Combined Ovarian Platelet-Rich Plasma and Low-Dose Weekly Rapamycin/Sirolimus in Poor-Prognosis IVF: A Preliminary Case Series

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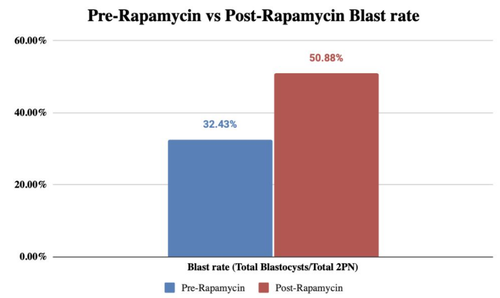
Background

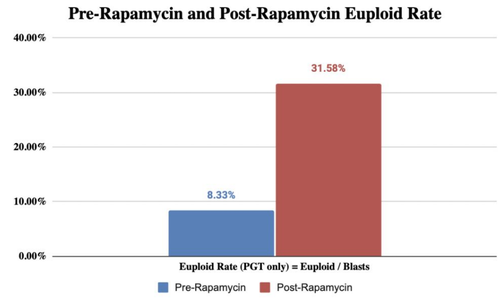
Ovarian aging results in diminished ovarian reserve and oocyte quality, significantly contributing to infertility. Current understanding of the pathophysiology of ovarian aging has identified various molecular pathways involving follicular atresia, oxidative stress, and microenvironmental changes [1]. Adjunct therapies targeting these pathways can aim to enhance outcomes of assisted reproductive technology (ART) methods. Platelet-rich plasma (PRP) is a regenerative therapy with a wide variety of clinical utility due to its high concentration of growth factors and cytokines that promote proliferative and anti-inflammatory cell pathways [2]. Within ART, intra-ovarian PRP therapy has been explored in patients diagnosed with ovarian insufficiency and diminished reserve, with pilot studies showing improved ovarian biomarkers, follicular activation, and even pregnancy in small cohorts [3]. Rapamycin (sirolimus), an mTOR inhibitor, has shown beneficial effects in animal and in vitro oocyte models by reducing oxidative stress, improving DNA repair, and preserving mitochondrial function in aging oocytes [4]. This report explores a combination of PRP with adjunct rapamycin that has not yet been described in published human IVF studies.

Results

Six patients comprised the analytic cohort for pre- versus post-rapamycin comparisons at our center. Cycles were categorized by exposure to adjunct rapamycin therapy as pre- or post-rapamycin, and all eligible cycles with available embryologic data were included; no patients were lost to follow-up for embryologic outcomes. Patient age at oocyte retrieval ranged from 34 to 45 years, with post-rapamycin cycles generally occurring at older maternal ages. Rapamycin exposure was initiated prior to post-rapamycin cycles at individualized intervals, and embryologic and frozen embryo transfer outcomes were incorporated into analyses.

Across patients, pre- vs post-intervention cycles contributed 37 vs 57 2PN embryos from our center. Blastocyst formation increased from 32.4% (12/37) pre-intervention to 50.9% (29/57) post-intervention (pooled). Among embryos sent for PGT, pooled euploid rates were 8.3% (1/12) pre-intervention vs 31.6% (6/19) post-intervention. Four of six patients conceived following the combined approach; all pregnancies were ongoing at last follow-up (mean maternal age 42.3 years). This included a 45-year-old with multiple prior failed cycles who developed multiple day-3 embryos post-intervention and achieved pregnancy after transfer of two day-3 embryos. No serious adverse events occurred. Rapamycin was well tolerated, and no PRP-related complications or cycle cancellations were reported.





Materials & Methods

This single-center retrospective case series compared pre- and post-intervention IVF cycles for six women aged 34–45 years, each with at least one prior failed IVF attempt and overall poor reproductive prognosis. Eligible cycles were identified through chart review, and each patient served as her own internal control to minimize inter-individual variability. Patients underwent ultrasound-guided transvaginal autologous ovarian platelet-rich plasma (PRP) injections (approximately 2–4 mL per ovary) prior to the post-intervention stimulation cycle. Rapamycin (5 mg orally once weekly) was administered as an adjunct throughout the post-intervention stimulation interval and discontinued after oocyte retrieval. Embryologic outcomes measured included total oocyte yield, number of 2PN embryos, blastocyst formation rate (blastocysts/2PN), and euploid rate (euploid embryos/biopsied blastocysts; mosaic embryos excluded). Clinical outcomes included biochemical pregnancy and clinical pregnancy confirmed by ultrasound. Treatment safety was assessed through chart review for adverse events. Descriptive statistics and per-patient mean values were calculated and compared between pre- and post-intervention cycles.

Discussion & Conclusion

In this retrospective observational case series of women with poor-prognosis IVF histories, the combination of intraovarian platelet-rich plasma (PRP) and adjunct low-dose weekly rapamycin was associated with improved embryologic outcomes and multiple clinical pregnancies following prior IVF failure. Post-intervention cycles demonstrated higher blastocyst formation rates and greater euploid yield on a per-patient basis compared with pre-intervention cycles, findings that were consistent in sensitivity analyses including cycles performed at outside centers. Notably, four of six patients achieved a clinical pregnancy following the combined approach, including one live birth, despite advanced maternal age and repeated prior IVF failure. These observed improvements are biologically plausible given the complementary mechanisms proposed for PRP and mTOR inhibition. Intraovarian PRP has been hypothesized to improve the ovarian microenvironment through delivery of growth factors, cytokines, and angiogenic mediators that may support follicular activation and early oocyte development, with small pilot studies reporting improvements in ovarian biomarkers, oocyte yield, and pregnancy outcomes in selected poor-responder populations [3,5,6]. Rapamycin, an mTOR pathway inhibitor, has demonstrated beneficial effects on oocyte quality in animal and in vitro models by reducing oxidative stress, enhancing DNA damage repair, and preserving mitochondrial function during oocyte maturation [4,7,8]. Although rapamycin use in this context remains experimental and the independent contribution of each intervention cannot be isolated in this small retrospective cohort, the concurrent improvement in embryologic competence following introduction of the combined strategy supports the hypothesis that regenerative ovarian therapies and metabolic modulation may act synergistically in selected poor-prognosis patients. These preliminary findings warrant confirmation in controlled studies powered to distinguish PRP versus mTOR effects, refine dose and timing strategies, identify best-responder profiles by age and ovarian reserve stratification, and evaluate live-birth outcomes. **Key Takeaway:** In this small retrospective cohort, combined intra-ovarian PRP and low-dose weekly rapamycin was associated with higher blastocyst formation, increased euploid yield, and multiple ongoing pregnancies.

References

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