups, PRP could be used as a first line treatment for the ovarian regeneration and the folliculogenesis reactivation of peri-menopausal women. PRP therapy may extend the fertility potential of peri-menopausal women, rendering oocyte donation IVF cycles as an ultimate option.

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