Regenerative Therapy 26 (2024) 478–488

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Meta-analysis highlight the therapeutic potential of stem cells for premature ovarian failure

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ARTICLE INFO

Article history:
Received 17 April 2024
Received in revised form
27 June 2024
Accepted 8 July 2024

Keywords:
Stem cell
Premature ovarian failure
Cell transplantation
Ovarian function
Regenerative medicine

ABSTRACT

Stem cell (SC) transplantation has shown potential as a therapeutic approach for premature ovarian failure (POF). Despite this, no quantitative analysis has been conducted on the efficacy of SC therapy for POF in humans. To address this gap, the present study conducted a meta-analysis to evaluate the effectiveness of the transplantation of SC in improving ovarian function among POF patients. A systematic review in this regard by searching PubMed, ScienceDirect, clinicalTrial.gov, and Cochrane's library databases was conducted to identify relevant studies, while associated reviews were also considered. The extracted data included parameters such as estradiol (E2), follicle-stimulating hormone (FSH), follicle count (FC), ovarian weight (OW), number of pregnancies, and live birth. As per the combined effect taking the last follow-up time, the level of FSH and AMH for the SC group was lower than these were at the baseline as (SMD: 1.58, 95% CI: 0.76 to 3.92, P-value: 0.185 > 0.05, I^2: 94.03%) and (SMD: 1.34, 95% CI: 0.77 to 1.92, P-value: 0.001 < 0.05, I^2: 0%) respectively. While the means of E2 and OW for the SC group was higher than these were at the baseline as (SMD: −0.47, 95% CI: −0.73 to −0.21, P-value: 0.001 < 0.01, I^2: 38.23%) and (SMD: −1.18, 95% CI: −2.62 to 0.26, P-value: 0.108 > 0.05, I^2: 76.68%) respectively. The overall effect size measured with proportion of pregnancy and live birth at a 5% level of significance expected SC transplantation results were as (combined proportion: 0.09, 95% CI: 0.03 to 0.15, P-value: 0.002 < 0.05, I^2: 46.29%) and (SMD: 0.09, 95% CI: 0.03 to 0.15, P-value: 0.003 < 0.05, I^2: 1.76%) respectively. Based on the fixed-effects model, the estimated average log odds ratio of Follicles count was 1.0234 (95% CI: 0.1252 to 1.9216). Therefore, the average outcome differed significantly from zero (P-value: 0.0255 < 0.05) due to SC transplantation. These results suggest that using SCs to restore ovarian function may be viable for treating POF. However, larger and better-quality investigations would need to be conducted in the future due to the heterogeneity of the examined studies.

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Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2024.07.001

1. Introduction

Premature ovarian insufficiency (POI), also referred to as premature ovarian failure (POF), is a condition characterized by hypergonadotropic hypogonadism, resulting in amenorrhea, infertility, estrogen deficiency, diminished follicles, and elevated gonadotropin levels affecting one in 100 women under 40 years [1,2]. POF can pose additional health risks to affected women, including depression, anxiety, poor marital quality and diminished sexual function, osteoporosis, cardiovascular disease, and neurodegenerative disorders [3,4]. Premature ovarian insufficiency (POI), or premature ovarian failure (POF), is diagnosed in women under the age of 40 based on increased follicle-stimulating hormone (FSH) and decreased levels of estradiol seen in two tests that were at least one month apart and amenorrhea that lasted for four to six months [5]. Although various factors such as genetics, autoimmune conditions, infections, prior chemoradiation therapies, and more have been implicated in developing POI, the precise cause remains largely unknown in many cases [6,7]. Numerous treatments have been proposed to address the complexities of POF; however, none have proven consistently effective as a first-line therapy. Available treatment options for POF encompass hormone replacement therapy (HRT), counseling, synthesized bioidentical hormones, androgen supplementation, Dehydroepiandrosterone (DHEA), oocyte donation, dietary interventions, exercise, and stem cell therapy. The most frequently recommended therapy for POF is HRT [8]. However, its role in improving fertility remains a subject of debate. Considering the potential risks associated with HRT, alternative therapies should be considered to alleviate symptoms and reduce risks in POF patients, particularly in those with a history of breast or ovarian cancer, as HRT has been associated with increased risks of blood clots, strokes, cancer, and other complications [9–11].

Applying stem cell therapy in POF patients holds potential benefits, particularly regarding potential ovum production in females. Stem cells are a type of cells that are present at various stages of fetal, embryo, and adult development. These cells are characterized by their lack of specialization and differentiation. Different areas of the human body contain stem cells, categorized according to their origin, such as adipose and skin tissue, amniotic fluid, umbilical cord, placenta, and bone marrow [12]. Recent studies have documented the utilization of various types of stem cells, including embryonic stem cells (ESCs), spermatogonial stem cells (SSCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs), have been utilized in stem cell-based therapies aimed at treating infertility [9,13,14]. Due to its potential to permanently restore damaged oocytes, the stem cell (SC) treatment for infertility hypothesis has attracted much interest. Evidence from a mouse model of chemotherapy-induced POF demonstrates that transplanted stem cells can engraft within ovarian tissue and reinstate ovarian function [15–17]. Transplanted stem cells (SCs) can potentially restore ovarian function through paracrine signaling mechanisms or differentiation into oocytes and granulosa cells [18]. However, it is important to note that most research on stem cell transplantation for POF treatment has focused on preclinical animal studies. Therefore, the validation of safety and efficacy through systematic clinical trials with a sufficiently large sample size is currently lacking. As a result, there is limited reporting on clinical investigations [2,14–16,18–22]. This study seeks to close this gap by conducting a systematic review and meta-analysis to examine the utilization of stem cell therapy in POF patients. The objective is to provide additional evidence supporting the potential of stem cell therapy as a viable clinical treatment for POF.

2. Materials and methods

2.1. Literature search

A thorough systematic search was conducted to locate relevant studies on the therapy of stem cells for premature ovarian failure (POF) in human subjects. Electronic databases, including PubMed, ScienceDirect, ClinicalTrials.gov, and the Cochrane Library, were systematically searched until June 2023. Specific keywords such as "stem cell", "premature ovarian failure", and "premature ovarian insufficiency" were utilized to filter the search results. The search was limited to studies published in the English language. Furthermore, the reference lists of eligible and previous review articles were manually examined to identify additional pertinent studies.

2.2. Inclusion/exclusion criteria

To be included in the analysis, studies had to meet the following criteria: a) Full-text articles published in English; b) Case-control studies; c) Clinical studies investigating the use of stem cells as a treatment for premature ovarian failure (POF) or premature ovarian insufficiency (POI); d) Studies with multiple follow-up assessments conducted within a timeframe of 3–12 months; and e) Studies reporting at least one of the following outcomes: follicle count, estradiol (E2), number of pregnancies and live births, follicle-stimulating hormone (FSH), Anti-Mullerian hormone (AMH) and ovarian weight. Studies were excluded from consideration based on the following criteria: a) Reviews, non-human studies, editorials, letters, and conference papers lacking sufficient data; b) studies with insufficient sample sizes or data reporting; c) Duplicate studies already included in the analysis; d) Non-English literature; e) Studies involving the use of stem cell factors rather than stem cell therapy itself; f) Studies that did not report any of the desired

outcomes; and g) Clinical research focused on premature ovarian failure (POF) patients with co-existing illnesses.

2.3. Data extraction

Two authors (UH and SS) independently extracted relevant information from each included study. The extracted information included the first author's name, year of publication, country of origin, study design, type and source of stem cells, characteristics of the premature ovarian failure (POF) patients, method of stem cell delivery, intervention techniques, the number of SCs and timing of transplantation, duration of follow-up, and key outcome measures. In cases where articles exclusively presented data through images, mean and standard deviation (SD) values were derived from the images.

3. Results

The study selection process is illustrated in Fig. 1, which provides a flow diagram depicting the results from the searches and the characteristics of the included studies. Initially, a total of 900 studies were identified through database searches. After evaluating the titles and abstracts, 1488 papers were excluded as they were either duplicate reports or irrelevant to the study's objective. A more detailed assessment was conducted on the remaining 12 publications. Among these, five articles were case studies of premature ovarian failure (POF), one did not present the necessary results, and one did not provide specific information on patient outcomes. Finally, the meta-analysis consisted of five studies, the details of which are presented in Fig. 1 [2,19–22]. The included studies in the meta-analysis were conducted in various countries, with one study from Spain [11], two from China [2,12], one from Serbia [13], and one from Iran [14], among others. Among these five investigations, one study reported all six outcome measures [12], two studies reported four outcome measures [2,11], and two studies reported five outcome measures [13,14]. Various types of SCs were used in the therapy group, including hUMSCs-human umbilical cord MSCs, adipose-derived stem cells, bone marrow-derived MSCs, and skin-derived MSCs. The transplanted cells ranged from 5×10^6 to 50×10^6. The stem cell treatment group consisted of a total of 153 patients. The follow-up periods in these

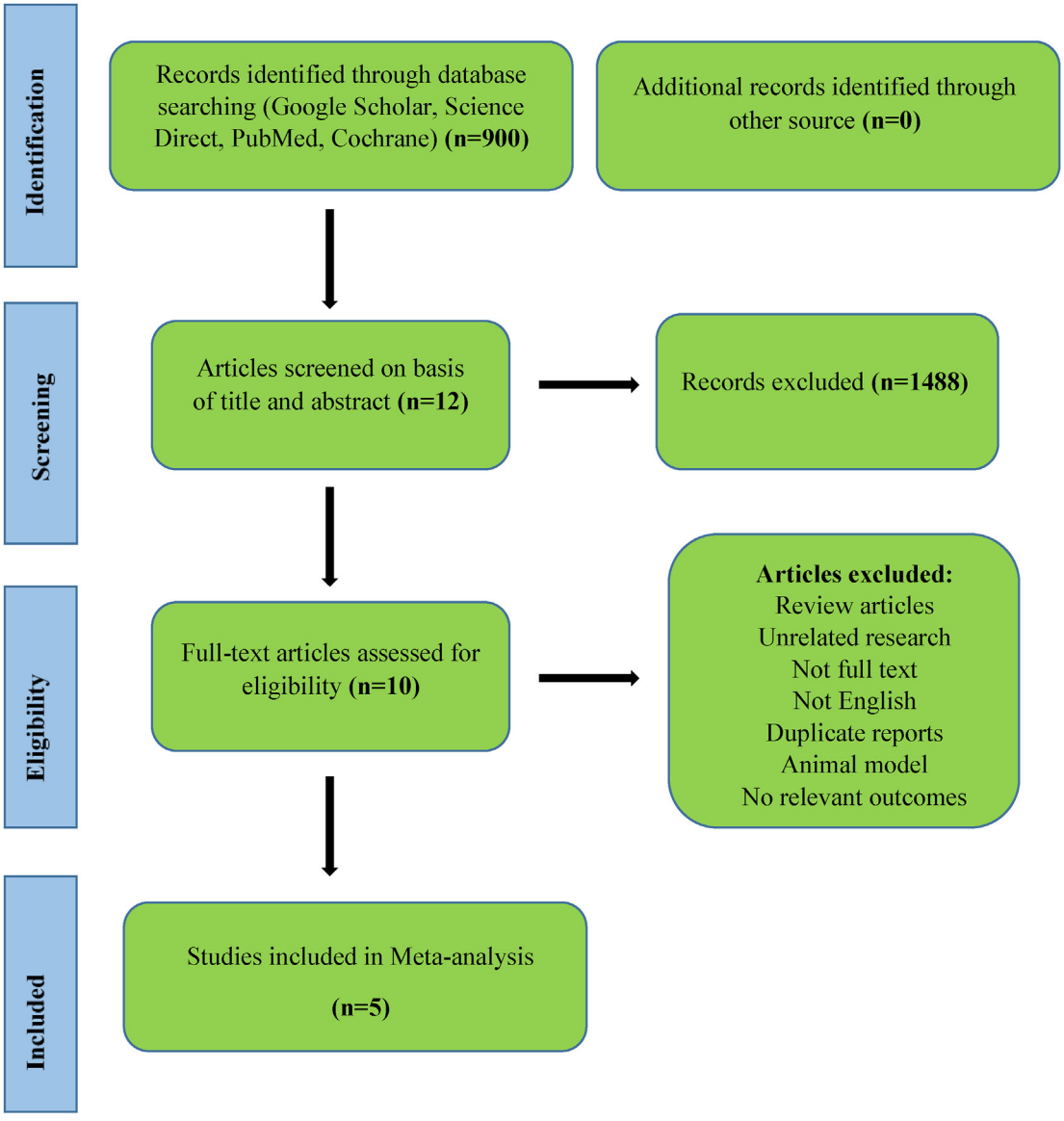


Fig. 1. Selection procedure for acceptable studies.

studies ranged from 1 to 12 months. Details of the included studies are summarized in Table 1.

3.1. Meta-analysis

The statistical analysis presented in this study examines the effects of stem cell transplantation on ovarian function in individuals diagnosed with premature ovarian failure (POF). The analysis encompasses several important parameters, including follicle count (FC), follicle-stimulating hormone (FSH), estradiol (E2), and ovarian weight (OW), as well as the number of pregnancies and live births.

The findings can be summarized as follows:

1. FSH and AMH Levels: The analysis compares follicle-stimulating hormone (FSH) and (AMH) anti-müllerian hormone levels in the stem cell group at the last follow-up time with their respective baseline values. The standardized mean difference (SMD) for FSH was 1.58 (95% CI: -0.76 to 3.92), indicating a lower level in the stem cell group than the baseline. However, the result was not statistically significant (P-value: 0.185 > 0.05). The I2 value of 94.03% suggests high heterogeneity among the included studies. On the other hand, for AMH, the SMD was 1.34 (95% CI: 0.77 to 1.92), indicating a lower level in the stem cell group than in the baseline, and the result was statistically significant (P-value: 0.001 < 0.05). The I2 value of 0% suggests low heterogeneity among the included studies.
2. E2 and OW: The analysis compared the mean estradiol (E2) and ovarian weight (OW) levels in the stem cell group at the last follow-up time with their respective baseline values. The standardized mean difference (SMD) for E2 was −0.47 (95% CI: -0.73 to −0.21), indicating an increase in the mean E2 levels in the stem cell group compared to baseline, and the result was statistically significant (P-value: 0.001 < 0.05). The I2 value of 38.23% suggests moderate heterogeneity among the included studies.
   For OW, the SMD was −1.18 (95% CI: -2.62 to 0.26), indicating an increase in the mean ovarian weight in the stem cell group compared to baseline, although the result was not statistically significant (P-value: 0.108 > 0.05). The I2 value of 76.68% suggests high heterogeneity among the included studies.
3. The Pregnancy and Live Birth proportion: The analysis examined pregnancy and live birth proportion in the stem cell group. The combined proportion for pregnancy was 0.09 (95% CI: 0.03 to 0.15), indicating a significant increase in the stem cell group compared to the baseline (P-value: 0.002 < 0.05). The I2 value of 46.29% suggests moderate heterogeneity among the included studies.
   Similarly, the standardized mean difference (SMD) for live birth was 0.09 (95% CI: 0.03 to 0.15), indicating a significant increase in the stem cell group compared to the baseline (P-value: 0.003 < 0.05). The I2 value of 1.76% suggests low heterogeneity among the included studies.
4. Follicle Count: The analysis calculates the average log odds ratio of follicle count using a fixed-effects model. The estimated value was 1.0234 (95% CI: 0.1252 to 1.9216), indicating a significant difference in follicle count between the stem cell group and baseline (P-value: 0.0255 < 0.05).

Based on the findings of this analysis, it is indicated that stem cell transplantation shows promise as a potential approach for restoring ovarian function and addressing premature ovarian failure (POF). However, it is essential to acknowledge this study's limitations, including the heterogeneity among the included

Table 1
Features of the included studies.

	Country	SC source	Cell type	Study design	Method	Population (n)	Cell quantity	Follow-up duration	Outcome	Ref.
1	China	human	UC-MSCs (Allogeneic)	Randomized controlled trial	Injection under transvaginal ultrasonographic (TVUS)-Guidance	16	10×10^6	Three months	FSH, E2, ovarian volume,	[2]
2	Spain	human	BMSCs (Autologous)	Autologous stem cell ovarian transplant (ASCOT) on ovarian reserve	Delivered through an intra-arterial catheter.	17	50×10^6	Five months	Serum AMH levels and (AFC), punctured follicles, and oocytes retrieved after stimulation	[19]
3	China	human	UCMSCs (Allogeneic)	Non-randomized clinical trial	Ultrasound-guided transvaginal injection	61	0.5×10^7	Six months	AFC per month; the size of ovaries; AMH, FSH, LH and E2	[20]
4	Serbia	human	BMSCs (Autologous)	Autologous *In Vitro* Activation of Ovaries by Stem Cells	Injection under transvaginal ultrasound	50	NA	3, 6, and 12 months	FSH, luteinizing hormone (LH), estradiol (E2), progesterone (PG)	[21]
5	Iran	Human	ADSCs (Autologous)	Non-Randomized	Injection under transvaginal ultrasonography laparoscopy	9	5×10^6, 10×10^6, or 15×10^6	1, 2 weeks,1.2, 3, 6, and 12 months	FSH and AMH and Antral follicle count	[22]

Premature Ovarian Failure (POF), Mesenchymal Stem Cells (MSCs), Bone marrow-derived mesenchymal stem cells (BMSCs), Human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCs), Adipose-derived stem cells (ADSCs), Estradiol (E2), Anti-Müllerian hormone (AMH), Antral follicle count (AFC), Follicle-stimulating hormone (FSH).

studies. Further research must validate and corroborate these findings before drawing definitive conclusions.

3.2. Statistical analysis

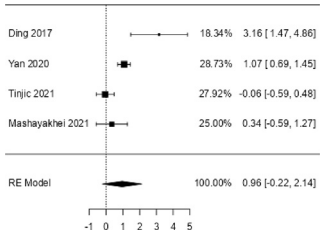
This systematic review and meta-analysis used the weighted mean difference (WMD) and the standardized mean difference (SMD = Baseline - MSC-treated group) to compare continuous variables between study groups. At the same time, the combined proportion and average log odd ratios were computed for discrete variables. WMD was utilized when measurement techniques and units varied between studies, but SMD was utilized when measurement methods and units of measurement were identical. P-values less than 0.05 and confidence intervals (CI) of 95% were considered statistically significant. The I^2 statistic was used to determine the heterogeneity of the included studies; I^2 values of 25%, 50%, and 75%–100% indicated low, medium, and high heterogeneity in the included research, respectively. When the effects were determined to be diverse ($I^2 > 50\%$ and $P < 0.10$), we employed a random-effects model for the meta-analysis [23]; otherwise, the data were analyzed using a fixed-effects model. In this meta-analysis, we compared the treatment group, i.e., Stem cells, and the control group (if any) from the included studies using Jamovi version 2.3 [24] and displayed the results on forest plots (Tables 1–6). In this investigation, heterogeneity and risk of bias were evaluated using the Q Cochrane test and I^2 statistic, evaluating the methodological quality using the Cochrane ROB and meta-regression analysis, and assessing publication bias with a funnel plot and regression tests such as Kendall's test, Begg's test, and Egger's test. In addition, study design, participant age, and the time interval between diagnosis and intervention, which may influence heterogeneity, were considered.

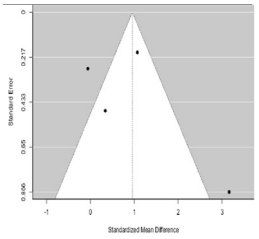
In Table 2, meta-analysis results for the levels of FSH with 3-, 6-, and 12-month follow-ups demonstrated that stem cell transplantation is associated with a reduction of FSH. According to the forest plots, the overall effect size measured with SMD revealed comparing the administration of the Stem cells and control group, which had shown the decrease in levels of FSH at a 5% level of significance in 3-, 6-, and 12-months follow-up as (SMD: 0.96, 95% CI: -0.22 to 2.14, P-value: 0.111 > 0.05, I^2: 91.38%), (SMD: 0.18, 95% CI: -0.41 to 0.78, P-value: 0.542 > 0.05, I^2:61.88%), and (SMD: 1.58, 95% CI: -0.76 to 3.92, P-value: 0.185 > 0.05, I^2: 94.03%) respectively. The SMDs in all follow-ups were statistically non-significant. Still, most (91.67%) observed SMDs in all included studies, along with 3-, 6-, and 12-month follow-ups, were positive, indicating that the FSH levels were reduced due to Stem cell transplantation.

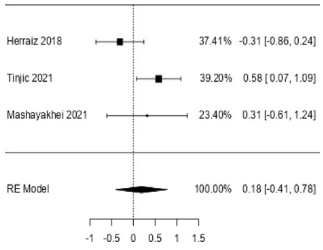
In Tables 3 and 4 studies for each were included in the meta-analysis and were estimated through a fixed effect (FE) model. The meta-analysis results for stem cell therapy were associated with increased pregnancy and live birth proportion. According to the forest plots, the overall effect size measured with proportion of pregnancy and live birth at a 5% level of significance due stem cell transplantation results were as (combined proportion: 0.09, 95% CI: 0.03 to 0.15, P-value: 0.002 < 0.05, I^2: 46.29%) and (SMD: 0.09, 95%

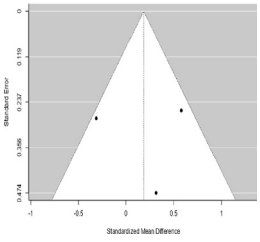
Table 2
Forest and Funnel plot showing how stem cell therapy improves follicle stimulating hormone compared with controls.

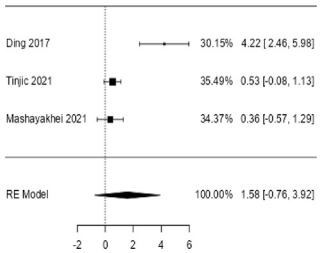
FSH with 3 months follow-up	Statistics	Standardizes mean difference	Funnel plot
Heterogeneity			
Tau^2 (τ^2)	1.2215		
I^2	91.38%		
d.f	3.000		
Q-test (χ^2)	20.038		
$P-value$	<0.001		
Test for overall effect			
$Z-test$	1.59		
$P-value$	0.111		
Publication bias assessment			
Begg & Mazumdar ($P-value$)	0.750		
Egger's regression ($P-value$)	0.119		
FSH with 6 months follow-up			
Heterogeneity			
Tau^2 **(τ^2)**	0.1665		
I^2	61.88%		
d.f	2.000		
Q-test (χ^2)	5.573		
$P-value$	0.062		
Test for overall effect			
$Z-test$	0.610		
$P-value$	0.542		
Publication bias assessment			
Begg & Mazumdar ($P-value$)	1.000		
Egger's Regression ($P-value$)	0.919		
FSH with 12 months follow-up			
Heterogeneity			
Tau^2 (τ^2)	3.9166		
I^2	94.03%		
d.f	2.000		
Q-test (χ^2)	16.102		
$P-value$	<0.001		
Test for overall effect			
$Z-test$	1.33		
$P-value$	0.185		
Publication bias assessment			
Begg & Mazumdar ($P-value$)	0.333		
Egger's Regression ($P-value$)	0.012		











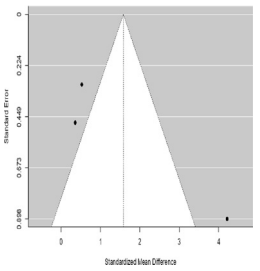
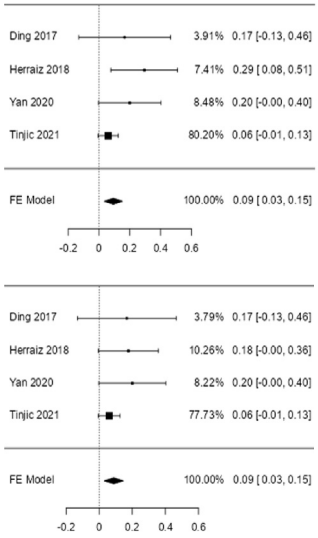


Table 3
Forest and Funnel plot showing how stem cell therapy improves pregnancy and live births as compared to controls.

Pregnancy with FE model	Statistics	Overall proportion	Funnel plot
Heterogeneity			
Tau^2 (τ^2)	0.000		
I^2	46.29%		
d.f	3.000		
Q-test (χ^2)	5.585		
$P-value$	0.134		
Test for overall effect			
$Z-test$	3.10		
$P-value$	0.002		
Publication bias assessment			
Kendall's ($P-value$)	0.750		
Regression for a funnel ($P-value$)	0.037		
Live birth with FE model			
Heterogeneity			
Tau^2 (τ^2)	0.000		
I^2	1.76%		
d.f	3.00		
Q-test (χ^2)	3.054		
$P-value$	0.383		
Test for overall effect			
$Z-test$	2.95		
$P-value$	0.003		
Publication bias assessment			
Kendall's ($P-value$)	0.750		
Regression for funnel ($P-value$)	0.105		



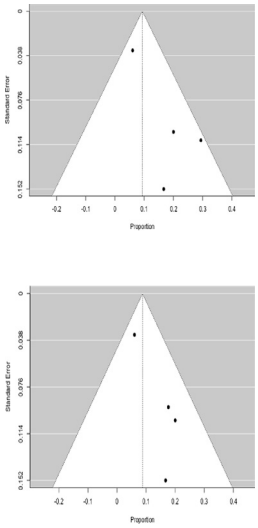
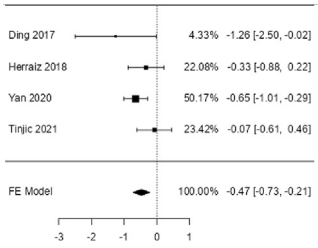
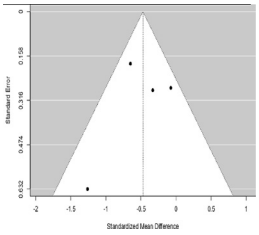


Table 4
Forest and Funnel plot demonstrating how stem cell therapy improves Estradiol E2 compared with controls.

E2 with 3 months follow-up	Statistics	SMD	Funnel Plot
Heterogeneity			
Tau^2 (τ^2)	0.000		
I^2	38.23%		
d.f	3.000		
Q-test (χ^2)	4.857		
P – value	0.183		
Test for overall effect			
$Z-test$	−3.580		
$P-value$	<0.001		
Publication bias assessment			
Begg & Mazumdar ($P-value$)	1.000		
Egger's Regression ($P-value$)	0.721		





CI: 0.03 to 0.15, P-value: 0.003 < 0.05, I^2:1.76%) respectively. These pregnancy and live birth proportions were statistically highly significant as P-value <0.01, showing that 9% of the women in these studies are likely to be pregnant and deliver a live birth after stem cell transplantation.

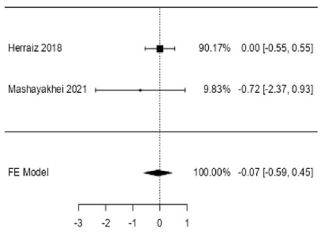
In Table 4, meta-analysis results for the score of estradiol with 3-month follow-up demonstrated that stem cell transplantation is associated with increased estradiol. It was also found that the stem cells significantly affected estradiol with a 3-month follow-up. According to the forest plots, the overall effect size measured with SMD revealed comparing the administration of the Stem cells and control group, which had shown the increase in estradiol at a 5% level of significance in 3-month follow-up as (SMD: -0.47, 95% CI: -0.73 to −0.21, P-value: 0.001 < 0.01, I^2: 38.23%). The SMDs were statistically significant, and most studies (100%) observed negative SMDs in all included studies along with 3-month follow, which indicated that the estradiol was increased due to Stem cell transplantation.

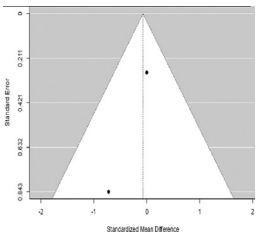
The results of the meta-analysis for the score of AMH with 1- and 2-month follow-up are shown in Table 5. According to the forest plots, the overall effect size measured with SMD revealed comparing the administration of the Stem cells and control group, which had shown the increase in AMH at a 5% level of significance in 1-month follow-up but a decrease in AMH with a 2-month follow-up as (SMD: -0.07, 95% CI: -0.59 to 0.45, P-value: 0.788 > 0.05, I^2: 0%) and (SMD: 1.34, 95% CI: 0.77 to 1.92, P-value: 0.001 < 0.05, I^2:0%) respectively. The SMDs were statistically non-significant in the 1-month follow-up, but the SMD was statistically significant in the 2-month follow-up. Since only two studies were found for meta-analysis, a fixed effect model was implemented in 1- and 2-month follow-ups due to non-significant heterogeneity. The majority of results of studies (66.67%) observed SMDs in all included studies along with 1-and 2-month follow-ups were positive, which indicated that the score of AMH was reduced due to Stem cell transplantation.

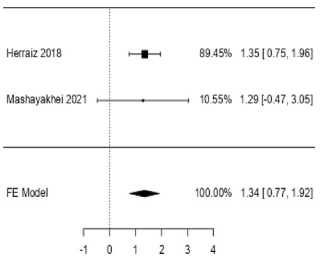
The dichotomous fixed effects models were implemented to estimate the log odds ratios of FC with 2-, 3-, 4-, and 6-month follow-ups and their results are presented in Table 6. For a 2-month follow-up, the observed log odds ratios ranged from 0.00 to 1.98, with the most optimistic estimates (75%). The estimated average log odds ratio based on the fixed-effects model was 0.4599 (95% CI: -0.2955 to 1.2153). Therefore, the average outcome did not differ significantly from zero (P-value: 0.2327 > 0.05). For a 3-month follow-up, the observed log odds ratios ranged from

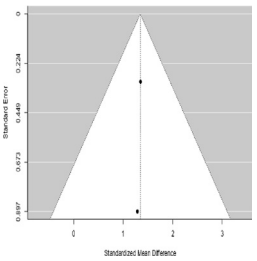
Table 5
Forest and Funnel plot displaying how stem cell therapy improves Anti-müllerian hormone (AMH) compared with controls.

AMH with 1 month follow-up	Statistics	SMD	Funnel Plot
Heterogeneity			
Tau^2 (τ^2)	0.000		
I^2	0%		
d.f	1.000		
Q-test (χ^2)	0.660		
$P-value$	0.416		
Test for overall effect			
$Z-test$	−0.268		
$P-value$	0.788		
Publication bias assessment			
Begg & Mazumdar ($P-value$)	1.000		
Egger's Regression ($P-value$)	0.416		
AMH with 2 month follow-up			
Heterogeneity			
Tau^2 (τ^2)	0.000		
I^2	0%		
d.f	1.000		
Q-test (χ^2)	0.005		
$P-value$	0.946		
Test for overall effect			
$Z-test$	4.610		
$P-value$	<0.001		
Publication bias assessment			
Begg & Mazumdar ($P-value$)	1.000		
Egger's Regression ($P-value$)	0.946		









0.0000 to 0.8718, with many negative estimates (0%). The estimated average log odds ratio based on the fixed-effects model was 0.5561 (95% CI: -0.2493 to 1.3616). Therefore, the average outcome did not differ significantly from zero (P-value: 0.1760 > 0.05). For a 4-month follow-up, the observed log odds ratios ranged from −1.8458 to 1.3889, with most estimates being negative (25%). The estimated average log odds ratio based on the fixed-effects model was 0.8083 (95% CI: -0.0910 to 1.7076). Therefore, the average outcome did not differ significantly from zero (P-value: 0.0781 > 0.05). For a 6-month follow-up, the observed log odds ratios ranged from 0.8718 to 1.2657, with most estimates being positive (100%). The estimated average log odds ratio based on the fixed-effects model was 1.0234 (95% CI: 0.1252 to 1.9216). Therefore, the average outcome differed significantly from zero (P-value: 0.0255 < 0.05).

The results of the meta-analysis for ovary weight with a 3-month follow-up are shown in Table 7. According to the forest plots, the overall effect size measured with SMD revealed comparing the administration of the Stem cells and control group, which had shown the increase in ovary volume at a 5% level of significance in 3-month follow as (SMD: -1.18, 95% CI: -2.62 to 0.26, P-value: 0.108 > 0.05, I^2: 76.68%). The combined SMD was statistically non-significant in the 3-month follow-up. Most studies (100%) observed SMDs in all included studies, along with 3-month follow-ups were negative, which indicated that the ovary volume was increased due to Stem cell transplantation.

3.3. Heterogeneity

Cochran's Q-test and I^2 statistic was applied to measure the heterogeneity of the true scores of the parameters: FSH, pregnancy, live birth, Estradiol, AMH, AFC, and ovary weight with their respective follow-up. According to the Q-test, the actual outcomes appeared to be heterogeneous significantly for the score of FSH with 3-, 6-, and 12-month follow-ups as (Q-test: 20.038, P-value: 0.001 < 0.05, tau^2: 1.2215, I^2: 91.38%), (Q-test: 5.573, P-value: 0.062 < 0.05, tau^2: 0.1665, I^2: 61.88%) and (Q-test: 16.102, P-value: 0.001 < 0.05, tau^2: 3.9166, I^2: 94.03%). Similar results can be found for pregnancy, live birth, Estradiol, AMH, FC, and ovary weight with their respective follow-up from Tables 2–6, where the random effect model is implemented for the significant heterogeneous true outcome; otherwise, the fixed effects model was used.

3.4. Risk of bias assessment

The assessment of risk bias is estimated through funnel plots, Begg's, Kendall's, and Egger's regression tests for each forest plot of the parameters: FSH, pregnancy, live birth, Estradiol, AMH, FC, and vary weight with their respective follow-up show in Tables from 2 to 7. The publication bias analysis indicated a non-significant bias at a 5% level of significance for FSH in all 3-, 6-, and 12-month follow-ups as (Begg & Mazumdar test, P-value: 0.750 > 0.05 and Egger's regression P-value: 0.119 > 0.05), (Begg & Mazumdar test, P-value: 1.000 > 0.05 and Egger's regression P-value: 0.919 > 0.05), (Begg & Mazumdar test, P-value: 0.333 > 0.05 and Egger's regression P-value: 0.012 > 0.05). Similar results for publication bias about the pregnancy, live birth, Estradiol, AMH, FC, and Ovary weight with their respective follow-up, can be found in Tables 2–6

4. Discussion

Premature ovarian failure (POF) is a complex condition with various causes, including autoimmune reactions, genetic defects, surgery, chemotherapy, and radiotherapy. Currently, effective treatments for POI/POF are lacking. However, stem cells (SCs) have emerged as a promising approach in regenerative medicine and tissue engineering due to their unique self-renewal properties and differentiation into multiple cell lineages. Stem cell therapy presents a novel strategy for restoring or preserving ovarian function in women undergoing radiotherapy or chemotherapy [25,26]. Clinical studies have been conducted to address the concerns associated with POF, particularly related to pregnancy outcomes, as POF significantly impacts women's health. These studies have focused on primary outcomes such as ovarian size and levels of serum hormones, including luteinizing hormone (LH), Anti-Müllerian hormone (AMH), estradiol (E2), and follicle-stimulating

Table 6
Forest and Funnel plot showing how stem cell therapy improves the effect of stem cell therapy on Follicles count (FC) compared with controls.

FC with 2 months follow-up	Statistics	Average Log Odd Ratio	Funnel Plot
Heterogeneity			
Tau^2 (τ^2)	0.000		
I^2	0%		
d.f	3.000		
Q-test (χ^2)	1.049		
$P-value$	0.789		
Test for overall effect			
$Z-test$	1.19		
$P-value$	0.233		
Publication bias assessment			
Kendall's ($P-value$)	0.750		
Regression for funnel ($P-value$)	0.572		
FC with 3 months follow-up			
Heterogeneity			
Tau^2 (τ^2)	0.000		
I^2	0%		
d.f	3.00		
Q-test (χ^2)	0.446		
$P-value$	0.931		
Test for overall effect			
$Z-test$	1.35		
$P-value$	0.176		
Publication bias assessment			
Kendall's ($P-value$)	0.750		
Regression for funnel ($P-value$)	0.710		
FC with 4 months follow-up			
Heterogeneity			
Tau^2 (τ^2)	0.000		
I^2	27.82%		
d.f	3.000		
Q-test (χ^2)	4.156		
$P-value$	0.245		
Test for overall effect			
$Z-test$	1.76		
$P-value$	0.078		
Publication bias assessment			
Kendall's ($P-value$)	0.750		
Regression for funnel ($P-value$)	0.084		
FC with 6 months follow-up			
Heterogeneity			
Tau^2 (τ^2)	0.000		
I^2	0%		
d.f	3.000		
Q-test (χ^2)	0.054		
$P-value$	0.997		
Test for overall effect			
$Z-test$	2.23		
$P-value$	0.026		
Publication bias assessment			
Kendall's ($P-value$)	0.750		
Regression for funnel ($P-value$)	0.940		

Table 7
Forest and Funnel plot representing the effect of stem cell therapy on improving Ovary Weight (OW) compared with controls.

OW with 3 months follow-up	Statistics	SMD	Funnel plot
Heterogeneity			
Tau^2 (τ^2)	1.2082		
I^2	76.68%		
d.f	2.000		
Q-test (χ^2)	9.834		
$P-value$	0.007		
Test for overall effect			
$Z-test$	−1.61		
$P-value$	0.108		
Publication bias assessment			
Begg & Mazumdar ($P-value$)	1.000		
Egger's Regression ($P-value$)	0.304		

hormone (FSH). Secondary outcomes, such as antral and dominant follicle counts (AFC)(DFC) per month, the number of pregnancies and several live births, good-quality embryos, the quantity of harvested and matured oocytes, and clinical pregnancy percentages, miscarriage, or ICSI/IVF live birth cycles, have also been investigated. Additionally, the studies have examined the incidence of adverse events such as temperature changes, vaginal bleeding, headaches, rash, infectious diseases, abnormal liver and renal function, and neoplasms [27].

Previous studies on animal models have demonstrated promising outcomes using SC-based therapy for premature ovarian failure (POF) caused by various underlying factors. However, these studies often lack quantitative evaluation, and there is currently a limited number of published randomized controlled trials involving human subjects. Initial human clinical investigations utilized mesenchymal stem cells (MSCs) derived from bone marrow (BM) for cell collection acquired through iliac crest aspiration. SC isolation and in vitro culturing were employed for these procedures [28]. A noteworthy case report by Gupta et al. documented a successful SC therapy resulting in the live birth of a healthy baby girl weighing 2.7 kg involving a 45-year-old perimenopausal woman [29].

Similarly, positive outcomes were observed in a study involving ten younger women with POF, where menstruation restoration was observed in 2 patients, and one patient achieved a pregnancy successfully, resulting in a live birth [30]. Another study involving 30 POF women aged 18–40 reported symptom improvements and one successful pregnancy [31]. These findings highlight the potential effectiveness of SC therapy in treating POI/POF and improving reproductive outcomes in affected individuals. Based on existing research, it has been observed that bone marrow-derived mesenchymal stem cells (BMDSC) have the potential to regulate cell apoptosis, enhance vascularization in ovaries and stromal cell proliferation, thereby promoting follicular growth in both human and mouse models [32]. Building upon this knowledge, a team of researchers conducted a pilot study involving 17 women diagnosed with premature ovarian failure (POF) to investigate the effects of ASCOT-autologous stem cell ovarian transplant on ovarian reserve. The preliminary results of this study showed promising outcomes, with six successful pregnancies resulting in the birth of three healthy newborns. Additionally, 81.3% of the women demonstrated improvements in ovarian function biomarkers, specifically anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) [19]. However, it is important to note that most of these studies are ongoing, and complete outcomes have not yet been reported. Considering this gap, a meta-analysis was conducted to evaluate the available human studies on stem cell therapy for POF, and the findings of this analysis are presented herein.

This meta-analysis selected various outcomes as reliable indicators of ovarian function recovery in POF patients. These outcomes included follicle-stimulating hormone (FSH), the number of pregnancies and live births, estradiol (E2), follicle count, and ovarian weight. These parameters strongly correlate with the risk of POF and are considered reliable predictors of ovarian function recovery [33]. This meta-analysis's findings indicate positive results regarding ovarian weight, E2 levels, FSH levels, follicle count, and the number of pregnancies following SC transplantation. These results suggest a promising therapeutic effect of SCs in POF treatment. The analysis demonstrates that stem cell transplantation significantly improves ovarian function in POF patients by restoring fertility, enhancing ovarian weight, normalizing sex hormone levels (E2 and FSH) in serum, and increasing the number of pregnancies. The observed benefits of SC therapy in POF can be attributed to stem cells' homing, differentiation, and paracrine function. Mechanisms through which SCs may repair the function of damaged ovaries in POF include differentiation into ovarian tissue-like cells, secretion of angiogenic growth factors, and mitigation of inflammation induced by chemotherapy [7,34,35]. These mechanisms provide substantial evidence supporting the potential advantages of SC therapy in enhancing the function of the ovaries in POF patients.

Although the current study carefully assessed the role of SCs in the therapy of premature ovarian failure (POF), it is important to acknowledge certain potential limitations when interpreting the findings. Firstly, while the study demonstrated the effectiveness of stem cell-based therapy in improving the function of ovaries in POF patients through various indicators such as lower FSH levels, increased E2 levels, restore fertility, and enhanced follicle development, it is crucial to consider the significant heterogeneity observed among the included studies. The fewer studies considered for individual outcomes may contribute to this heterogeneity. Therefore, future research will need to encompass larger sample sizes and adhere to the earlier classification criteria.

This study selected follicle count, FSH, the number of pregnancies, ovary weight, and E2 as the primary outcomes. However, whether SC-based therapy yields additional benefits, such as improvements in the menstrual cycle or LH-luteinizing hormone levels, remains unclear and warrants more investigation through additional clinical trials. By exploring these aspects, a more comprehensive understanding of the potential advantages and broader effects of SC therapy for POF can be gained.

The various case reports provide additional evidence suggesting that SC therapy may be a viable option for treating individuals with premature ovarian failure (POF). These reports indicate improvements in ovarian function, increased endometrial thickness, and enhanced endometrial blood flow in the patients who underwent stem cell therapy [29,36,37]. However, it is important to acknowledge the limitations of these studies, including the lack of monitoring of folliculogenesis and serum hormone level detection and the absence of long-term follow-up to assess menstruation recovery. Therefore, further research/investigation is necessary to determine the efficacy of SC transplantation in patients of POF, and future clinical randomized controlled trials are warranted. Nevertheless, the positive outcomes reported in previous studies, such as improved hormonal profiles, resumption of menstruation, and successful pregnancy outcomes following stem cell transplantation, support the potential of SC-based therapies as a treatment option for POF. Additionally, a meta-analysis of clinical trials involving POF patients has demonstrated significant improvement in ovarian function with SC transplantation, further emphasizing the promising nature of this approach.

5. Limitations

Less number of human studies along with small sample sizes, variations in stem cell types, ambiguous treatment regimens, and variations in patient ages and follow-up times, all have a significant impact on the findings and interpretations of this meta-analysis. Here is a detailed explanation of how each factor affects this meta-analysis: **Small Sample Size**- A small sample size reduces the statistical power of the analysis, making it difficult to detect significant effects. It also increases the margin of error, which can lead to less reliable and less generalizable findings. With only five human studies, the conclusion drawn is likely to be less robust and more susceptible to random variation. It limits the ability to confidently generalize the results to a broader population. **Variability in Stem Cell Types**- Different types of stem cells may have varying efficacy and safety profiles. This heterogeneity can lead to inconsistent results, making it challenging to determine which stem cell type is most effective. **Unclear Treatment Protocols-** Lack

of clarity and consistency in the use of immunosuppressants can lead to varied outcomes, as these drugs can significantly affect the success of allogeneic stem cell transplantation by preventing rejection. Unclear treatment protocols create difficulties in standardizing the intervention across studies, which undermines the ability to draw definitive conclusions about the effectiveness and safety of the treatment. **Variability in Age-** Age can influence the responsiveness to stem cell therapy, with potentially different outcomes in younger versus older patients. This variability adds another layer of complexity to interpreting the results. It also complicates the interpretation of findings, as it may be unclear whether the observed effects are due to the treatment itself or the age-related differences in response. **Variability in Follow-Up Durations-** Differences in follow-up durations can lead to inconsistent data on the long-term effectiveness and safety of the treatment. Short follow-up periods may miss late-emerging benefits or adverse effects. Inconsistent follow-up makes it challenging to assess the sustained impact of the treatment, leading to potentially incomplete or premature conclusions about its efficacy.

All these characteristics together lead to a significant degree of heterogeneity, which makes it difficult to synthesize the results of studies and limits the generalizability of data on the efficacy of stem cells from umbilical cords in treating premature ovarian failure. Because of this, it is important to evaluate the results of a meta-analysis carefully and emphasize the need for more carefully planned, standardized investigations.

In conclusion, the findings from the available studies suggest that stem cell therapy offers promise as a treatment option for early ovarian failure. The encouraging results from this research such as restored hormone profiles, menstrual return, and successful pregnancy outcomes after stem cell transplantation support the possibility of SC-based therapies as a POF therapeutic option. Furthermore, the promising nature of this strategy is further highlighted by a meta-analysis of clinical trials including patients with POF that showed a considerable increase in ovarian function after SC transplantation. However, it is crucial to acknowledge the limitations of the meta-analysis, such as the scarcity of clinical studies and small sample sizes. We acknowledge the potential sources of heterogeneity among the studies, which may include due to several factors. Firstly, variations in patient characteristics across the included studies, such as age, underlying health conditions, and previous treatment history, may contribute to differences in treatment responses and outcomes. Additionally, discrepancies in study methodologies, including variations in stem cell types, delivery methods, and cell quantities used, can lead to variability in treatment effects. Furthermore, differences in outcome measurement techniques, follow-up durations, and definitions of outcomes among studies can introduce further heterogeneity into the data.

6. Future prospects

Further investigation is warranted to validate these findings and establish the long-term safety and effectiveness of SC transplantation in treating premature ovarian failure (POF). The long-term safety of stem cell therapy remains a significant concern. While short-term results may indicate positive outcomes, it is crucial to understand the potential risks and adverse effects that may arise over extended periods. Long-term studies are needed to monitor patients for any delayed complications, such as abnormal cell growth or immune reactions, to ensure the therapy remains safe years after treatment. Despite the fact that SC-related cancers have not yet been reported in human patients, tumors may nevertheless emerge due to their tendency to promote metastatic growth. SCs are drawn to areas of tissue injury and inflammation, and as part of their normal healing function, SCs can settle within an environment that is carcinogenic. Nevertheless, the lack of adverse effects and the safety of SCs-related therapies is a central priority of fundamental research and clinical trials.

Another critical issue is the cost-effectiveness of stem cell therapy. Research is required to evaluate the overall expenses of stem cell therapies compared to those of conventional therapies. This includes considering long-term cost reductions, such as whether stem cell therapy can prevent the need for more medical care down the road. This will allow us to assess whether stem cell therapy is cost-effective for both patients and healthcare systems.

It is also crucial to establish consistent clinical practices for treating Premature Ovarian Failure with stem cell therapy. This includes standardizing when doctors should diagnose the condition and when to start stem cell therapy. Having clear guidelines ensures that all patients receive the best possible care and improves the effectiveness of the treatment. Specifically, well-designed clinical trials with larger sample sizes and meticulous planning are needed. These future investigations will help create a more thorough knowledge of the potential advantages and risks associated with stem cell transplantation in POF treatment.

Authors' contributions

AU conceptually designed and drafted this manuscript; DLG reviewed and revised the draft, KA did the statistical analysis, NK revised the draft and supervised the team; SS and UH assisted in the material collection of the draft.

Funding

R3 Medical Research LLC, United States funded this research as employer of all the authors.

Ethical approval and consent to publish

All the authors read and approved this manuscript for publication.

Availability of data and materials

All the data and material of this manuscript will be accessible to the readers.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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