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REVIEW

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The effect of exercise on anti-Mullerian hormone levels in patients with polycystic ovary syndrome: a systematic review and meta-analysis

Mohsen Kazeminia[1], Fatemeh Rajati[2] and Mojgan Rajati[3*]

Abstract

Background: Polycystic ovary syndrome (PCOS) is considered as the most common endocrinopathy among women of childbearing age and the most important cause of anovulatory infertility. The present study aimed to estimate the pooled effect of exercise on anti-Mullerian hormone (AMH) levels in PCOS women using systematic review and meta-analysis.

Main body: The present study was conducted according to the PRISMA guidelines from 2011 to October 2021. All published studies, which met the inclusion criteria, were searched in SID, MagIran, Embase, PubMed, Scopus, Web of Science (WoS) databases, and Google Scholar motor engine using related MeSH/Emtree terms, which were combined with free text word. Finally, 12 articles were included in the meta-analysis. As a result of the combination of the studies, after exercise, AMH level in the intervention group significantly decreased up to 0.517 ± 0.169 more than that in the control group ($P < 0.05$). The results of subgroup analysis demonstrated that the effect of resistance training for 16 weeks was higher on women with body mass index (BMI) (≥ 25 kg/m^2) and AMH (≥ 10 ng/mL) before the intervention. GRADEpro software was used to grade the level of evidence.

Conclusion: This systematic review and meta-analysis showed that either strength exercise or aerobic exercise decrease the AMH level in PCOS women. It seems more duration of the exercise has a more potential advantage to reduce the AMH levels in women with PCOS. Although the results graded by very low-quality evidence, it is recommended to include exercise in the treatment programs of PCOS patients.

Keywords: Anti-Mullerian hormone, Exercise, Polycystic ovary syndrome, Systematic review, Meta-analysis

Background

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder and the most important cause of anovulatory infertility in women of reproductive age [1]. The global prevalence of PCOS has been reported between 5 and 10% [2, 3], which is associated with symptoms, such as oligomenor*rhea* or amenorrhea and acne [4]. Causes of PCOS may be a range of endocrine disorder, such as hypothalamic-pituitary-adrenal (HPA) axis dysfunction, ovarian disorders, and insulin signaling [5].

Some of the risk factors, such as insulin resistance, dyslipidemia, and oxidative stress, cause early onset of type 2 diabetes and cardiovascular disease among PCOS patients, as the risk of heart attack (myocardial infarction) in women with PCOS is 7.4 times higher than that in other women [6]. Given that insulin resistance is determinant in the manifestations of PCOS, it is considered as the primary goal for managing PCOS. The results of

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previous studies indicated that hyperinsulinemia and insulin resistance cause metabolic syndrome and play an important role in the development of reproductive disorders in women with PCOS [7]. The prevalence of metabolic syndrome in women with PCOS is 3.35 times higher than that in other women [8].

Insulin has profound effects on the ovarian stroma and follicle levels. Furthermore, insulin stimulates the secretion of ovarian androgens, and increased androgen levels can destroy growing follicles and interfere with the emergence of a dominant follicle [9]. An increase in the number of follicles and androgen levels in women with PCOS leads to the increased production of AMH [10].

AMH is a homodimeric glycoprotein belonging to the transforming growth factor (TGF)-β family, produced by the granulosa cells of ovarian antral follicles, starting at the puberty until menopause. The amount of AMH reflects the size of the growing follicles and the ovarian reserve function in women. In addition, AMH is involved in regulating follicle growth [11]. AMH levels gradually decline with age, indicating a decrease in the number of follicles and the onset of menopause [12]. The determination of serum AMH level is currently proposed as a valid marker of ovarian function in evaluating the female infertility and may predict the possibility of targeted treatment of infertility [13].

PCOS treatment includes pharmacological and non-pharmacological methods, such as changing lifestyle, losing weight, and using proper diet and dietary supplements [14, 15]. Despite the importance of exercise in improving metabolic status, the majority of PCOS patients lack regular physical activity [16]. The interaction between exercise and the treatment of the complications of PCOS has been the focus of researchers recently [14].

The World Health Organization (WHO) defines the physical activity as any body movement that needs more energy expenditure than rest, whereas exercise refers to planned physical activity with a structured frequency, intensity, and duration [17].

Frequent primary studies examined the effect of exercise on AMH levels among PCOS patients, and there are discrepancies between their results. One of the applications of systematic review and meta-analysis studies is the elimination of inconsistencies and the unification of information. Therefore, the present study aimed to review the effect of exercise on AMH level in patients with PCOS using systematic review and meta-analysis

Method

The present systematic review and meta-analysis was done based on the four-phase protocol of PRISMA 2009 (http://www.prisma-statement.org/), including identification, screening, eligibility, and inclusion [18]. Two researchers (M. R. and M. K.) independently extracted the data and reviewed eligible articles to reduce publication bias and error. Any disagreement between the two researchers was resolved by the consensus and consultation with a third researcher (F. R.).

Identification of studies

This systematic review was performed by searching the Persian databases of SID (https://www.sid.ir) and MagIran (https://www.magiran.com) and the English databases of Embase, PubMed, Scopus, and Web of Science (WoS) using related free text word including "Resistance Training," "Strength Training," "Endurance Training," "Exercise*," "Physical Activity," "Anti Mullerian Hormone," "AMH," "Polycystic ovarian syndrome," "Polycystic Ovary Syndrome," and "PCOS." Furthermore, the free text word was combined with controlled vocabulary (i.e., MeSH terms and Emtree terms, for PubMed and Embase, respectively). As the literature used the physical activity and exercise interchangeably, we included both keywords and their synonyms in our search strategy. No time limitation was considered for the search to retrieve as comprehensive as possible related studies by October 2021. The Google Scholar and references of all articles with inclusion criteria were manually reviewed to maximize the comprehensiveness of the search. Table 1 represents the search strategy of different databases (Table 1).

Inclusion criteria

The inclusion criteria were original scientific-research articles, interventional studies, studies examined the effect of physical activity, or any type of exercise on AMH levels in PCOS women with sufficient data (reporting mean ± SD, AMH level before and after the intervention in the intervention and control groups).

Exclusion criteria

The exclusion criteria included the irrelevant studies, cross-sectional studies, case reports, case series, case studies, papers presented at conferences, letter to the editor, qualitative studies, dissertations, systematic review and meta-analysis, animal studies, and lack of access to the full text of the articles.

Selection process of studies

All articles from various databases were imported into EndNote X8 software. After removing the duplicates, the title and abstract of the studies were thoroughly screened to eliminate the irrelevant studies. Then, the full text of all remaining articles was carefully inspected for eligibility. The quality assessment of all studies selected for the systematic review and meta-analysis was done.

Table 1 Search strategies

Database	Search type	Search strategy	Date	Number
PubMed	Advance search	("Resistance Training"[All Fields] OR "Strength Training"[All Fields] OR "Endurance Training"[All Fields] OR "Exercise*"[All Fields] OR "Exercising"[All Fields] OR "Physical Activity"[All Fields] OR "Resistance Training"[Mesh Terms] OR "Endurance Training"[Mesh Terms] OR "Exercise Therapy"[Mesh Terms]) AND ("Antimullerian Hormone"[All Fields] OR "Anti-Mullerian Hormone"[All Fields] OR "Anti-Mullerian Hormone"[All Fields] OR "AMH"[All Fields] OR "Anti-Mullerian Hormone"[Mesh Terms]) AND ("Polycystic Ovarian Syndrome"[All Fields] OR "PCOS"[All Fields] OR "Polycystic Ovary Syndrome"[All Fields] OR "Polycystic Ovary Syndrome"[Mesh Terms])	15 October 2021	21
Scopus	Basic search	(TITLE-ABS-KEY (*"resistance training"*) OR TITLE-ABS-KEY (*"strength training"*) OR TITLE-ABS-KEY (*"endurance training"*) OR TITLE-ABS-KEY (*"exercise*"*) OR TITLE-ABS-KEY (*"exercising"*) OR TITLE-ABS-KEY (*"physical activity"*)) AND (TITLE-ABS-KEY (*"anti mullerian hormone"*) OR TITLE-ABS-KEY (*"Anti-mullerian hormone"*) OR TITLE-ABS-KEY (*"AMH"*) OR TITLE-ABS-KEY (*"Antimullerian Hormone"*)) AND (TITLE-ABS-KEY (*"Polycystic Ovarian Syndrome"*) OR TITLE-ABS-KEY (*"polycystic ovary syndrome"*) OR TITLE-ABS-KEY (*"PCOS"*))	16 October 2021	34
WoS	Advance search	TS=("Resistance Training" OR "Strength Training" OR "Endurance Training" OR "Exercise*" OR "Exercising" OR "Physical Activity") AND TS=("Anti Mullerian Hormone" OR "Anti-Mullerian Hormone" OR "Antimullerian Hormone" OR "AMH") AND TS=("Polycystic Ovary Syndrome" OR "Polycystic Ovarian Syndrome" OR "PCOS")	16 October 2021	44
Embase	Advance search	**#1:** 'resistance training':ab,ti OR 'strength training':ab,ti OR 'endurance training':ab,ti OR 'exercise*':ab,ti OR 'exercising':ab,ti OR 'physical activity':ab,ti OR 'resistance training'/exp/mj OR 'endurance training'/exp/mj OR 'exercise'/exp/mj OR 'exercise therapy'/exp/mj **#2:** 'anti mullerian hormone':ab,ti OR 'anti-mullerian hormone':ab,ti OR 'antimullerian hormone':au OR 'amh':af OR 'anti mullerian hormone'/exp/mj **#3:** 'polycystic ovarian syndrome':ab,ti OR 'pcos':ab,ti OR 'polycystic ovary syndrome':ab,ti OR 'polycystic ovary syndrome'/exp/mj **#4:** #1 AND #2 AND #3	17 October 2021	28
Google Scholar	Basic search	("Physical Activity" OR "Exercise" OR "Resistance Training" OR "Strength Training" OR "Endurance Training") AND ("Anti-Mullerian Hormone" OR "AMH") AND ("Polycystic Ovary Syndrome" OR "PCOS")	18 October 2021	100
MagIran	Basic search	("Physical Activity" OR "Exercise" OR "Resistance Training" OR "Strength Training" OR "Endurance Training") AND ("Anti-Mullerian Hormone" OR "AMH") AND ("Polycystic Ovary Syndrome" OR "PCOS")	20 October 2021	22
SID	Basic search	("Physical Activity" OR "Exercise" OR "Resistance Training" OR "Strength Training" OR "Endurance Training") AND ("Anti-Mullerian Hormone" OR "AMH") AND ("Polycystic Ovary Syndrome" OR "PCOS")	20 October 2021	28

Qualitative evaluation of the studies

The methodological quality of studies was assessed using the Joanna Briggs Institute (JBI) checklist for randomized controlled trials (RCT) [19], which consists of 13 different items, including randomization, allocation concealment, similarity of treatment groups at baseline, blind assignment of the participants, blindness of the administrators, blindness of the evaluators of the outcomes, similar treatment in groups except intervention, follow-up, intention to treat analysis, similarity in assessing outcomes, reliability of the method of measuring results, appropriate statistical analysis, and trial design appropriate. It is possible to identify the sources of bias by using the criteria that the reviewers qualified with answers, such as yes, no, unclear, or not applicable. The prevalence of "yes" scores (number of "yes") was calculated for each individual evaluation question. The total score range based on the number of "yes" is between 0 and 13. A score of 1–4 was considered "low quality," a score of 5–8 was considered "medium quality," and a score of 9–13 was considered "high quality" [20]. Two researchers (F. R. and M. K.) independently analyzed each criterion of the JBI. Table 2 illustrates the results of qualitative evaluation of studies based on JBI checklist items.

Data extraction

Data were manually extracted from all final articles entered into the systematic review and meta-analysis by a pre-prepared checklist. Items of this checklist included first author, year of publication, country, age, sample size, mean ± SD, and level of AMH before and after intervention in the case and control groups, *P*-value, type of intervention, study design, and diagnostic tool.

Statistical analysis

Mean, standard deviation (SD), and standardized mean difference (SMD) were used to combine the results of different studies. The heterogeneity of studies was

Table 2 Qualitative evaluation of studies based on JBI checklist items

Author (reference)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Quality score (number "yes")
Saremi and Yaghoubi [21]	Yes	Yes	No	Yes	NA	NA	Yes	Yes	No	Yes	Yes	Yes	Yes	9, high
Saremi et al. [22]	Yes	No	No	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8, medium
Saremi and Rajabi [23]	Yes	Yes	No	Yes	NA	NA	Yes	Yes	No	Yes	Yes	Yes	Yes	9, high
Saremi et al. [24]	Yes	Yes	No	Yes	NA	NA	Yes	Yes	No	Yes	Yes	Yes	Yes	9, high
Al-Eisa et al. [25]	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11, high
Vosnakis et al. [26]	Yes	Yes	Yes	NA	NA	NA	No	No	Yes	Yes	No	Yes	Yes	7, medium
Hosseini et al. [27]	Yes	Yes	Yes	NA	NA	NA	No	Yes	Yes	No	Yes	Yes	Yes	8, medium
Nybacka et al. [28]	Yes	No	No	Yes	NA	NA	No	Yes	Yes	Yes	Yes	Yes	Yes	8, medium
Wu et al. [29]	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12, high
Moran et al. [30]	Yes	Yes	Yes	NA	NA	NA	Yes	Yes	No	Yes	No	Yes	Yes	8, medium
Leonhardt et al. [31]	Yes	No	Yes	Yes	Yes	NA	No	Yes	Yes	Yes	Yes	Yes	Yes	10, high
Nidhi et al. [32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	12, high

assessed using I^2 index, and random effects model was applied due to the high heterogeneity between the results of studies included in the meta-analysis ($I^2 > 50\%$). The parameter changes between the studies were calculated in this model. Therefore, the results of random effects model in heterogeneous conditions are more generalizable than those of fixed effect model. I^2 index more than 50% was considered as high heterogeneity [33]. Funnel plot and Egger's regression intercept were used to assess the publication bias. Furthermore, the meta-regression was used to investigate the relationship between SMD of AMH level before and after the intervention in the intervention and control groups using the year of publication, sample size, mean age, quality evaluation score, and mean difference of BMI before and after the intervention. The comprehensive meta-analysis software (version 2) was employed for meta-analysis. $P < 0.05$ was considered as statistically significant.

GRADE evaluation

The evidence outcome was further evaluated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach recommended by the guidelines including study limitations, consistency between studies, directness (ability to generalize), precision (sufficient or precise data) of results, and publication bias. Five levels of evidence may then be developed for pooled outcome as follows: high, moderate, low, very low quality of evidence, and no evidence. As we only included RCTs in grading, decisions to downgrade the quality of studies were recorded by footnotes to describe the reasons.

Results

The summary of how articles enter the meta-analysis

The systematic literature search retrieved 277 articles, of which 168 duplicates were eliminated. After screening the title and abstract of the articles, 93 irrelevant studies were removed, and 4 articles were excluded by reviewing their full text, due to not meeting eligibility criteria. Finally, 12 articles with inclusion criteria were included in the meta-analysis. Figure 1 illustrates the PRISMA 2009 flow diagram (Fig. 1).

General characteristics of the studies

The total sample size was 332 in the intervention group and 245 in the control group. The oldest study was conducted in 2011 and the most recent study in 2021. The highest number of studies was performed in Iran with 5 articles. The study of Vosnakis et al. [26] with 61 subjects in the intervention group had the highest sample size. The majority of studies used ELISA as diagnostic tool for AMH assay. Table 3 illustrates the characteristics of studies included in the systematic review and meta-analysis (Table 3).

Meta-analysis of mean difference and standardized standard deviation before and after physical activities in intervention and control groups based on RCT studies

According to the results of the meta-analysis of RCTs, there is a high heterogeneity between studies ($I^2 = 80.78$), so the random effects model was used to combine the studies. As a result of combining the studies, the AMH level index after physical activities in the intervention group showed a significant decrease of 0.66 ± 0.304 (95% confidence interval) more units than the control group, which was statistically significant ($P < 0.05$). The forest plot (Fig. 2) shows the estimate obtained from the

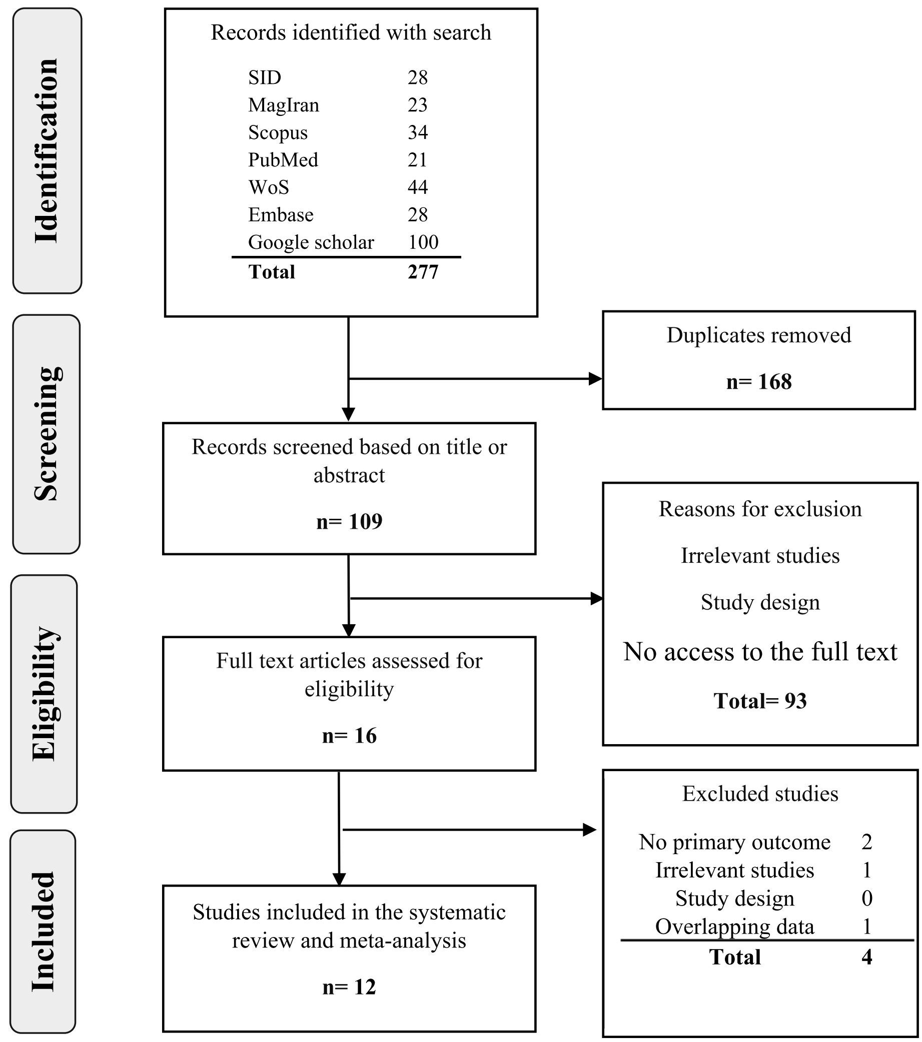

Fig. 1 The Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA 2009) flow diagram of study inclusion

combination of all studies and the standardized mean difference in each study. The 95% confidence interval is indicated by the horizontal line of each square (Fig. 2).

Meta-analysis of mean difference and standard deviation before and after exercise in the intervention and control groups

Based on the results of the present meta-analysis and considering a high heterogeneity among included studies (I^2 = 69.59), the random effects model was used to combine the effect size of the studies. As a result of the combination of studies, the AMH level after exercise in the intervention group indicated a statistically significant decrease of 0.517 ± 0.169 (95% CI) more than that in the control group ($P < 0.05$). The forest plot demonstrates the SMD ± 95% CI of each study and the pooled SMD ± 95% CI of all included studies (Fig. 3). In the present study, the largest difference between the SMD of AMH level in the control and intervention groups was 2.12 ± 0.32, related to the study of Leonhardt et al. [31]. According to Egger's regression intercept, there was no publication bias at the 0.1 level in the studies ($P = 0.949$) (Fig. 4). The results of sensitivity analysis revealed that the pooled estimation does not change significantly with the elimination of any of the studies (Fig. 5).

The relationship between the year of publication, sample size, mean age, and quality assessment score based on the JBI checklist with the SMD of AMH level before and after the intervention in the intervention and control groups was examined using meta-regression (Figs. 6, 7, 8 and 9). Results showed with increasing sample size and quality assessment score, SMD had an increasing trend (Figs. 7 and 9). In addition, a decreasing trend of the SMD of AMH level with increasing the year of publication and

Table 3 The characteristics of studies included in the systematic review and meta-analysis

Author, year (reference)	Place of study	Age (year) Intervention group	Sample size		BMI (kg/m^2)		Mean ± SD of intervention group (ng/ml)			Mean ± SD of control group (ng/ml)			Type of intervention	Type of study	Diagnostic tool
			Control group	Intervention group	Before	After	Before	After	*p*-value	Before	After	*p*-value			
Saremi and Yaghoubi 2016 [21]	Iran	28.31 ± 5.3 (18–50)	10	10	24.88 ± 1.23	25.26 ± 1.37	14.4 ± 5.2	14.1 ± 5.5	> 0.05	11.22 ± 4.1	11.6 ± 3.9	> 0.05	8 weeks of resistance training in three sessions per week (each training session includes 1 to 2 rounds of 5 to 20 repetitions with an intensity of 40 to 60% of a maximum repetition)	Semi-experimental with pre-test-post-test design	ELISA
Saremi et al., 2013 [22]	Iran	30.24 ± 4.41 (20–40)	11	11	28.29 ± 5.73	28.48 ± 6.29	14.44 ± 7.62	15.93 ± 7.74	0.2	16.44 ± 5.47	17.20 ± 6.44	-	8 weeks of aerobic exercise three sessions per week (40–45 min per session)	Semi-experimental with pre-test-post-test design and control group	ELISA
Saremi and Rajabi 2016 [23]	Iran	28.16 ± 4.29 (20–40)	10	10	32.42 ± 4.65	25.26 ± 1.37	12.3 ± 4.1	12.1 ± 4.5	> 0.05	10.36 ± 4.4	10.4 ± 3.7	> 0.05	8 weeks of aerobic exercise three sessions per week (50–60 min per session)	Semi-experimental with pre-test-post-test design	ELISA
Saremi et al., 2014 [24]	Iran	28.16 ± 4.29 (20–40)	10	10	30.01 ± 4.7	29.08 ± 4.6	10.11 ± 3.8	7.6 ± 3.6	< 0.05	15.1 ± 3.5	17.2 ± 2.8	-	8 weeks of pilates training three times a week (60 min per session)	Semi-experimental with pre-test-post-test design and control group	ELISA
Al-Eisa et al., 2017 [25]	Egypt	27.9 ± 4.1	30	30	33.45 ± 2.75	28.5 ± 2.25	10.5 ± 3.56	8.92 ± 3.23	< 0.05	9.5 ± 5.45	7.9 ± 4.25	-	12 weeks of aerobic exercise	Semi-experimental with pre-test-post-test design	ELISA
Vosnakis-1, 2013 [26]	Greece	26.95 ± 4.77	20	61	34.83 ± 6.39	31.9 ± 6.09	7.07 ± 4.86	10.87 ± 5.84	0.003	5.34 ± 1.84	5.00 ± 2.55	0.596	12 weeks of aerobic exercise	Semi-experimental with pre-test-post-test design	ELISA
Vosnakis-2, 2013 [26]	Greece	26.95 ± 4.77	20	61	34.83 ± 6.39	30.21 ± 5.78	7.07 ± 4.86	8.26 ± 4.91	0.005	5.34 ± 1.84	5.16 ± 3.11	0.963	24 weeks of aerobic exercise	Semi-experimental with pre-test-post-test design	ELISA
Hosseini et al., 2019 [27]	Iran	30.01 ± 1.70 (20–35)	20	20	27.01 ± 1.15	26.54±1.03	10.67 ± 0.75	10.4 0± 0.77	0.001	12.65 ± 1.23	12.41 ± 0.94	0.16	8 weeks of resistance exercise	Randomized clinical trial (registration: not reported)	ELISA
Nybacka Nybacka et al., 2013 [28]	Sweden	31.3 ± 4.8	14	17	34.8 ± 5.2	34.1 ± 5.7	6.6 ± 3.9	6.6 ± 4.2	-	7.1 ± 4.3	6.1 ± 4.0	-	16 weeks three times a week resistance exercise	Randomized clinical trial (registration: ISRCTN48342048)	ELISA
Wu et al., 2021 [29]	China	32.7 ± 3.2	19	19	23.8 ± 3.0	21.3 ± 2.1	17.6 ± 5.1	14.8 ± 3.6	0.021	18.4 ± 5.8	17.9 ± 4.7	0.684	12 weeks of aerobic exercise	Randomized clinical trial (registration: not reported)	ELISA

Table 3 (continued)

Author, year (reference)	Place of study	Age (year) Intervention group	Sample size		BMI (kg/m^2)		Mean ± SD of intervention group (ng/ml)			Mean ± SD of control group (ng/ml)			Type of intervention	Type of study	Diagnostic tool
			Control group	Intervention group	Before	After	Before	After	*p*-value	Before	After	*p*-value			
Moran et al., 2011 [30]	Australia	30.6 ± 7.1	7	8	33.1 ± 3.6	32.9 ± 4.0	5.91 ± 2.05	4.59 ± 1.53	0.007	5.85 ± 2.3	5.0 ± 2.1	-	12 weeks of resistance exercise 3 times a week and 1-h session	Randomized clinical trial (registration: ISRCTN84763265)	-
Leonhardt et al., 2015 [31]	Sweden	29.5 (21–37)	29	30	26.6 (20.4–44.3)	24.5 (20.6–37.6)	6.70 ± 2.26	3.98 ± 1.56	-	6.60 ± 2.3	8.28 ± 2.5	-	16 weeks of resistance exercise 3 times a week and 1-h session	Randomized clinical trial (registration: ClinicalTrials.gov (identifier NCT00484705))	ELISA
Nidhi et al., 2013 [32]	India	16.22 ± 1.13	45	45	20.39 ± 2.00	20.41 ± 2.07	6.25 ± 3.79	3.73 ± 2.25	0.006	6.45 ± 3.91	5.57 ± 2.79	-	12 weeks, yoga exercises in a 1-h session once a day	Randomized clinical trial (registration: REFCTRI-2008 000291)	-

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hosseini, 2019	0.035	0.316	0.100	-0.585	0.655	0.110	0.912
Nybacka, 2013	0.243	0.362	0.131	-0.467	0.953	0.671	0.502
Wu, 2021	0.549	0.331	0.109	-0.098	1.197	1.662	0.096
Moran, 2011	0.259	0.520	0.270	-0.760	1.277	0.498	0.618
Leonhardt, 2015	2.120	0.325	0.106	1.482	2.758	6.514	0.000
Nidhi, 2013	0.647	0.216	0.047	0.223	1.071	2.992	0.003
	0.660	0.304	0.093	0.063	1.256	2.167	0.030

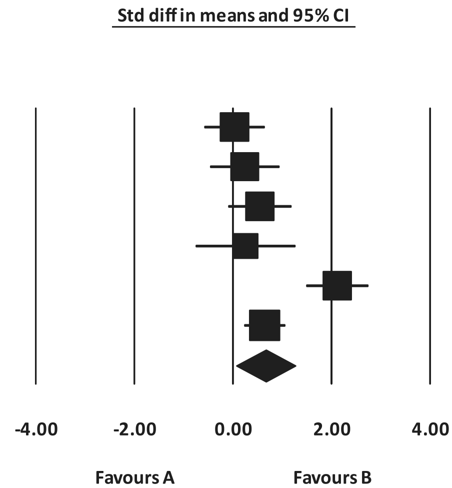

Fig. 2 Forest plot of the studies included in the meta-analysis before and after the intervention of the control group and the intervention group based on RCTs

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Saremi-1, 2016	0.143	0.448	0.201	-0.735	1.020	0.319	0.750
Saremi-2, 2013	0.103	0.427	0.182	-0.734	0.939	0.240	0.810
Saremi-3, 2016	0.058	0.447	0.200	-0.818	0.935	0.130	0.896
Saremi-4, 2014	1.430	0.501	0.251	0.447	2.412	2.853	0.004
Al-Eisa, 2017	0.005	0.258	0.067	-0.501	0.511	0.021	0.984
Vosnakis-1, 2013	0.790	0.265	0.070	0.270	1.309	2.980	0.003
Vosnakis-2, 2013	0.302	0.259	0.067	-0.206	0.809	1.166	0.244
Hosseini, 2019	0.035	0.316	0.100	-0.585	0.655	0.110	0.912
Nybacka, 2013	0.243	0.362	0.131	-0.467	0.953	0.671	0.502
Wu, 2021	0.549	0.331	0.109	-0.098	1.197	1.662	0.096
Moran, 2011	0.259	0.520	0.270	-0.760	1.277	0.498	0.618
Leonhardt, 2015	2.120	0.325	0.106	1.482	2.758	6.514	0.000
Nidhi, 2013	0.647	0.216	0.047	0.223	1.071	2.992	0.003
	0.517	0.169	0.028	0.187	0.848	3.066	0.002

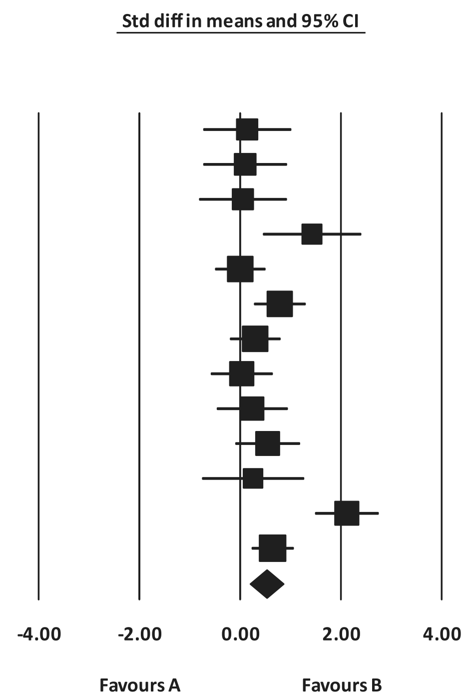

Fig. 3 Forest plot of studies included (RCTs and non-RCTs) in the meta-analysis before and after the intervention of the control group and the intervention group

the mean age was observed (Figs. 6 and 8). However, the trend of any of these potential factors was not statistically significant ($P > 0.05$).

Subgroup analysis

Due to the high between-study heterogeneity, the subgroup analysis was used based on the type of exercise, BMI before the intervention, AMH level before the intervention, and the number of weeks of intervention. Based on the results of the subgroup analysis, exercise had a positive effect of both resistance and aerobic training. Women with $BMI < 25$ kg/m^2 can more slightly benefit from the exercise more than women with $BMI \geq 25$. AMH (≥ 10 ng/mL) is before the intervention (Table 4).

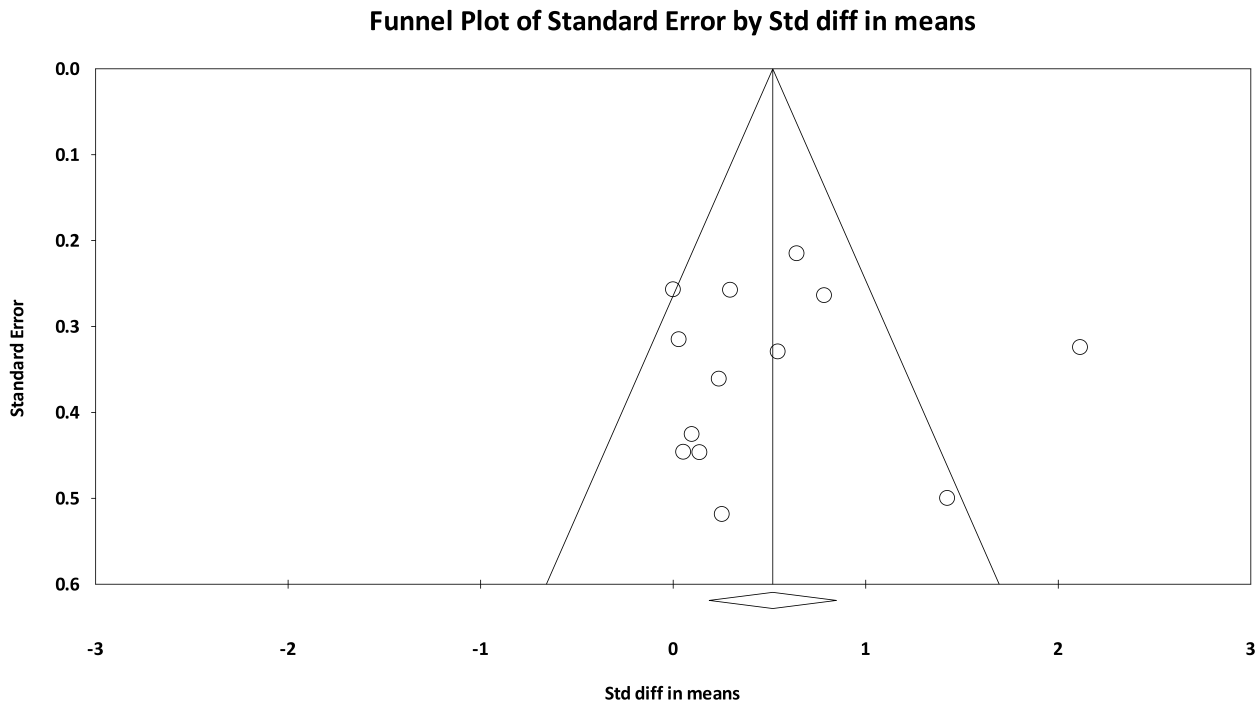

Fig. 4 The funnel plot of (RCTs and non-RCTs) studies included in the meta-analysis before and after the intervention in the control and intervention groups

Study name	Statistics with study removed						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Saremi-1, 2016	0.543	0.178	0.032	0.194	0.892	3.052	0.002
Saremi-2, 2013	0.547	0.178	0.032	0.198	0.896	3.075	0.002
Saremi-3, 2016	0.549	0.177	0.031	0.202	0.896	3.099	0.002
Saremi-4, 2014	0.462	0.171	0.029	0.128	0.797	2.709	0.007
Al-Eisa, 2017	0.569	0.177	0.031	0.222	0.916	3.212	0.001
Vosnakis-1, 2013	0.490	0.185	0.034	0.128	0.852	2.653	0.008
Vosnakis-2, 2013	0.538	0.186	0.035	0.174	0.903	2.894	0.004
Hosseini, 2019	0.561	0.178	0.032	0.211	0.910	3.144	0.002
Nybacka, 2013	0.540	0.181	0.033	0.185	0.894	2.984	0.003
Wu, 2021	0.514	0.184	0.034	0.154	0.874	2.801	0.005
Moran, 2011	0.533	0.177	0.031	0.185	0.880	3.001	0.003
Leonhardt, 2015	0.384	0.105	0.011	0.177	0.590	3.648	0.000
Nidhi, 2013	0.503	0.191	0.036	0.129	0.878	2.635	0.008
	0.517	0.169	0.028	0.187	0.848	3.066	0.002

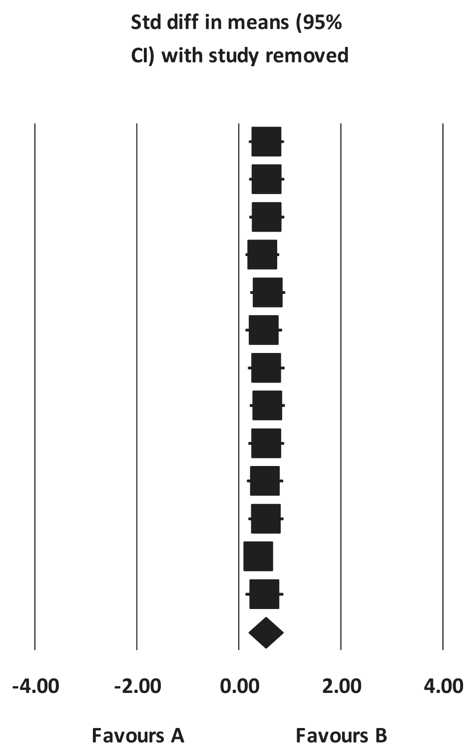

Fig. 5 Sensitivity analysis chart before and after the intervention of the control group and the intervention group based on the random effects model

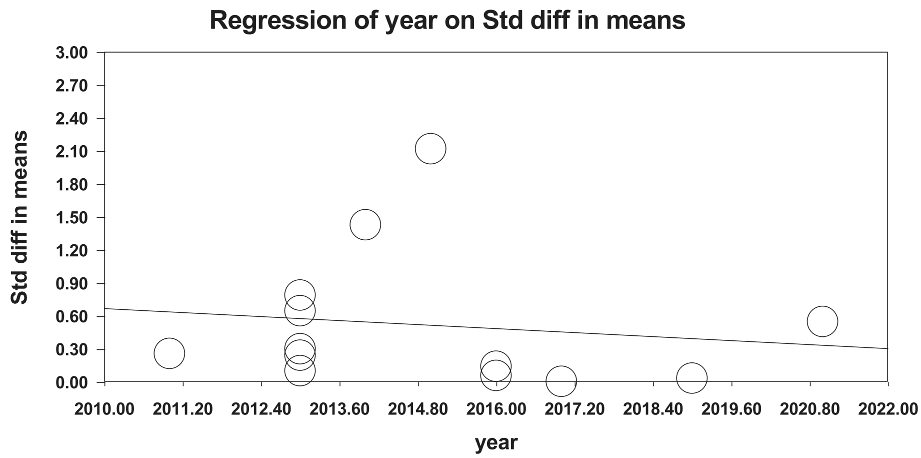

Fig. 6 The meta-regression of the relationship between the year of the publication and the standardized mean difference before and after the intervention in the control and intervention groups

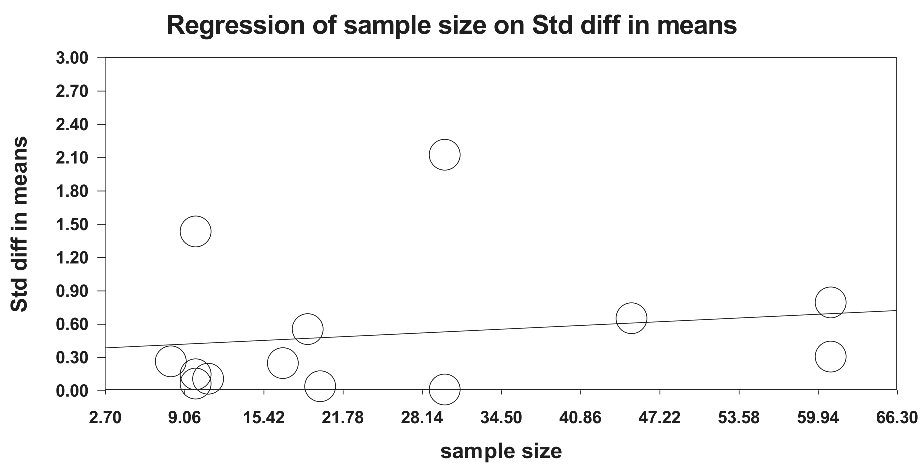

Fig. 7 The meta-regression of the relationship between the sample size and SMD before and after the intervention in the control and intervention groups

Quality of the evidence

We graded the quality of the evidences as very low for AMH outcome. According to the risk of bias summary. There was a high risk of bias regarding study design and incomplete reporting. The nature of exercise intervention made it impossible to use a double-blind study design. In addition, most of the studies did not mention blinding of assessors, but others were unclear. In addition, a few studies explained a method to generate a random allocation sequence and reported a method to reach allocation concealment. From the results of the meta-analysis, we found that no study had a total of more than 400 participants [34]. In summary, the results of this meta-analysis should be interpreted with caution; the GRADE evidence profile is available at Table 5.

Discussion

The present study aimed to estimate the effect of exercise on AMH levels in patients with PCOS using systematic review and meta-analysis. After combining the data from the 12 articles, the AMH level after exercise in the intervention group was significantly lower than that in the control group, indicating the positive effect of exercise on reducing AMH levels. Various systematic review and meta-analysis studies reported the positive effects of exercise and regular exercise on the management of PCOS symptoms, regular menstruation, and fertility [35, 36]. Exercise reduce total body fat, which stores estrogen and produces steroid hormones [36]. Researchers believe that regular exercise is a healthy and natural method for management of PCOS, apart from clinical therapies [37]. In

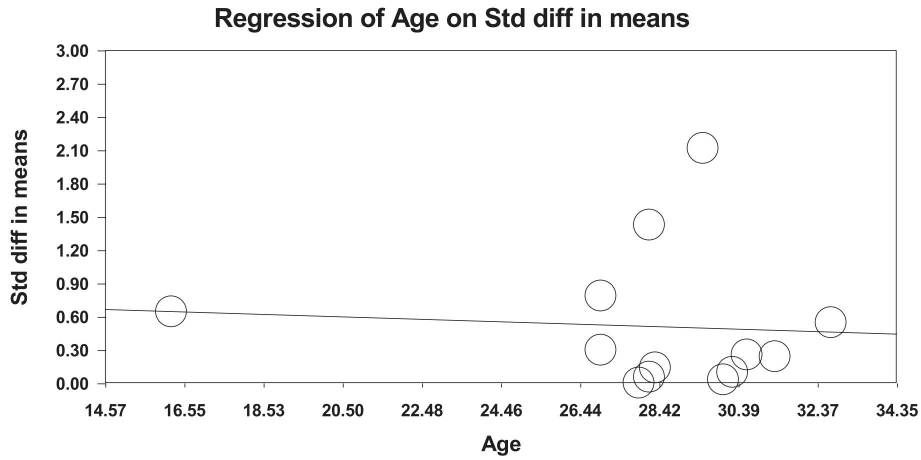

Fig. 8 The meta-regression of the relationship between mean age and SMD of AMH before and after the intervention in the control and intervention groups

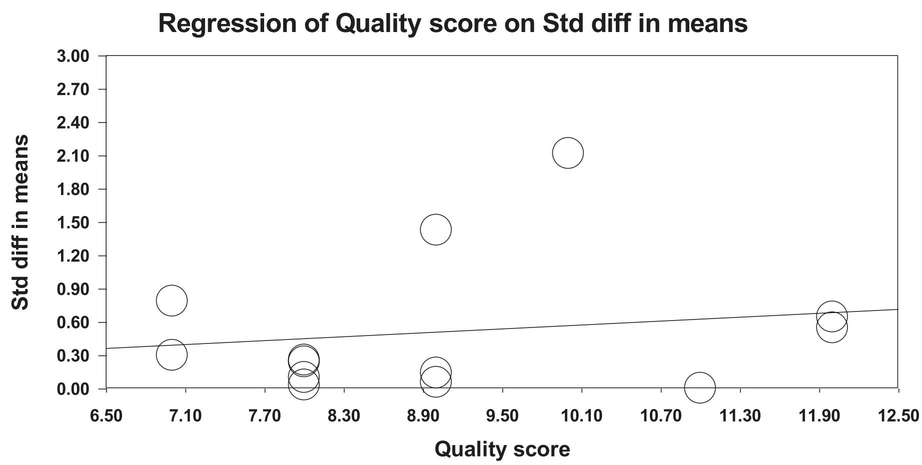

Fig. 9 The meta-regression of the relationship between the quality evaluation score of JBI checklist and SMD before and after intervention in the control and intervention groups

Table 4 Subgroup analysis of the included studies according to type of exercise, BMI, number of weeks of intervention, and AMH

Subgroups		Number of articles	Sample size		I^2	Egger's regression intercept	Std. diff. in means (lower limit — upper limit)	Standard error
			Intervention group	Control group				
Type of exercise	Resistance	5	96	92	85.06	0.633	0.63 (0.17–1.43)	0.40
	Aerobic	6	181	98	4.43	0.604	0.30 (0.0–0.56)	0.13
BMI before intervention	≤ 25 (kg/m^2)	3	74	74	0.000	0.235	0.55 (0.22–0.88)	0.16
	> 25 (kg/m^2)	10	258	171	76.55	0.815	0.53 (0.09–0.97)	0.22
Number of weeks of intervention	8 weeks	5	61	61	37.12	0.282	0.26 (0.10–0.62)	0.23
	12 weeks	4	118	76	37.16	0.981	0.41 (0.11–0.71)	0.20
	16 weeks	2	47	43	93.26	-	1.18 (0.65–3.02)	0.93
AMH before intervention	≤ 10 (ng/ml)	6	222	135	78.99	0.945	0.74 (0.22–1.27)	0.27
	> 10 (ng/ml)	7	110	110	25.68	0.248	0.23 (0.03–0.50)	0.13

Table 5 GRADE evidence profile of exercise vs. no exercise in women with PCOS on reduction of AMH level

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Exercise**	**No. of exercise**	**Relative (95% *CI*)**	**Absolute (95% *CI*)**		
Anti Mullerian hormone (follow-up: mean 12.33 weeks)												
6	Randomized trials	Very serious[a]	Very serious[b]	Not serious	Serious[c]	None	139	134	-	SMD **0.66 SD more** (0.06 more to 1.26 more)	⊕◯◯◯ Very low	Critical

CI confidence interval, *SMD* standardized mean difference

[a] there was a high risk of bias regarding study design and incomplete reporting. Random sequence generation, allocation concealment, and binding in most the studies are not mentioned or are unclear

[b] downgraded two level because I^2 was more than 80%

[c] downgraded one level because of imprecision; the total number of the participants is < 400

fact, exercise decreases the levels of androgen and other estrogens, as well as 17-beta-estradiol, improves menstrual frequency [38], and increases ovarian hormones. Accordingly, exercise can improve the mechanisms associated with ovarian dysfunction [30].

Some studies demonstrated that performing exercise independent of weight change can help the improvement of metabolic indices. The reduction of oxidative stress and systemic inflammation, improvement of hormonal balance and adipokines secreted from adipose tissue, and the efficiency of cellular metabolism are some of the mechanisms of exercise [39, 40].

However, the effect of exercise and regular exercise on the management of all PCOS symptoms has not always been positive and significant. Benham et al. (2018) in their meta-analysis study reported that there were insufficient published data to describe the effect of exercise interventions on ovulation quantitatively [35].

The highest quality assessment score based on JBI checklist criteria was related to the studies of Wu et al. [29] and Nidhi et al. [32], which indicated that exercise significantly decreases AMH levels in women with PCOS. Furthermore, the results of meta-regression revealed that the positive effect of exercise on reducing the AMH levels enhances by improving the methodological quality of studies, indicating that if the study was conducted based on the robust studies, the effect of exercise may be greater. The meta-regression also showed that age was not the determinants of heterogeneity in changes of the AMH level. However, it was a nonsignificantly decreasing trend of the SMD of the AMH level with increasing age. Thus, the age-related effect of exercise on the level of AMH in PCOS women remains still changeable. However, a recent scoping review showed that resistance training has greater effect on the health outcomes, such as visceral adiposity and improved insulin resistance.

Based on the subgroup analysis, resistance training has a positive effect on AMH levels in women with PCOS. Resistance training is a form of exercise with important physiological effects on the body. As reported in studies, strength training increases strength and muscle mass, improves insulin sensitivity, decreases adipocyte (visceral fat), and reduces the risk of metabolic syndrome [39]. A recent review shows that resistance training is a non-pharmacological management to improve metabolic parameters in individuals with metabolic syndrome and in some cases even acts better than aerobic exercise alone [40]. However, we can claim performing the aerobic training had a more valid result with a decrease of 0.30 due to low heterogeneity ($I^2 = 4.43$) after subgroup analysis. The subgroup analysis based on BMI with cutoff of 25 showed that the obese or overweight women with PCOS can significantly benefit from the exercise in reduction of the AMH level. The pooled effect size, however, is not valuable enough due to more than 76% heterogeneity. However, the exercise could decrease the AMH level by 0.55 in women with $BMI \leq 25$, considering the 0.0% heterogeneity. Although this result was extracted from only 3 studies with 148 women who were in group with $BMI \leq 25$, it is recommended that healthcare providers and physicians integrate exercise interventions further to the medication to get better result in reduction of AMH level. The results of subgroup analysis demonstrated that in women with PCOS, performing 8-week exercise yielded the less reduction of AMH than that of 12 weeks exercise program. It may be related to the effect of exercise on the lipid profile. As the duration of exercise influences the changes in lipid profile, raising the high-density lipoprotein (HDL) level and significantly reducing low-density lipoprotein (LDL) level can be achieved by increasing the frequency of training sessions per week (more than 3 sessions per week) or increasing the duration of each session or training period. As we observed a high heterogeneity in subgroup of 16 weeks, this argument is more plausible when we compare the 8-week exercise group and the 12-week exercise group in subgroup analysis. After subgroup analysis, both groups have reported a low heterogeneity equal to almost 36%. Therefore, it is documented that 12 weeks of exercise are more effective in reducing AMH than 8 weeks of exercise.

Although exercise have positive impact on women with PCOS who had AMH level equal and less than 10 ng/ml, given the high heterogeneity of included studies in this subgroup, we cannot comment on how much this effect is. But we observed a 0.24 decrease in women with AMH level more than 10 ng/ml with low heterogeneity of included studies (almost 25%). Therefore, we recommend the aerobic exercise for achieve a decrease of 0.24 ng/ml AMH level in this subgroup.

Given the high prevalence of PCOS in the women [2, 3] and its consequences and complications on their quality of life, cost-effectiveness of exercise, and its effect on physical and mental health status, it is recommended that healthcare providers and policy makers should pay more attention to promote exercise in developing infrastructure for exercise facilities. However, we graded the quality of the evidences as very low. Therefore, we need to have more high-quality RCTs to observe a more precision effect size.

The results of this study should be considered some limitations, including the lack of uniform reporting of articles, nonrandom selection of some samples, lack of similarity in study design, low sample size for meta-analysis in some subgroups, and the lack of access to the full text of articles presented at conferences. Except for two studies (29 and 30), sample sizes of included were small, limiting the generalizability to the wider PCOS population. Furthermore, there was a few studies on the effect of some types of exercise, such as yoga and pilates. It is suggested to conduct robust trials to determine the minimum level of exercise in terms of frequency, intensity, and duration to improve AMH levels in women with PCOS.

Conclusion

The results of the present systematic review and meta-analysis illustrated that either strength exercise or aerobic exercise decreases the AMH level in PCOS women. Exercise training for 12 weeks (rather than 8 weeks) has a more potential advantage to reduce the excessive expression of AMH levels in women with PCOS. The exercise in patients with $BMI \leq 25$ kg/m^2 decreases the AMH level up to 0.55 ng/ml. Therefore, it is recommended to include exercise in the treatment programs of PCOS patients. However, this effect is supported by very low quality of evidence. Well-designed and high-quality trials are needed to confirm developing the quality of evidence in this area.

Abbreviations

SID: Scientific Information Database; WoS: Web of Science; MeSH: Medical Subject Headings; JBI: Joanna Briggs Institute; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; AMH: Anti-Mullerian hormone; PCOS: Polycystic ovary syndrome.

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Authors' contributions

MK and FR contributed to the design, and MK and MR participated in most of the study steps. MK and MR prepared the manuscript. FR and MK assisted in designing the study and helped in the interpretation of the study. The authors read and approved the final manuscript.

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Availability of data and materials

Datasets are available through the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval was received from the ethics committee of deputy of Research and Technology, Kermanshah University of Medical Sciences (IR.KUMS.REC.1400.576).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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