

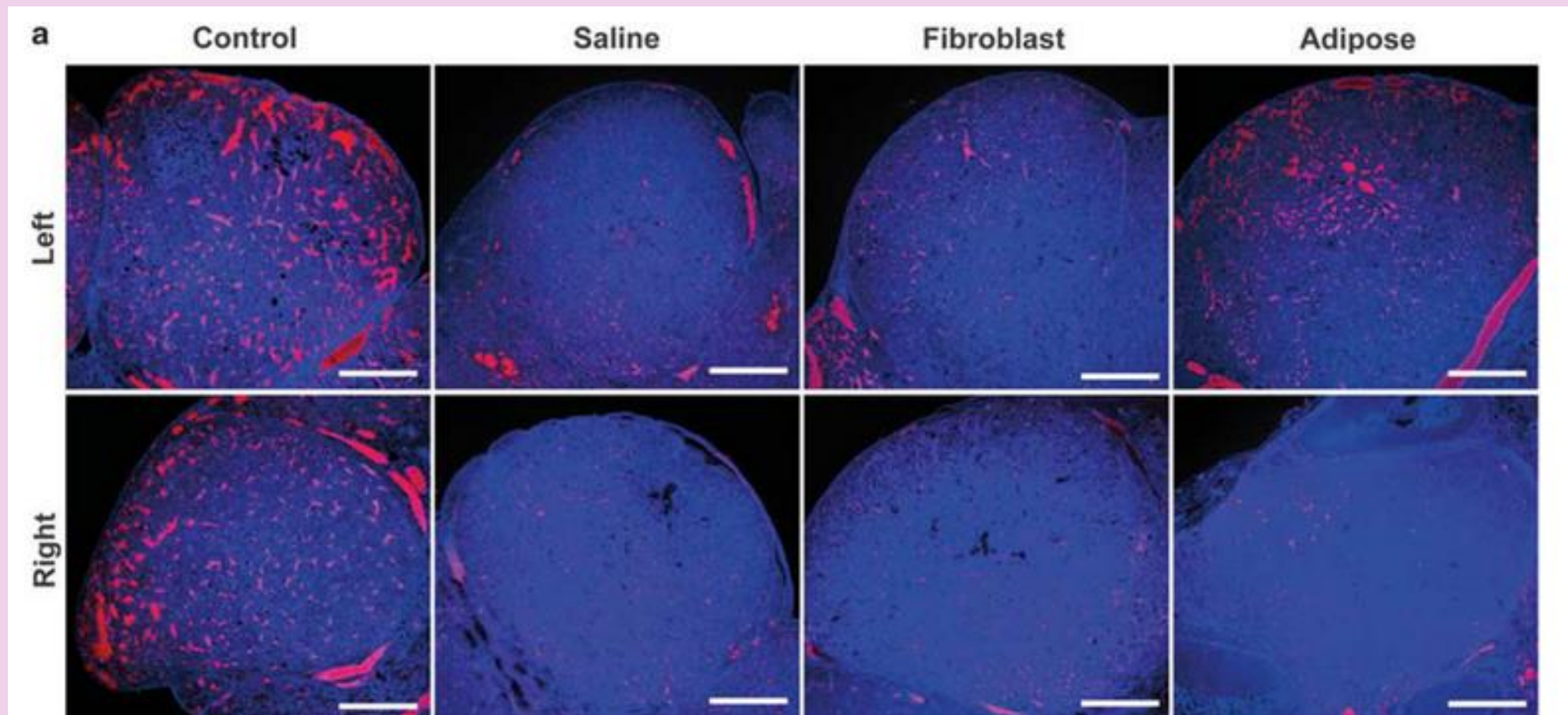
Novel approaches for treating female infertility caused by primary ovarian insufficiency: A role for Mesenchymal Stem Cells

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01. Introduction

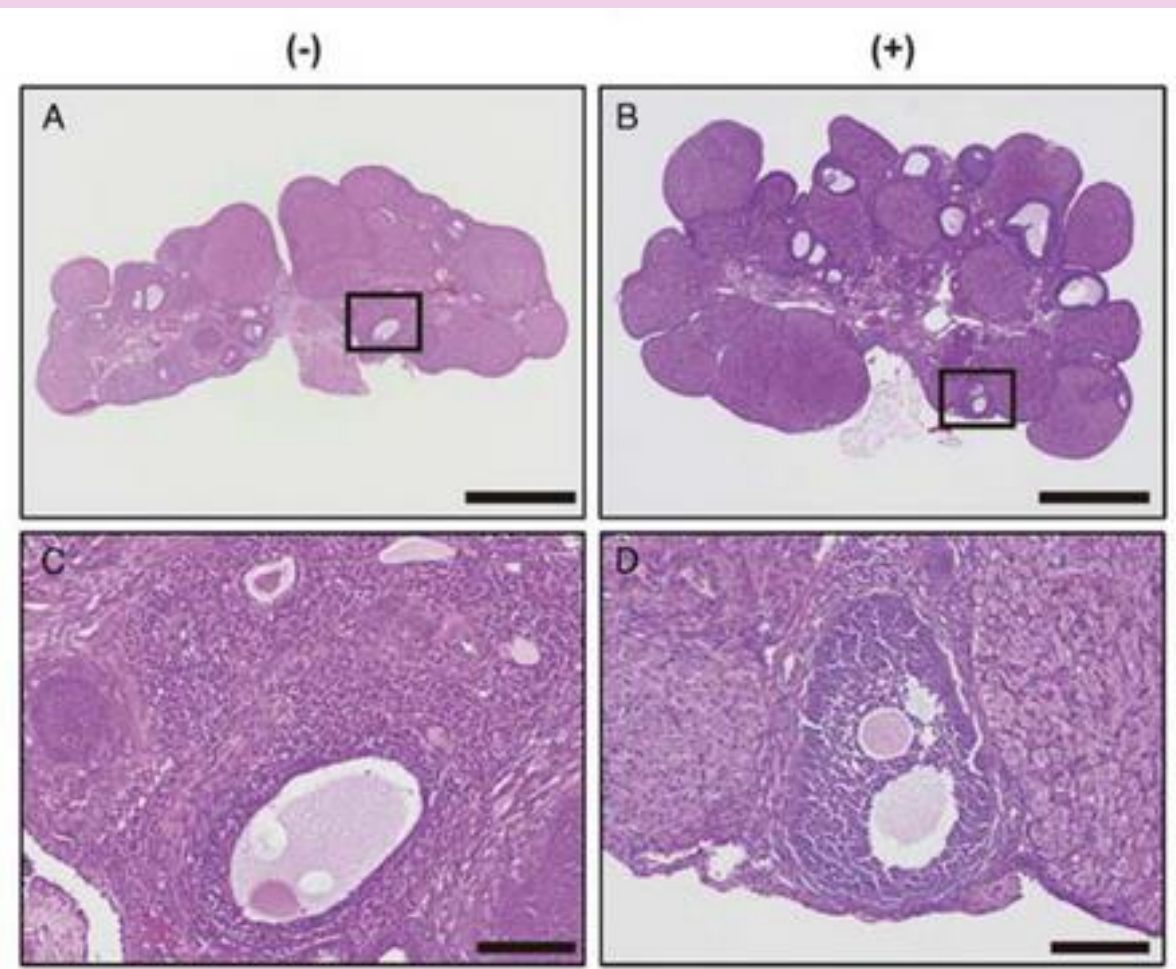
This systematic review aims to evaluate the therapeutic potential of mesenchymal stem cells (MSCs) in treating primary ovarian insufficiency (POI), a cause of 5-10% of female infertility cases worldwide. The primary hypothesis is that MSCs restore ovarian function through their secreted factors, which reduce oxidative stress, promote angiogenesis, and inhibit apoptosis. It also investigates whether MSC-based therapies, including cell-free approaches using MSC-conditioned media (MSC-CM), could provide a safer and more effective alternative to conventional treatments for POI.



Angiogenesis on cyclophosphamide-(CTX)-treated ovaries after adipose-derived mesenchymal stem cell (A-MSC) and tail fibroblast transplantation (Takehara et al., 2013)

02. Objective

This review aimed to synthesize findings from in vitro and in vivo studies to evaluate MSC-based treatments. In vitro studies assessed MSC effects on apoptosis and oxidative stress, while in vivo studies used chemotherapy-induced POI animal models to compare MSC transplantation with MSC-CM, focusing on improving ovarian follicle viability and function.



Analysis of ovaries after adipose derived stem cell transplantation, MSC-transplanted groups displayed an increase in ovarian follicle number (Takehara et al., 2013)

03. Methodology

Papers were selected using the PRISMA protocol, focusing on study size (>10 animals in preclinical studies and >100 participants in clinical trials) and study type (controlled experimental and cohort studies). Of 405 screened studies, 15 were included: 3 for meta-analysis and 12 for qualitative synthesis. Data was summarised by experimental model and geographical context and analysed statistically using ANOVA and t-tests (p < 0.05). A separate review identified MSC roles in oxidative stress reduction and angiogenesis.

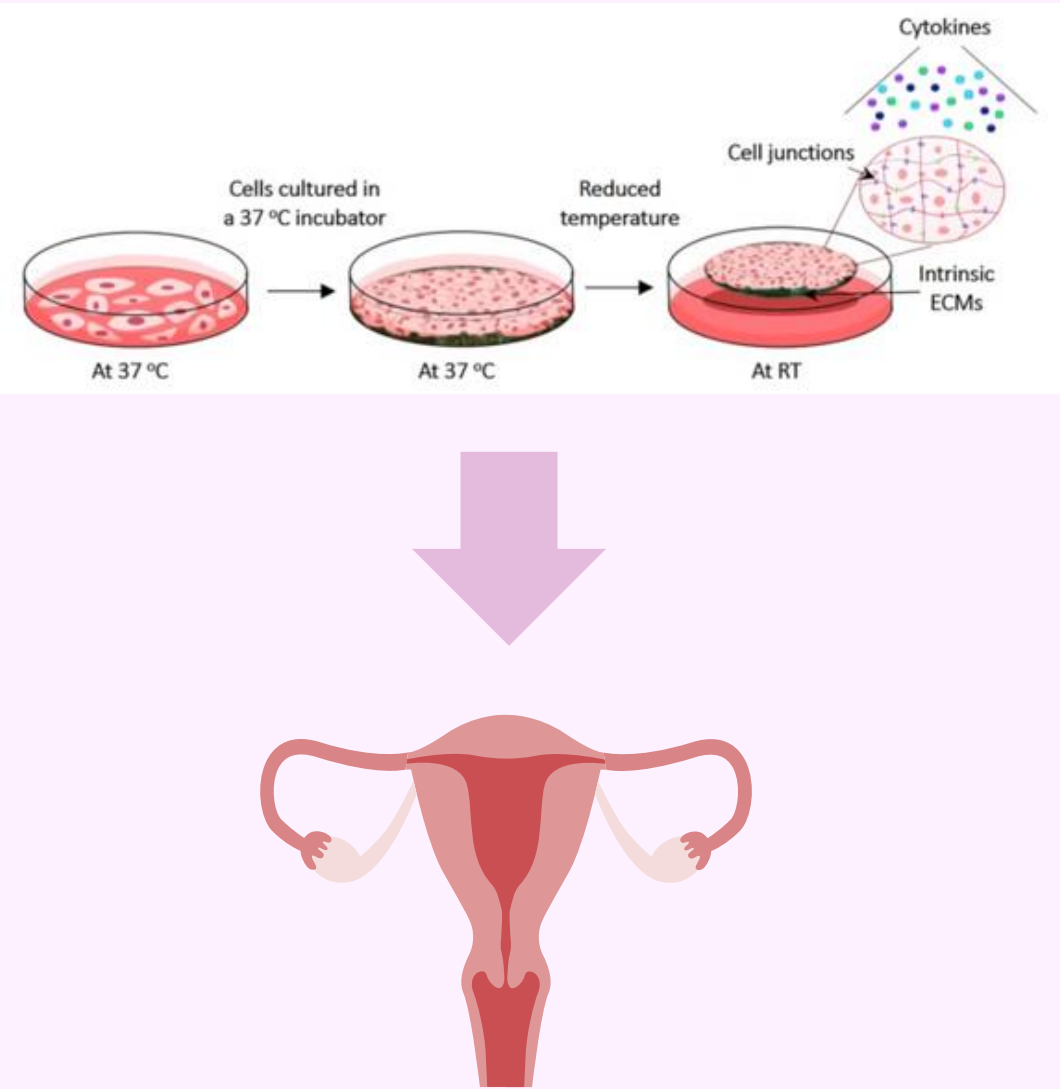
04. Results

In vitro studies showed that MSCs significantly improved follicle viability, with apoptosis reduced by 50% in treated groups compared to controls (p < 0.01). ROS levels decreased by 70%, and antioxidant enzyme activity increased by over 40% (p < 0.01). TGF-β family genes, critical for folliculogenesis, were upregulated by 150% (p<0.01). In vivo, chemotherapy-induced POI models treated with MSCs or MSC-CM exhibited a 2-3 times increase in follicle-stimulating hormone and oestradiol levels (p < 0.001). Ovulation rates improved, with intraovarian MSC transplantation restoring ovarian function in 85% of treated animals compared to 25% with intravenous delivery. Histological analyses revealed substantial regeneration of follicular structures.



05. Analysis

In vitro, MSCs and MSC-conditioned media (MSC-CM) significantly improved follicle viability, reduced apoptosis, and lowered oxidative stress markers. In vivo experiments showed hormonal recovery, reduced follicular atresia, and increased expression of regenerative cytokines (VEGF, IGF-1, IL-10). Notably, MSC-CM achieved comparable outcomes to live MSCs, supporting a paracrine mechanism of action. These findings suggest MSC-CM may offer a safe, cell-free therapeutic strategy for treating primary ovarian insufficiency.



Different methods of transplantation of the BMSC/CM may impact their restorative effect, previous studies have used IV injections which are less invasive, however site specific may be more beneficial for ovary restoration

06. Conclusion

MSCs demonstrate strong potential for restoring ovarian function through paracrine mechanisms, secreting VEGF, IGF-1, and HGF, which promote angiogenesis, reduce oxidative stress, and inhibit apoptosis. Intraovarian transplantation consistently outperformed intravenous delivery, showing superior efficacy in restoring hormonal balance and ovulation. Cell-free therapies using MSC-CM showed comparable benefits, presenting a safer and more scalable treatment alternative. These findings position MSCs as a transformative solution for ovarian dysfunction, offering a pathway to regenerating ovarian tissue and improving fertility outcomes. Future research should focus on optimizing MSC-CM formulations and validating these results in large-scale human trials.

07. References

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