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Effect of metformin on anti-mullerian hormone levels in women with polycystic ovarian syndrome: a systematic review and meta-regression analysis of randomized controlled trials with

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Abstract

Background Several interventional studies have evaluated the potential anti-Mullerian hormone (AMH)-reduction effect of metformin. However, the results are still contradictory. In order to obtain a better viewpoint from them, this study aimed to comprehensively investigate the effects of metformin on AMH in the women with polycystic ovarian syndrome (PCOS).

Methods Scopus, PubMed/Medline, Web of Science, Cochrane, and Embase databases were searched using standard keywords to identify all controlled trials investigating the AMH levels following metformin administration. Pooled weighted mean difference and 95% confidence intervals were achieved by random-effects model analysis for the best estimation of outcomes.

Results Sixteen studies with 484 participants' were included in this article. The pooled findings showed that AMH levels in the single arm clinical trials were significantly reduced (pooled WMD of -3.06 ng/ml; 95% confidence interval [CI] -4.03 to -2.10; $P < 0.001$) after use of metformin. Furthermore, compared to the control group, in randomized clinical trials, a reduced significant effect on AMH levels was observed following use of metformin (pooled WMD of -3.47 ng/ml; 95% CI -7.14 to -0.19; $P = 0.047$). Furthermore, higher reduction in the AMH levels with a metformin dosage ≤ 1500 mg/day and duration of treatment ≤ 12 weeks when compared to higher dosages and duration of intervention, observed in this meta-analysis.

Conclusions In conclusion, results this meta-analysis of clinical trials confirms the beneficial effect of the treatment with metformin in the reduction of the AMH levels in women.

Keywords Metformin, AMH, Women, PCOS, Meta-analysis

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Introduction

Anti-Mullerian hormone (AMH) is a dimeric glycoprotein member of the superfamily of peptide growth/differentiation factors as such the transforming growth factor- β (TGF- β) [1]. In women, AMH is expressed by the granulosa cells and secreted into the circulation from birth to menopause. At birth, levels of AMH are hard to detectable, however, it increases significantly at puberty, slowly reducing during the reproductive period, until it become undetectable at menopause [2].

In addition to being an ovarian reserve marker, AMH plays a potential role in the pathophysiology diagnosis and treatment of several ovarian pathologies, including polycystic ovary syndrome (PCOS) [2, 3]. In PCOS, AMH levels are higher due to an increase in the number of antral follicles and in the production pre antral follicle. Although not yet accepted as a diagnostic criterion for PCOS, AMH is very useful in anticipating hyper-responsiveness to ovarian stimulation. AMH neutralizes the action of follicle-stimulating hormone (FSH) and thus may play a role in PCOS ovulatory disorders [4]. Moreover, in PCOS, increased levels of circulating insulin contribute to hyperandrogenism, which causes a derangement in folliculogenesis, thereby contributing to polycystic ovary morphogenesis and higher than normal AMH [5, 6].

Due to the role of the insulin resistance in the pathophysiology of PCOS and increased of the AMH levels, insulin-sensitizing drugs as such metformin have been used in the treatment of this syndrome, having been postulated that such agents would reduce the insulin resistance and, consequently, AMH levels in women with PCOS [5, 7].

Yin et al. [8] performed a meta-analysis to assess the effect of using seven types of drugs, including metformin, on AMH levels in women of reproductive age, which showed a significant reduction in AMH levels in women with PCOS after treatment with metformin. However, we identified additional studies with potential for inclusion in a new meta-analysis, which may increase the robustness and accuracy of the analyses. Furthermore, to our knowledge, to date, no systematic review and meta-analysis including meta-regression analysis has been published on the topic.

To conduct a systematic meta-analysis investigating the influence of metformin on anti-Mullerian hormone (AMH) levels in women, utilizing data from 16 relevant studies with a total of 484 participants. The primary goal is to assess the overall impact of metformin on AMH levels, considering both single-arm and randomized clinical trials. Additionally, the objective includes examining the dosage and duration-dependent effects of metformin treatment on AMH reduction, with a specific focus on lower dosages (≤ 1500 mg/day) and shorter durations

(≤ 12 weeks). The study aims to provide insights into the potential benefits of metformin in lowering AMH levels among women and encourages further research and individualized clinical considerations to enhance the understanding of these observed effects.

Methods

Search strategy

The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) criteria were followed for conducting this study [9]. Without regard to language or time restrictions, a thorough search was carried out in the PubMed/MEDLINE, Web of Science, SCOPUS, and Embase databases from the beginning to March 2023. Additionally, similar papers and gray literature were considered in the search. Medical subject headings (MeSH) and Emtree (Embase subject headings) were selected to search the online databases, as follow: ("Metformin" OR "Dimethylbiguanidine" OR "Glucophage" OR "Metformin HCl" OR "Metformin Hydrochloride") AND ("Anti-Mullerian Hormone" OR "AMH" OR "Mullerian Inhibiting Factor" OR "Mullerian Inhibitory Substance" OR "Mullerian Inhibiting Hormone" OR "Mullerian Regression Factor") AND ("Clinical Trials as Topic" OR "Cross-Over Studies" OR "Double-Blind Method" OR "Single-Blind Method" OR "Random Allocation" OR "Clinical Trial"). The reference lists of the publications retrieved and linked review studies were manually searched to identify potentially overlooked qualifying trials.

Eligibility criteria

Using titles, abstracts, or the complete texts of the research, two writers separately removed duplicate articles before finding and reviewing relevant publications. In the end, the papers were separated based on the following standards: (1) Randomized or single arm clinical trials studies; (2) metformin has been given as an intervention in individual's aged 12 and over with PCOS (PCOS, was diagnosed based on the Rotterdam consensus statements criteria, and included at least two of the following three characteristics: menstrual irregularity due to oligo and/or anovulation (having an interval of >35 days between menstrual periods and/or amenorrhea, described as the absence of vaginal bleeding for at least six months), polycystic ovaries morphology on ultrasound exam (12 or more small follicles in an ovary), and clinical symptoms or biochemical markers of hyperandrogenism and exclusion of other etiologies [10]); and (3) baseline and post in both group (intervention and control) AMH was recorded. The most recent or longest follow-up period was used when a research revealed results at more than one follow-up time. Studies with duplicated data, studies with ambiguous information,

causes of heterogeneity, a pre-defined subgroup analysis based on the dosage and duration of the intervention were conducted. A sensitivity analysis was done to determine the contribution of each research to the overall mean difference. In order to establish if there was publication bias, we utilized the official Egger's test [16].

Results

Figure 1 depicts a flowchart of the research selection process with exclusion criteria. This value indicates that the aforementioned electronic databases generated 684 articles. After removing publications with duplicate research, there were 495 total. Following an assessment of the research's titles and abstracts, 453 papers were dropped since they didn't meet the inclusion requirements. 42

articles were found utilizing the full-text search during the secondary screening. For the reasons listed above, 26 of the investigations were dropped. Finally, 16 [5, 17–31] papers with 19 treatments arm were included in the quantitative meta-analysis since they matched the qualifying requirements.

Study characteristics

The features of the pooled articles are shown in Table 2. Our surveys reveal that three studies were conducted in the American continent, 2 studies in the Asian continent and the rest of the articles in the European continent. All articles were published between 2005 and 2018 and follow up intervention ranged from 8 to 48 weeks. The mean age of participants ranged from 15.2 to 32.06

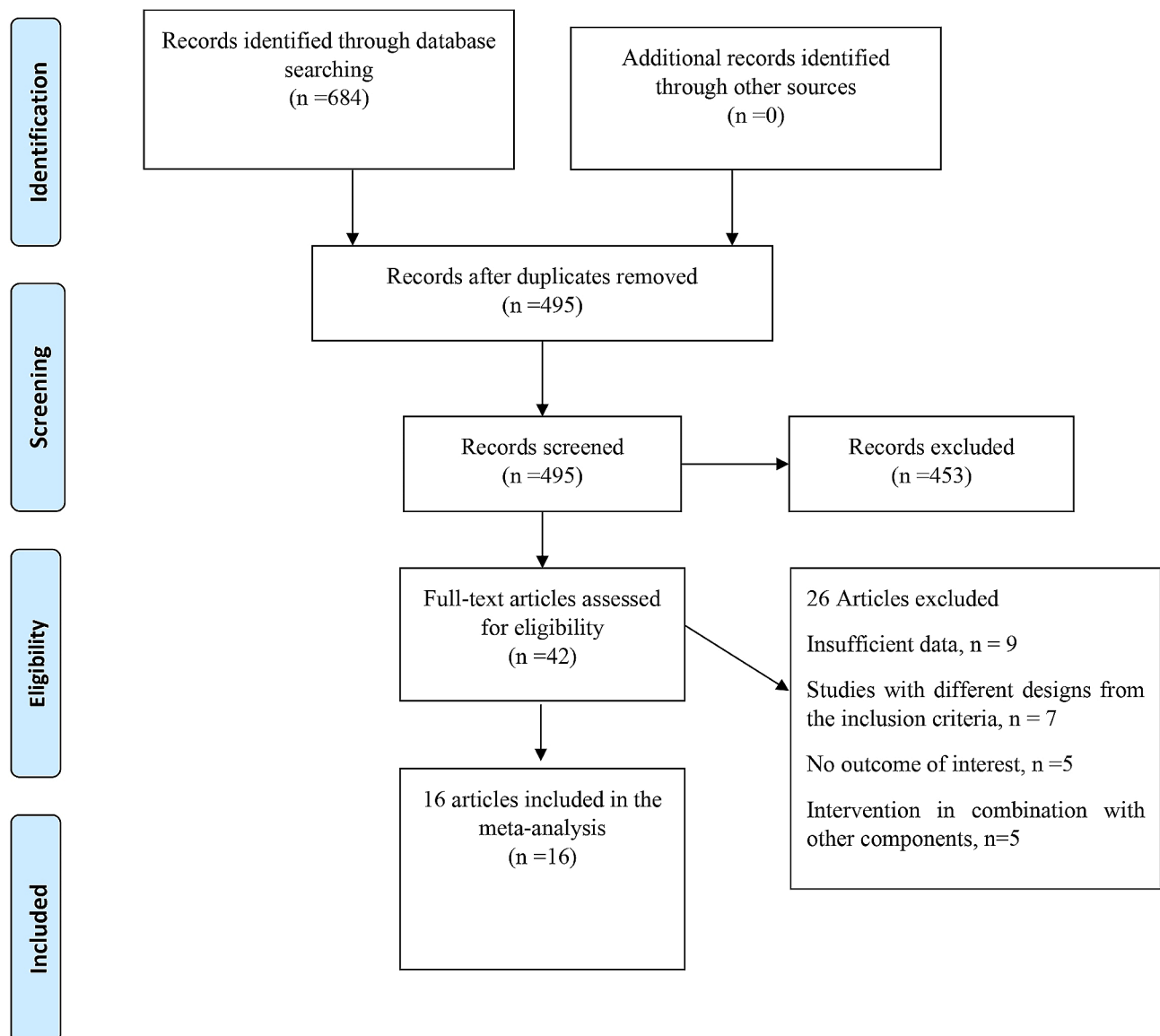


Fig. 1 Flow chart of the included studies, including identification, screening, eligibility and the final sample included

Table 2 Characteristics of eligible studies

Author	Publication Year	Country	Study Design	Mean Age year	Sample Size intervention	Sample Size control	Duration of intervention (Weeks)	Dose of intervention (mg/day)	Type of control	Mean BMI
Foroozanfard et al.	2017	Iran	Single arm clinical trial	25.3	30	-	8	1500	-	26.1
Tomova et al.	2011	Bulgaria	Single arm clinical trial	26.59	13	-	24	2550	-	30.73
Sauerbrun-Cutler et al.	2012	USA	Single arm clinical trial	31.5	16	-	12	1500	-	NR
Nascimento et al.	2013	Brazil	Single arm clinical trial	26.3	16	-	8	1500	-	29.1
Panidis et al.	2010	Greece	Single arm clinical trial	21.07	15	-	24	1700	-	21.56
Neagu et al.	2012	Romania	Single arm clinical trial	NR	11	-	8	2550	-	NR
Romualdi et al.	2011	Italy	Single arm clinical trial	24.4	28	-	24	1700	-	33.59
Piltonen et al.	2005	Finland	Single arm clinical trial	30.6	26	-	24	1500	-	30.1
Dursun et al.	2015	Turkey	Single arm clinical trial	15.2	20	-	24	2000	-	30.6
Fleming et al.	2005	USA	Single arm clinical trial	30.2	82	-	32	1500/2550	-	37.1
Falbo et al.	2010	Italy	Single arm clinical trial	27.4	10	-	48	1700	-	23
Wiweko et al.	2017	Indonesia	Randomized clinical trial (parallel)	28.25	20	18	48	1500	100 mg DLBS3233 DLBS3233 is a herbal medicine produced in Indonesia	28.02
Tagliaferri et al.	2017	Italy	Randomized clinical trial (crossover)	25.62	34	34	24	1700	Placebo	32.55
Chhabra et al.	2018	India	Randomized clinical trial (parallel)	28.81	35	35	24	1700	Placebo	NR
Madsen et al.	2015	Denmark	Randomized clinical trial (crossover)	31.5	45	42	12	1700	Placebo	33.7
Fabregues et al.	2010	Spain	Randomized clinical trial (parallel)	32.06	15	15	24	1700	Placebo	25.6

BMI: body mass index; N/R: not reported

years at the baseline. The doses prescribed in the studies were between 1500 and 2550 mg per day, and 11 studies were conducted with single arm clinical trial design and 5 studies were conducted as RCT. The mean BMI at the baseline level was between 21.56 and 37.1 in the studies included. In addition, all the participants in the studies were PCOS patients.

The findings of the evaluation of the eligible studies' quality are shown in Table 1. Additionally, a score of 7.7 (good quality) was determined after the NutriGrade score system was used to assess the quality of the current meta-analysis.

Meta-analysis results

Pooled findings of the meta-analysis of random-effects model indicated that AMH levels in the single arm clinical trials were significantly reduced (pooled WMD of -3.06 ng/ml; 95% confidence interval [CI] -4.03 to -2.10; $P < 0.001$) after use of metformin. Furthermore, compared to the control group, in randomized clinical trials, a reduced significant effect on AMH levels was observed

following use of metformin (pooled WMD of -3.47 ng/ml; 95% CI -7.14 to -0.19; $P = 0.047$). Also, significant heterogeneity was noted among the studies for this outcome (Cochran Q test, $P < 0.001$, $I^2 = 87.7\%$ for single arms clinical trials and Cochran Q test, $P < 0.001$, $I^2 = 92.1\%$ for randomized clinical trials). Subgroup analysis were performed to find the possible origin of heterogeneity (Figs. 2 and 3).

Subgroup analysis

We subsequently stratified the articles based on the dosage of metformin (mg) and duration of intervention (weeks) in the single arms clinical trial studies (Fig. 4). The results of subgroup analysis showed that metformin during the intervention ≤ 12 weeks (WMD: -4.42 ng/ml, 95% CI: -6.62 to -2.22, $I^2 = 84.5\%$) and with a dose ≤ 1500 mg per day (WMD: -4.71 ng/ml, 95% CI: -7.31 to -2.11, $I^2 = 81.6\%$) causes a greater decrease in AMH levels than the intervention > 12 weeks (WMD: -2.70 ng/ml, 95% CI: -3.93 to -1.46, $I^2 = 88.8\%$) and at a

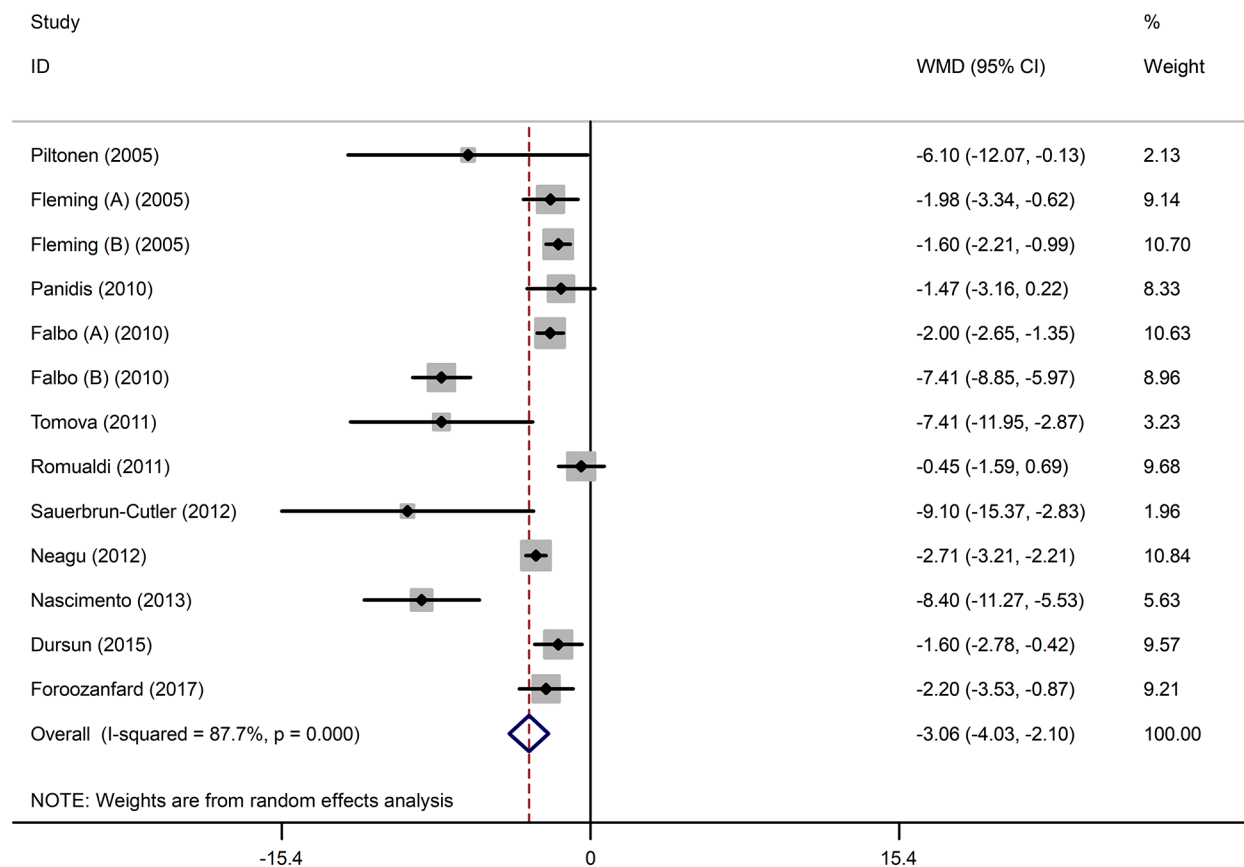


Fig. 2 Forest plot of single arms clinical trial of the effects of metformin on anti-mullerian hormone (AMH) (ng/ml) levels

dose > 1500 mg (WMD: -2.63 ng/ml, 95% CI: -3.72 to -1.53, $I^2 = 90.6\%$).

Meta-regression

Meta-regression to estimate the AMH levels regarding on absolute dosage and duration of the metformin use were performed, but no significance was observed (Coef = 0.0020715, $P = 0.446$ for dose of intervention; Coef = 0.0437079, $P = 0.490$ for duration of intervention; see Fig. 5).

Sensitivity analysis

In order to discover the effect of each article (in the single arm and randomized clinical trials) on the pooled effect size for AMH levels, we step-by-step discarded each trial from the analysis. The leave-one-out sensitivity analysis indicated the robustness of the results (Supplementary Fig. 1).

Publication bias

Evaluating the publication bias by visual inspection of the funnel, no evidence for publication bias based on the Begg's tests were detected ($P = 0.071$ for single arms

clinical trial studies for $P = 0.327$ for randomized clinical trial studies) (Supplementary Fig. 2).

Discussion

Results of meta-analyses of random-effects models indicated for both single arm clinical trials and randomized clinical trials that the use of metformin reduced AMH levels. Besides, in single-arm clinical trials, a higher reduction in the AMH levels was observed with metformin dosage ≤ 1500 mg per day and duration of treatment ≤ 12 weeks. However, in the meta-regression analysis, no significant results were observed for AMH levels in relation to absolute dosage and duration of metformin use.

Results from a previous meta-analysis, which included 12 clinical trials, showed a 1.79 ng/ml reduction (WMD: -1.79, 95%CI: -2.32 to -1.26) in AMH levels after metformin treatment in women with PCOS [8]. On the other hand, by including more studies, our meta-analysis showed even greater significant reductions in AMH levels after the use of metformin in women with PCOS, both in single-arm clinical trials and in randomized controlled clinical trials.

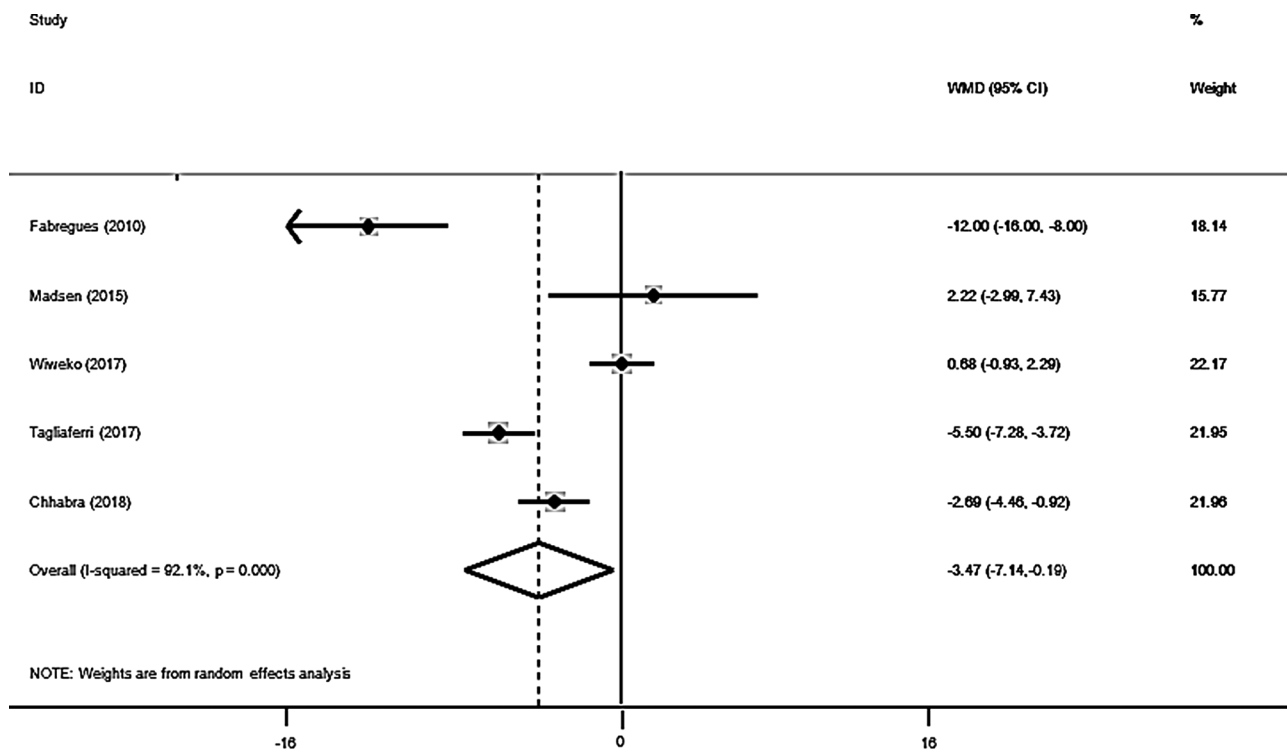


Fig. 3 Forest plot of randomized controlled trials investigating the effects of Metformin on Anti-Mullerian Hormone (AMH) (ng/ml) levels

a)

b)

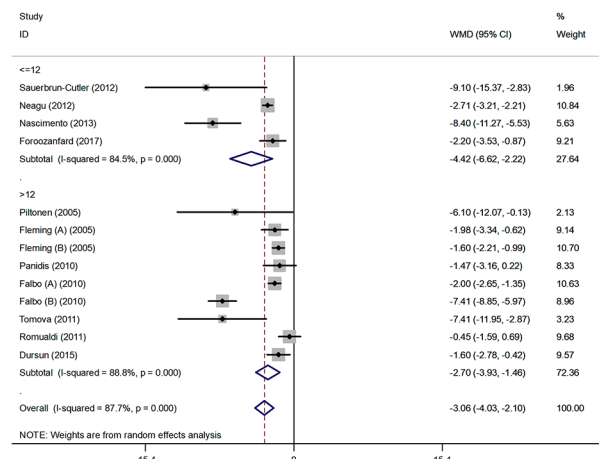
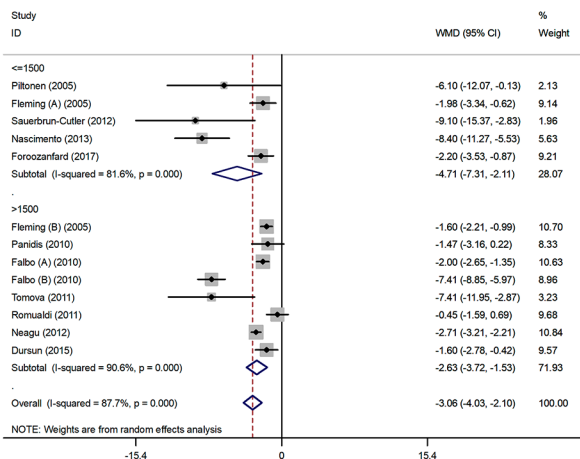


Fig. 4 Forest plot of single arms clinical trial of the effects of Metformin on Anti-Mullerian Hormone (AMH) (ng/ml) levels based on (a) dose of intervention (mg) and (b) duration of study (week)

Metformin is the most common antihyperglycemic agent, being also indicated for treatment of patients with PCOS. As a first-line treatment for insulin resistance, metformin can improve insulin sensitivity and control blood glucose levels, which can also reduce androgen levels and improve ovulation [7, 32]. In this sense, AMH levels are a useful biochemical marker of prognostic for metformin treatment in PCOS [7].

Higher reduction in the AMH levels with a metformin dosage ≤ 1500 mg/day and duration of treatment ≤ 12 weeks when compared to higher dosages and duration of intervention, observed in this meta-analysis, suggests that a dosage of until 1500 mg metformin daily for until three months would already be effective enough for considerable reduction of AMH levels in women with PCOS. It is important to highlight that treatment with

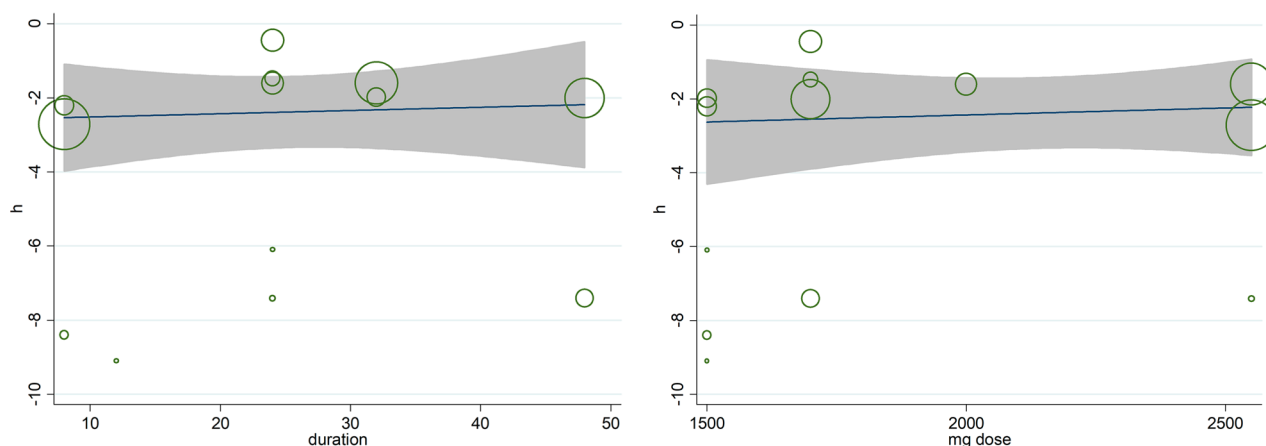


Fig. 5 Meta-regression analysis encompassing AMH changes according to the duration of intervention (Weeks), dose of intervention (mg) in the single arms clinical trial

metformin at higher doses and for a prolonged period is associated with gastrointestinal alterations [33], reinforcing that it is valid to seek the lowest effective dose and the shortest time of use to reduce adverse effects to patients. The results of subgroup analyses according to treatment dosage or duration are, however, surprising. We hypothesize that individuals with polycystic ovary syndrome (PCOS) who are prescribed greater doses of metformin or longer treatment durations may experience a more severe disease state, such as severe insulin resistance. Increasing the dosage or extending the therapy of metformin is unlikely to change its impact on AMH levels. The decrease in AMH levels due to metformin medication may not be readily apparent in these individuals. However, it is possible that excessive doses and/or prolonged use of metformin could have side effects that hinder its effectiveness in normalizing AMH levels. These subgroup analyses suggest that the severity of disease in PCOS patients can predict the effectiveness of metformin treatment.

No significant results in the meta-regression analysis, in turn, indicates that the relation of the absolute dosage and use duration of metformin with AMH levels in patients with PCOS is not linear, suggesting that there is not a biological gradient in this relation.

Women with PCOS have AMH serum levels that are 2–3 times greater than those of healthy women [34, 35]. Granulosa cells of pre-antral and small antral follicles mostly release this hormone. Due to enhanced specific secretion and increased follicle numbers, there may be more of this hormone in the blood than usual [34, 36]. Insulin stimulates the activation of primordial follicles, according to research conducted on animals [37]. Pituitary gonadotropins are partially required for the activation of primordial follicles, according to investigations on hypophysectomized animals [38]. Another prevalent

component that may be linked to PCOS and contribute to anovulation, hyperandrogenism, and a rise in AMH in this condition is hyperinsulinemia [39]. AMH inhibits the activation of primordial follicles [40]. Thus, metformin and other insulin-sensitizing medications are utilized by the majority of PCOS-afflicted females [29].

The current study has some strengths despite its limitations, including a rigorous methodology based on the PRISMA guidelines, a thorough literature search that included multiple independent databases, separate and duplicate searches, selection of the selected studies, and data extraction, as well as the use of a third party to resolve disagreements. Additionally, the current study probably had the biggest impact size for each outcome evaluated at PCOS.

The following are limitations. First off, the accuracy of the subgroup analysis of GnRH-a may have been compromised because we were unable to get in touch with several authors to gather the original data. Second, even though we were able to find pertinent publications in several databases, there are certain unpublished data that we are still unable to access. Thirdly, it is challenging to control the confounding factors because original research included a variety of control groups, including healthy women, infertile women, elderly women, and women with varied PCOS diagnostic criteria. Other limitations of this study include the low quality of reviewed articles, lack of examination of subtypes of PCOS, as well as some confounding factors affecting the disease, such as lifestyle and use of oral contraceptives.

In conclusion, results this meta-analysis of clinical trials confirms the beneficial effect of the treatment with metformin in the reduction of the AMH levels in women, presumably by an insulin-dependent mechanism of action, which may be useful in the treatment and control of the PCOS. For clinical practice, the findings suggest

that the combination of lower daily doses of metformin (up to 1500 mg) for a shorter period (up to 3 months) is already sufficient to verify the effects of this drug on AMH levels with a better gastrointestinal tolerability, thus this dosage and duration should be preferred when treating patients with PCOS.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12902-024-01570-z>.

Supplementary Material 1

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Author contributions

A.H, and Mh.S contributed in conception, design, and statistical analysis. Mh.S, E.IM, and M.MR contributed in data collection and manuscript drafting. Mh.S and A.H supervised the study. All authors approved the final version of the manuscript.

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Data availability

Data is available upon request from the corresponding author for the article due to privacy / ethical restrictions.

Declarations

Ethics approval and consent to participate

This study was approved by the research council and ethics committee Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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