Review / Derleme

DOI: 10.4274/tjod.galenos.2025.57485

Turk J Obstet Gynecol 2025;22(2):163-9

The role of secretome in restoring ovarian function: A systematic review and meta-analysis of *in vivo* studies in mice with premature ovarian insufficiency

Yumurtalık fonksiyonunun geri kazandırılmasında sekretomun rolü: Erken yumurtalık yetmezliği olan farelerde in vivo çalışmaların sistematik bir incelemesi ve meta-analizi

Stella Kawilarang[1], I Gede Eka Wiratnaya[2], I Wayan Putu Sutirta Yasa[3], I Nyoman Gede Budiana[4]

[1]*Udayana University Faculty of Medicine, Department of Biomedical Science, Bali, Indonesia*

[2]*Udayana University Faculty of Medicine, Department of Orthopedic and Traumatology, Bali, Indonesia*

[3]*Udayana University Faculty of Medicine, Department of Clinical Pathology, Bali, Indonesia*

[4]*Udayana University Faculty of Medicine, Department of Obstetrics and Gynecology, Bali, Indonesia*

Abstract

To evaluate the efficacy of secretomes in restoring ovarian function in premature ovarian insufficiency (POI) in a mouse model, researchers emphasizing their potential as a novel, cell-free therapy. This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines and included studies from four databases through December 2023. The bias risk was assessed using the tool for animal studies, which is Systematic Review Centre for Laboratory Animal Experimentation risk-of-bias. Outcomes, including the hormonal levels of estradiol (E2), anti-müllerian hormone (AMH), and follicle-stimulating hormone (FSH) were analyzed, with statistical comparisons made between the secretome-treated and control groups. Four studies encompassing sixty mice were included. The meta-analysis showed a significant increase in E2 levels in the secretome group [mean difference (MD)=37.45, 95% confidence interval (CI): 5.78 to 69.11; p=0.02]. No significant difference in AMH levels was observed; however, a sensitivity analysis resulted in the difference becoming statistically significant (MD=1.83, 95% CI: 0.95 to 2.71; p<0.0001). Moreover, the analysis revealed a significant reduction in FSH levels in the secretome group (MD=-36.80, 95% CI: -61.91 to -11.69; p=0.004) even after the sensitivity analysis. Our findings demonstrated enhanced outcomes with secretome therapy in the management of POI. Further research, particularly involving human subjects, is necessary to validate these findings.

Keywords: Hormones, ovarian function tests, premature ovarian failure, primary ovarian insufficiency, secretome

Öz

Bir fare modelinde prematüre yumurtalık yetmezliğinde (POI) sekretomların yumurtalık fonksiyonunu geri kazanmadaki etkinliğini değerlendirmek için araştırmacılar, yeni, hücresiz bir tedavi olarak potansiyellerini vurgulamaktadır. Bu sistematik inceleme ve meta-analiz, Sistematik İncelemeler ve Meta-Analizler için Tercih Edilen Raporlama Öğeleri 2020 yönergelerini izlemiş ve Aralık 2023'e kadar dört veri tabanından çalışmaları içermiştir. Yanlılık riski, Laboratuvar Hayvan Deneyleri için Sistematik İnceleme Merkezi yanlılık riski olan hayvan çalışmaları aracı kullanılarak değerlendirilmiştir. Östradiol (E2), anti-müllerian hormon (AMH) ve folikül uyarıcı hormon (FSH) hormonal seviyeleri de dahil olmak üzere sonuçlar, sekretomla tedavi edilen ve kontrol grupları arasında yapılan istatistiksel karşılaştırmalarla analiz edilmiştir. Altmış fareyi kapsayan dört çalışma dahil edilmiştir. Meta-analiz, sekretom grubunda E2 seviyelerinde önemli bir artış olduğunu göstermiştir [ortalama fark (OF) = 37,45, %95 güven aralığı (GA): 5,78 ila 69,11; p=0,02]. AMH düzeylerinde anlamlı bir fark gözlenmemiştir; ancak duyarlılık analizi sonucunda fark istatistiksel olarak anlamlı hale gelmiştir (OF=1,83, %95 GA: 0,95

Corresponding Author/Sorumlu Yazar: Stella Kawilarang MD,
Udayana University Faculty of Medicine, Department of Biomedical Science, Bali, Indonesia
E-mail: stel.kawilarang@gmail.com **ORCID ID:** orcid.org/0000-0001-9770-1193

Received/Geliş Tarihi: 05.02.2025 **Accepted/Kabul Tarihi:** 28.03.2025 **Epub:** 10.04.2025 **Publication Date/Yayınlanma Tarihi:** 04.06.2025

Cite this article as: Kawilarang S, Wiratnaya IGE, Yasa IWPS, Budiana ING. The role of secretome in restoring ovarian function: a systematic review and meta-analysis of *in vivo* studies in mice with premature ovarian insufficiency. Turk J Obstet Gynecol. 2025;22(2):163-9

ila 2,71; p<0,0001). Ayrıca, analiz, duyarlılık analizinden sonra bile sekretom grubunda FSH seviyelerinde önemli bir düşüş olduğunu ortaya koymuştur (MD=-36,80, %95 CI: -61,91 ila -11,69; p=0,004). Bulgularımız, POI tedavisinde sekretom tedavisi ile daha iyi sonuçlar elde edildiğini göstermiştir. Bu bulguları doğrulamak için özellikle insan denekleri içeren daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Hormonlar, yumurtalık fonksiyon testleri, prematüre yumurtalık yetmezliği, primer yumurtalık yetmezliği, sekretom

Introduction

Premature ovarian insufficiency (POI), also referred to as premature ovarian failure (POF), occurs when ovarian function stops before the age of 40, and is widely known as early menopause. This condition is a primary factor of female infertility under 40, impacting an estimated 3.7% of women[1]. The prevalence of POI varies among different ethnic groups, and approximately 15% of cases are associated with a family history, indicating a potential genetic basis for the disorder[2].

The current typical therapeutic approach for POI involves taking continuous hormone replacement therapy (HRT) to alleviate estrogen deficiency symptoms and reduce the risks of osteoporosis and cardiovascular disease. This treatment is generally recommended until the age of natural menopause. However, HRT works only by mimicking the effect of hormones, which does not restore ovarian function or fertility[3]. Recently, the secretome, which consists of proteins including extracellular matrix proteins, proteins shed from the cell membrane, and vesicle proteins, has emerged as a promising treatment for POI. It shows therapeutic effects such as promoting the formation of new blood vessels, known as angiogenesis, reducing inflammation, and evading immune responses, potentially improving the restoration of ovarian function and fertility[4].

Due to the comparable features of the estrous cycle in mice and the human menstrual cycle, mouse models serve as crucial tools for investigating POI pathogenesis and advancing therapeutic strategies[5]. Previous meta-analyses, such as those conducted by Hu et al.[5] and Kim et al.[6], have also utilized POI mouse models, highlighting the effectiveness of stem cell therapy in restoring fertility in POI models and patients, while a meta-analysis by Luo et al.[6-8] showed that stem cell-derived extracellular vesicles (EVs) are safe and effective in treating animal models of POI, with promising potential to enhance fertility outcomes.

Stem cells, EVs, and secretomes are distinct regenerative approaches with unique characteristics. Stem cells rely on cellular transplantation, while EVs act as carriers of cellular signals. On the other hand, secretomes consist of bioactive molecules such as growth factors and cytokines; they offer a broader, cell-free therapeutic option with reduced risks of immune rejection and are not limited to vesicular structures only[9]. While meta-analyses have explored stem cells and EVs, the role of secretomes in treating POI has yet to be systematically analyzed. This systematic review presents the first meta-analysis of *in vivo* studies regarding the efficacy of secretomes in restoring ovarian function in mice with POI, highlighting their therapeutic potential.

Materials and Methods

Literature Searching

This meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines[8]. The meta-analysis was based on published articles and therefore did not require ethical approval. This research was conducted across four databases (Science Direct, Sage Journals, PubMed, and ProQuest) through December 2024. The search strategy used essential keywords and Medical Subject Headings (MeSH) terms such as “secretome”, “premature ovarian insufficiency”, “primary ovarian insufficiency”, and “premature ovarian failure”. Boolean operators (AND/OR) were utilized to refine search results.

Study Selection

Animal studies focusing on the use of secretome in POI mouse models were included. Studies were excluded if they did not involve POI mouse models or failed to assess hormonal levels, including estradiol (E2), anti-müllerian hormone (AMH), or follicle-stimulating hormone (FSH), as outcomes. All records were imported into EndNote X9, where duplicates were removed using the software’s identification tool. Titles, abstracts, and full-text articles were reviewed by two reviewers independently, with any disagreements resolved through consultation with an additional author.

Data Extraction

Three investigators were involved in the data extraction, which was performed independently. Any difference was resolved by consensus or by consulting an additional author. Extracted data included study characteristics (authors, publication year, mice model experiment, and stem cell-derived secretome). Hormonal levels (E2, AMH, and FSH) were evaluated for each study, with numerical data extracted from graphs using WebPlotDigitizer, followed by statistical analysis to evaluate the outcomes. The results include a grouped analysis of E2, AMH, and FSH levels comparing the untreated or control group and the secretome-treated group.

Risk of Bias Analysis

The risk of bias was independently assessed by two investigators using the Systematic Review Centre for Laboratory Animal Experimentation risk-of-bias tool for animal studies[9]. This evaluation addressed ten key domains: (1) generation of sequence, (2) characteristics of baseline, (3) concealment of allocation, (4) random housing, (5) blind caregivers and investigators, (6) random outcome assessment, (7) outcome

assessment blinded to assessors, (8) incomplete data outcome, (9) selective outcome reporting, and (10) other bias sources. Each domain was categorized as "Yes" if low risk of bias, "No" if high risk of bias, or "Unclear" if the study text provided insufficient information to make a definitive judgment. Any discrepancies were discussed and resolved through consultation with an additional reviewer.

Statistical Analysis

E2, AMH, and FSH levels were compared between the secretome-treated group and the control group for analysis. Heterogeneity was evaluated using the I^2 statistic, with a p-value <0.05 considered indicative of substantial heterogeneity. Sensitivity analyses, excluding studies with potential bias, were conducted when significant heterogeneity was detected. All statistical analyses were performed using Cochrane Review Manager software version 5.4.

Results

Two hundred forty-seven articles were gathered from the literature search, and 4 met the eligibility criteria to be analyzed, as depicted in Figure 1. Between 2021 and 2024, those studies involving a total of 60 mice were published.

All studies were assessed to have a low risk of bias in sequence generation, attrition bias, reporting bias, and other sources of bias. However, all studies showed an unclear risk of bias regarding allocation concealment, performance bias, and detection bias related to blinding. For baseline characteristics, two studies [Park et al.[10] and Le et al.[13]] had a low risk of bias, while the other two [Zhang et al.[11] and Nabil Salama et al.[12]] had an unclear risk. Regarding random outcome assessment, two studies [Park et al.[10] and Le et al.[13]] demonstrated a low risk of bias, whereas the remaining two [Nabil Salama et al.[12] and Le et al.[13]] were categorized as indeterminate risk (Table 1).

The meta-analysis showed an increase in E2 levels in the secretome group, which is significant when compared to the control group, [mean difference (MD) = 37.45, 95% confidence interval (CI): 5.78 to 69.11; p=0.02], with considerable heterogeneity (I^2=98%) (Figure 2). Excluding two studies in the sensitivity analysis strengthened the reliability of the findings (Figure 3). After exclusion, E2 levels remained significantly higher in the secretome group than the control group (MD=34.45, 95% CI: 26.95 to 41.95; p<0.0001), with a marked reduction in heterogeneity (I^2=29%). This analysis affirms that the link between secretome intervention and elevated E2 levels remains statistically significant, even after accounting for potential biases, thereby further supporting the consistency and robustness of the results across studies.

The pooled analysis of the included studies revealed no significant MD in AMH levels between the secretome group and the control group (MD=3.71, 95% CI: -0.55 to 7.97; p=0.09), with a high degree of heterogeneity observed (I^2=98%) (Figure 4). However, the sensitivity analysis, which excluded one study, demonstrated a substantial reduction in heterogeneity to 0%. Furthermore, after excluding this study, the difference between the groups became significant based on the statistics, with an MD of 1.83 (95% CI: 0.95 to 2.71; p<0.0001) (Figure 5).

The pooled analysis of all included studies showed that FSH levels in the secretome group reduce in significant amount if compared with the control group (MD=-36.80, 95% CI: -61.91 to -11.69; p=0.004) (Figure 6). The sensitivity analysis, which excluded one study, confirms the robustness of the findings (Figure 7). FSH levels were significantly reduced in the secretome group compared to the control group (MD=-25.58, 95% CI: -38.35 to -12.81; p<0.0001), with a decrease in heterogeneity (I^2=62%). This analysis indicates that the association between secretome intervention and reduced FSH levels remains statistically significant, even after accounting for potential bias, thereby reinforcing the strength and consistency of the findings across studies.

Discussion

This meta-analysis evaluates the potential of secretome therapy in restoring ovarian function by assessing its impact on E2, AMH, and FSH levels as the main parameters of female hormones regarding fertility. The results demonstrate that the secretome group exhibited significantly increased E2 and AMH levels and decreased FSH levels compared to the control group, as supported by sensitivity analyses. For E2, the sensitivity

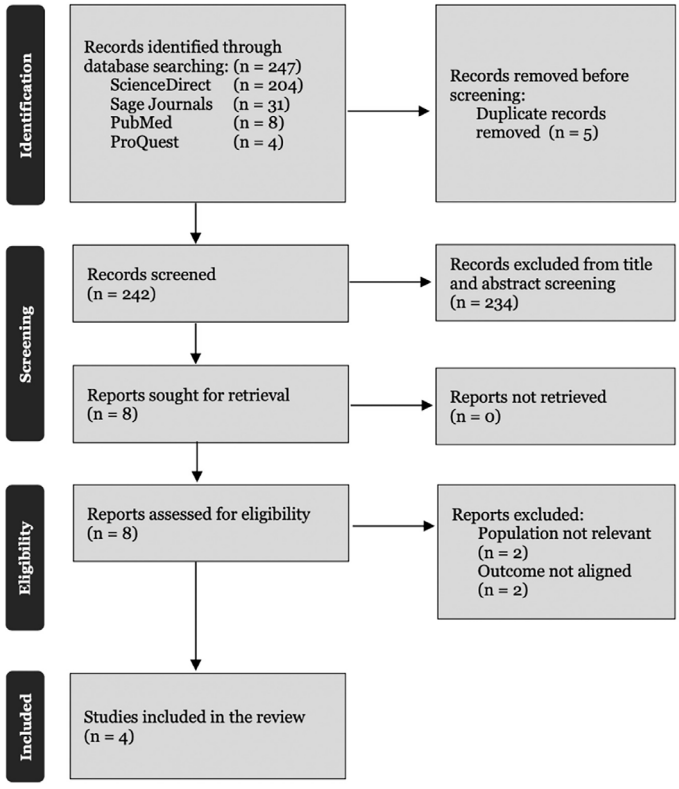

Figure 1. PRISMA flow diagram depicting study selection

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 1. Risk of bias assessment using SYRCLE risk of bias tool for animal studies

Study	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Other bias
	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete outcome data	Selective outcome data	Other sources bias
Park et al. 2021[10]	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes
Zhang et al. 2021[11]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes
Salama et al. 2023[12]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Le et al. 2024[13]	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes

SYRCLE: Systematic Review Centre for Laboratory Animal Experimentation

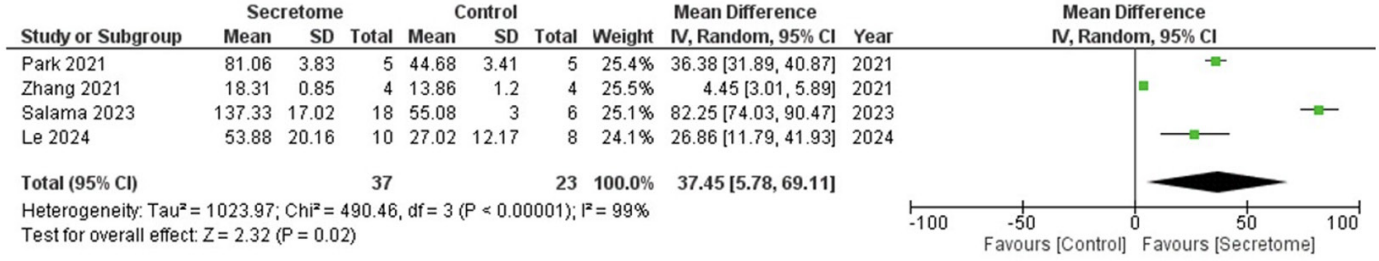

Figure 2. Forest plot: Pooled analysis of E2 levels between the secretome group and the control group

E2: Estradiol, SD: Standard deviation, CI: Confidence interval, IV: Interval variable

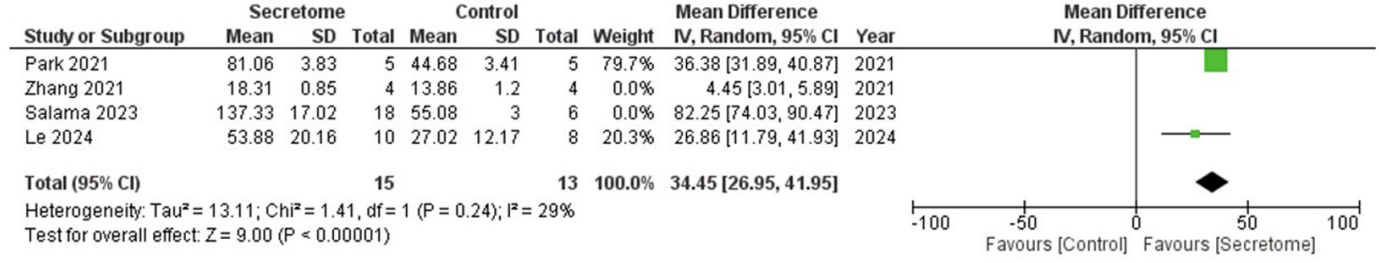

Figure 3. Forest plot: Sensitivity analysis of E2 levels between the secretome group and control group

E2: Estradiol, SD: Standard deviation, CI: Confidence interval, IV: Interval variable

analysis excluded the study by Zhang et al.[11] due to notable variations in baseline E2 levels among the mice. Additionally, sensitivity analyses for E2, AMH, and FSH excluded the study by Nabil Salama et al.[12] as it involved distinct baseline characteristics, particularly a substantial age discrepancy among the mice, as shown in Table 2.

E2 is a steroid hormone that is related to the ovarian follicle development and egg maturity. Elevated E2 levels in larger follicles play a crucial role in the selection of a dominant follicle and the induction of the LH surge required for ovulation. However, POI is associated with disrupted folliculogenesis, such as diminished follicular recruitment and dysfunction and premature follicular atresia. As a result, E2 serves as a critical marker of follicle quality in folliculogenesis and holds a potential role for restoring ovarian function in patients with POI[14]. Our study showed the E2 levels in the secretome group increased by a significant amount compared to the control. The results of this analysis further validate the consistency and robustness of the link between secretome intervention and elevated E2 levels, demonstrating that the relationship holds across multiple

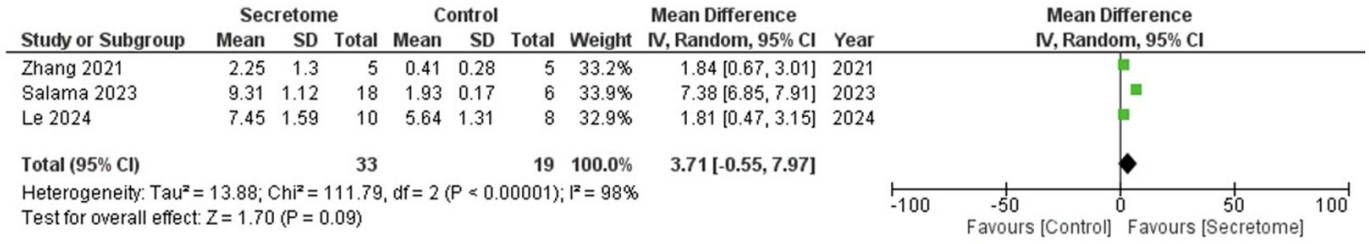

Figure 4. Forest plot: Pooled analysis of AMH levels between the secretome group and the control group

AMH: Anti-müllerian hormone, SD: Standard deviation, CI: Confidence interval, IV: Interval variable

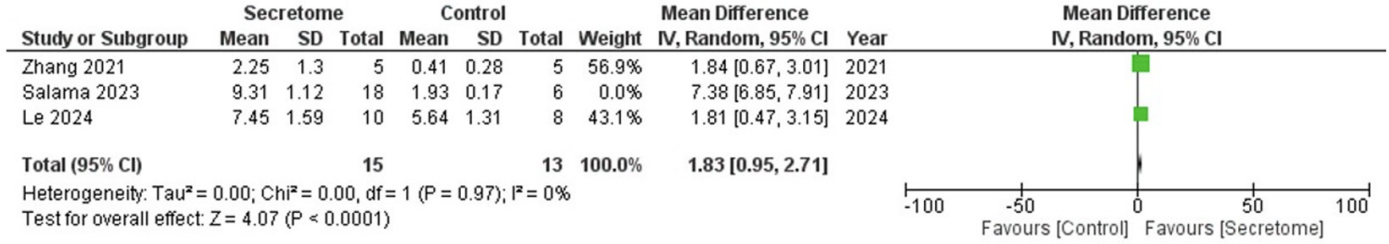

Figure 5. Forest plot: Sensitivity analysis of AMH levels between the secretome group and control group

AMH: Anti-müllerian hormone, SD: Standard deviation, CI: Confidence interval, IV: Interval variable

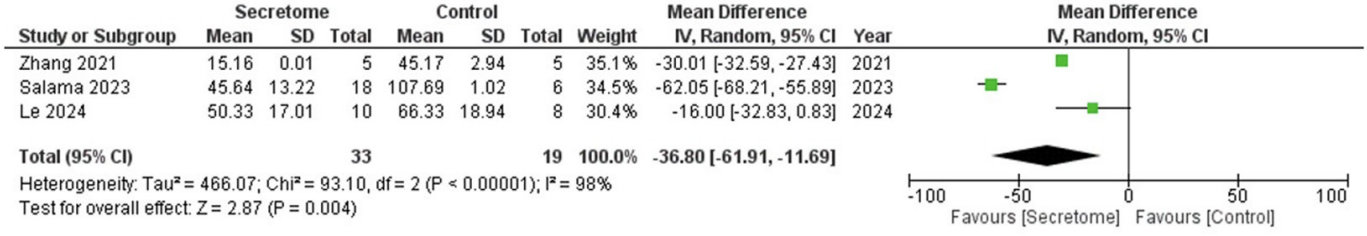

Figure 6. Forest plot: Pooled analysis of FSH levels between the secretome group and the control group

FSH: Follicle-stimulating hormone, SD: Standard deviation, CI: Confidence interval, IV: Interval variable

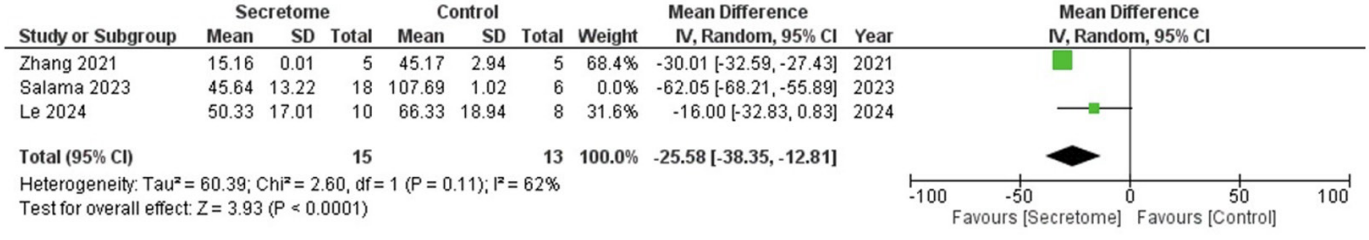

Figure 7. Forest plot: Sensitivity analysis of FSH levels between the secretome group and control group

FSH: Follicle-stimulating hormone, SD: Standard deviation, CI: Confidence interval, IV: Interval variable

studies. This strengthens the evidence for the reliability of the secretome effect in developing targeted therapeutic strategies in POI patients.

In this study, we observed a significant increase in AMH levels in the secretome-treated group compared to the control group, suggesting that secretomes may exert a protective effect on ovarian reserve. Granulosa cells of the growing follicles secrete AMH, which is a glycoprotein and has been shown an important role in maintaining ovarian reserve in both murine models and humans[11,15]. As a member of the transforming growth factor-β superfamily, AMH serves as a pivotal growth factor in the ovary by inhibiting primordial follicles recruitment and modulating

Table 2. Characteristic of included studies

Study	Mice model experiment				Stem cell-derived secretome
	Model	Type	Age	Drugs used	
Park et al. 2021[10]	Chemotherapy-induced POI mice model	Female C57BL/6 mice	6 weeks old	Busulfan, Cyclophosphamide	Human BM-MSC secretome
Zhang et al. 2021[11]	Chemotherapy-induced POI mice model	Female Sprague-Dawley rats	5-7 weeks old	Cisplatin	ORP secretome by embedding HUC-MSC
Salama et al. 2023[12]	Chemotherapy-induced POI mice model	Female C57BL/6 mice	2-3 months old	Cisplatin	Human BM-MSC secretome
Le et al. 2024[13]	Chemotherapy-induced POI mice model	Female C57BL/6J mice	7 weeks old	Cyclophosphamide	Human placenta choriodecidual membrane tissues ER+pc MSC secretome

BM: Bone marrow, ER+pc: Estrogen receptor positive, HUC: Human umbilical cord, MSC: Mesenchymal stem cell, ORP: Ovarian regenerative patch, POI: Premature ovarian insufficiency

follicular sensitivity to FSH during folliculogenesis[16] and diminishing the chemotherapy-induced ovarian dysfunction, thereby reducing the risk of POI[17]. These findings highlight the importance of secretomes, as one of the therapeutic strategies promising for the management of POI.

Our study also revealed a decrease in FSH levels in the group that was treated with secretome compared to the control group. This reduction is likely due to the effect of secretomy by promoting angiogenesis, facilitating tissue repair, and supporting follicular survival in damaged ovaries. By alleviating chronic inflammation that causes disruption to ovarian function and disrupts hormonal feedback mechanisms, the secretome has the benefit of restoring hormonal homeostasis. The vascular endothelial growth factor and insulin-like growth factor are the growth factors present in the secretome that stimulate follicular development, while their anti-apoptotic properties protect ovarian follicles. Collectively, these mechanisms enhance ovarian function, re-establishing effective negative feedback to the pituitary gland and subsequently reducing FSH production[18-20]. Based on all the parameters evaluated in this meta-analysis, it is shown that secretome has a positive impact on the management of POF, especially regarding the fertility issue, and can become one of the options rather than HRT.

Study Limitations

This systematic review and meta-analysis has several limitations. The small sample sizes in the included studies are not optimal for the generalizability of our findings. Moreover, variations in baseline characteristics and the different types of stem cell-derived secretome used may affect the results. Future studies with larger sample sizes and methods that are further standardized are needed to strengthen the evidence and enable updates to this meta-analysis.

Conclusion

Our study found that secretome therapy significantly improved outcomes in the management of POI. Specifically, the therapy resulted in increased E2 and AMH levels and decreased the level of FSH. These hormonal changes are indicative of restored ovarian function, suggesting that secretome therapy may help address the hormonal imbalance characteristic of POI. Additionally, our findings demonstrate improvements in other symptoms associated with POI, further supporting the potential of secretome therapy as a promising treatment. However, while these results are encouraging, further studies, particularly those involving human subjects, are essential to fully evaluate the efficacy and safety of secretome therapy in this context. Large-scale, well-designed clinical investigations are needed to evaluate these findings, especially the long-term outcomes, and establish clear guidelines for their clinical application.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., I.G.E.W., I.N.G.B., Concept: S.K., I.G.E.W., I.W.P.S.Y., Design: S.K., I.G.E.W., Data Collection or Processing: S.K., I.G.E.W., I.N.G.B., Analysis or Interpretation: S.K., I.G.E.W., I.W.P.S.Y., Literature Search: S.K., I.G.E.W., I.N.G.B., Writing: S.K., I.W.P.S.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Kapoor E. Premature ovarian insufficiency. Curr Opin Endocrinol Metab Res. 2023;28:100435.
2. Rudnicka E, Kruszewska J, Klicka K, Kowalczyk J, Grymowicz M, Skórska J, et al. Premature ovarian insufficiency – aetiopathology, epidemiology, and diagnostic evaluation. Menopausal Rev. 2018;17:105-8.
3. American College of Obstetricians and Gynecologists. Hormone therapy in primary ovarian insufficiency. ACOG Committee Opinion No. 711. Published May 2017.
4. Park HS, Ashour D, Elsharoud A, Chugh RM, Ismail N, Andaloussi AE, et al. Towards cell free therapy of premature ovarian insufficiency: human bone marrow mesenchymal stem cells secretome enhances

angiogenesis in human ovarian microvascular endothelial cells. HSOA J Stem Cells Res Dev Ther. 2019;5:019.

5. Hu L, Tan R, He Y, Wang H, Pu D, Wu J. Stem cell therapy for premature ovarian insufficiency: a systematic review and meta-analysis of animal and clinical studies. Arch Gynecol Obstet. 2024;309:457-67.
6. Kim HJ, Kim G, Lee J, Lee Y, Kim JH. Secretome of stem cells: roles of extracellular vesicles in diseases, stemness, differentiation, and reprogramming. Tissue Eng Regen Med. 2022;19:19-33.
7. Luo Y, Chen J, Ning J, Sun Y, Chai Y, Xia F, et al. Stem cell-derived extracellular vesicles in premature ovarian failure: an up-to-date meta-analysis of animal studies. J Ovarian Res. 2024;17:182.
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;29:372.
9. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2024;14:43.
10. Park HS, Chugh RM, El Andaloussi A, Hobeika E, Esfandyari S, Elsharoud A, et al. Human BM-MSC secretome enhances human granulosa cell proliferation and steroidogenesis and restores ovarian function in primary ovarian insufficiency mouse model. Sci Rep. 2021;11:4525.
11. Zhang S, Zhu D, Li Z, Huang K, Hu S, Lutz H, et al. A stem cell-derived ovarian regenerative patch restores ovarian function and rescues fertility in rats with primary ovarian insufficiency. Theranostics. 2021;11:8894-908.
12. Nabil Salama A, Badr EAE, Holah NS, El Barbary AA, Hessien M. Conservative hypomethylation of mesenchymal stem cells and their secretome restored the follicular development in cisplatin-induced premature ovarian failure mice. Reprod Sci. 2024;31:1053-68.
13. Le DC, Ngo MT, Kuo YC, Chen SH, Lin CY, Ling TY, et al. Secretome from estrogen-responding human placenta-derived mesenchymal stem cells rescues ovarian function and circadian rhythm in mice with cyclophosphamide-induced primary ovarian insufficiency. J Biomed Sci. 2024;31:95.
14. Chauvin S, Cohen-Tannoudji J, Guigon CJ. Estradiol signaling at the heart of folliculogenesis: its potential deregulation in human ovarian pathologies. Int J Mol Sci. 2022;23:512.
15. Shin EY, Kim DS, Lee MJ, Lee AR, Shim SH, Baek SW, et al. Prevention of chemotherapy-induced premature ovarian insufficiency in mice by scaffold-based local delivery of human embryonic stem cell-derived mesenchymal progenitor cells. Stem Cell Res Ther. 2021;12:431.
16. Man L, Lustgarten Guahmich N, Vyas N, Tsai S, Arazi L, Lilienthal D, et al. Ovarian reserve disorders, can we prevent them? A review. Int J Mol Sci. 2022;23:15426.
17. Li X, Liu S, Chen X, Huang R, Ma Lisi, Weng H, et al. GnRHa protects the ovarian reserve by reducing endoplasmic reticulum stress during cyclophosphamide-based chemotherapy. NPJ Breast Cancer. 2021;7:132.
18. Chatzianagnosti S, Dermitzakis I, Theotokis P, Kousta E, Mastorakos G, Manthou ME. Application of mesenchymal stem cells in female infertility treatment: protocols and preliminary results. Life. 2024;14:1161.
19. Prayitno GD, Lestari K, Sartika CR, Djuwantono T, Widjaya A, Muharam R, et al. Potential of mesenchymal stem cells and their secretomes in decreasing inflammation markers in polycystic ovary syndrome treatment: a systematic review. Medicines. 2022;10:3.
20. Luis-Calero M, Ortiz-Rodríguez JM, Fernández-Hernández P, Muñoz-García CC, Pericuesta E, Gutiérrez-Adán A, et al. Influence of secretome obtained from preovulatory follicular fluid on energy metabolism and meiotic competence of equine cumulus–oocyte complexes. J Equine Vet Sci. 2023;125:104670.