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REVIEW

Therapy with probiotics and synbiotics for polycystic ovarian syndrome: a systematic review and meta-analysis

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Abstract

Objective Several randomized controlled trials (RCTs) have investigated the use of probiotic/synbiotic in PCOS patients, without clarifying the real use in clinical practice. The aim of this meta-analysis was to evaluate the effectiveness of probiotics and synbiotics on metabolic, hormonal and inflammatory parameters of PCOS.

Methods Electronic databases (MEDLINE, Scopus, EMBASE, ScienceDirect, The Cochrane Database of Systematic Reviews and ClinicalTrials.gov) were searched from their inception until May 2019. The study protocol was registered in PROSPERO with number CRD42018111534. Randomized controlled trials (RCTs) of PCOS's women undergoing therapy at least 8 weeks with probiotics or synbiotics or without therapy were included. The primary outcomes were changes in anthropometric parameters, glucose/insulin metabolism, lipid profile, sex hormones profile, inflammation markers.

Results 587 patients were included in nine RCT. The administration of probiotic/synbiotic were associated with a significant improvement in FPG, FBI, HOMA I-R, BMI. It also modified Ferriman-Gallway, serum triglycerides, serum testosterone, hs-CRP, NO, TAC, GSH, and MDA. Subgroup analysis of the type of intervention showed that probiotics were associated with greater testosterone and FPG reduction; synbiotics administration resulted in a more pronounced decrease of the FBI. Subgroup analyses on the duration of therapy showed that, probiotic/synbiotic administration had a significantly greater effect on QUICK-I in the case of women with 12-weeks of therapy than in the 8-weeks therapy group. Nevertheless, we did not observe any significant difference was observed in terms of FBI, HOMA-IR, and FPG.

Conclusions Probiotics and synbiotics seem to either an effect on/influence metabolic, hormonal and inflammatory parameters, or can influence them. Consequently, it could lead to an improvement of fertility in PCOS.

Keywords Probiotics · Polycystic ovarian syndrome · Synbiotic · Infertility · Testosterone

Introduction

Polycystic ovary syndrome (PCOS) is a polygenic, endocrine disorder that affects women during reproductive age. It was determined that, in fact, it affects about 116 million women worldwide (3.4% of the global population). Furthermore, there is a variable prevalence in different ethnic groups (ranging from 2.2 to 26%) [1]. PCOS is associated with chronic anovulation and infertility associated with hormonal/metabolic unbalances including insulin resistance, hyperandrogenism, hypercholesterolemia and systemic inflammation [2, 3]. Recently, it was showed that the gut microbiome performs a key role in human health and disease [4]. Gut microbes offer multiple benefits to the host, including protection against pathogens and regulation of host immunity and intestinal barrier integrity [5].

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Gut microbiome regulates host metabolism, and several gut microbiome phenotypes are associated with chronic diseases [6–8]. Since gut microbiome regulates different physiologic functions which are compromised in PCOS (i.e. energy homeostasis, glucose metabolism, systemic inflammation), the gut microbiome might be involved in the pathogenesis of PCOS. In addition to studies in humans, several studies in rodent models reported a significant association between the gut microbiome and PCOS [9, 10].

According with the theory of ''Dysbiosis of Gut Microbiota'', gut microbiome can activate the host's immune system, triggering a chronic inflammatory response that impairs insulin receptor function causing a condition of insulin resistance. The resulting hyperinsulinaemia interferes with follicular development, while driving excess of androgen production by the thecal cells of ovary [11]. In addition, changes in the gut microbiome are correlated with hyperandrogenism [12, 13], suggesting that testosterone may influence the composition of the gut microbiome in women.

Probiotics and synbiotics are dietary supplements containing live microorganisms which are administrated with the purpose of restoring the gut microbiome [6, 14, 15]. Therefore, the aim of this systematic review and meta-analysis was to provide a summary of evidence on the effect of probiotics/synbiotics on metabolic, hormonal and inflammatory parameters of PCOS, to identify the effect on potential fertility mediators.

Material and methods

Study design

This is a systematic review and meta-analysis of RCTs evaluating the effectiveness of probiotics and synbiotics on biochemical, metabolic and inflammatory parameters of PCOS. We registered the study protocol in PROSPERO before the start of the literature search (registration number CRD42018111534). The review was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This is an aggregate data meta-analysis because individual data are not available in the RCTs.

Search strategy

Electronic databases (MEDLINE, Scopus, EMBASE, ScienceDirect, The Cochrane Database of Systematic Reviews and ClinicalTrials.gov) were searched from their inception until May 2019. For this meta-analysis, we only collected data from RCT. Key search terms were as follows: probiotics OR synbiotics [Mesh/Entree] AND polycystic ovarian syndrome OR PCOS.

Inclusion criteria

Language studies reported in English language.

Study designs randomized controlled trials.

Population women with PCOS according to Rotterdam criteria undergoing therapy with probiotics or symbiotics.

Intervention therapy with probiotics or synbiotics.

Timing of intervention administration of probiotics or synbiotics at least for 8 weeks.

Control group women with PCOS without therapy with probiotics or synbiotics or placebo.

Study outcomes and outcomes measures

The present study aimed initially to evaluate the effects of probiotics and synbiotics on hormonal parameters, such as serum total testosterone (ng/ml) (Reference range: 0.37–2.1), sex hormone binding globulin ([SHBG] nmol/l), free androgen index (FAI), dehydroepiandrosterone-sulfate ([DHEAS] µg/mL), follicle stimulating hormone ([FSH] IU/L) (Reference range: 0.5–61.2), luteinizing hormone ([LH] IU/L) (Reference range 2.0–22.0), LH to FSH ratio (LH/FSH). The inflammatory markers evaluated in our study were changes in serum high sensitivity C reactive protein ([hs-CRP] ng/ml), C reactive protein ([CRP] mg/dl), nitric oxide ([NO] µmol/L), total antioxidant capacity ([TAC] mmol/L), total glutathione ([GSH] µmol/L), malondialdehyde ([MDA] µmol/L), interleukin-6 ([IL-6] pg/ml), interleukin-10 ([IL-10] pg/ml), tumor necrosis factor alpha ([TNF-α] pg/ml). The main outcome about the metabolic characteristics of the studied populations showed changes in fasting plasma glucose ([FPG] mg/dl) (Reference range: < 7.0), fasting blood insulin ([FBI] µIU/mL) (Reference range: 20.9–173.8), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (Reference range < 2.0), quantitative insulin sensitivity check index (QUICK-I).

We considered as secondary outcomes: body weight (kg), assessed with minimal clothing and without shoes by standard scale to the nearest 0.1 kg., BMI (kg/m^2), calculated as Weight (kg)/Height (m^2) and normalweight defined as a BMI between 18.5–25.0, abdominal girth (cm) and modified Ferriman–Gallwey score (0–36 points., serum low-density lipoprotein ([LDL] mg/dl), very low-density lipoprotein ([VLDL] mg/dl), high-density lipoprotein ([HDL] mg/dl) (Reference range: > 1.0), total cholesterol (mg/dl) (Reference range < 5.2), triglycerides (mg/dl) (Reference range < 1.65).

Study selection and data extraction

After a full screening of titles, abstracts and full texts, the selection included studies based on the availability of information regarding the intake of probiotic/synbiotic. We successively performed a manual search of the reference lists of included studies and review articles. Titles and abstracts were screened independently by two authors (MC, AV). In the screening process, published and unpublished studies were considered. The same authors independently assessed studies for inclusion and extracted data about study features (design, country and time of the study), populations (participant's number and characteristics), and the type of intervention and timing of administration. A manual search of references within the included studies was also performed in order to avoid missing any relevant data. MC and AV completely read the RCTs selected for meta-analysis.

Assessment of risk of bias

Two authors (AV, MC) independently assessed the methodological quality of included studies, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [16]. Seven specific domains related to the risk of bias were assessed: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective data reporting; other biases. The author's judgments were divided into "low", "high" or "unclear" risk of bias. For the estimation of "selective data reporting", we evaluated study protocols, when available. If not available, studies were judged at unclear risk of bias. We compared the results and solved the disagreements by consensus.

Data analysis

Data analysis was performed by two Authors (AV, MC) using Review Manager Version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). They compared the results and discussed the differences. The criteria for inclusion in the quantitative data analysis were the presence of at least two different studies investigating the specific outcomes analyzed.

We compared continuous variables by using the means and standard deviations of changes from the baseline outcomes. We also carried out all analyses were carried out with an intention-to-treat approach (mean changes per women randomized). Results were expressed as mean differences (MD) among Groups (95% CI). Regarding the mean difference approach, the standard deviations are used together with the sample sizes to compute the weight given to each study. The changes from the baseline measurements were not described. Therefore, they were calculated as differences between final and baseline means (μd = μ1—μ2). We estimated changes of standard deviations were calculated by using the formula $SD_{change} = sqrt\ (SD_1^2 + SD_2^2 — (2*corrt \times SD_1 \times SD_2))$, where the correlation coefficient was calculated as $corr = (SD_1^2 + SD_2^2 — SD\ change^2)/(2 \times SD_1 \times SD_2)$. The significance level set at P was < 0.05. We measured heterogeneity using I-squared (Higgins I^2). The calculated and extracted effect estimates were combined in a meta-analysis according to the generic inverse variance method and using the DerSimonian and Laird method for a random-effects model. Subgroup analysis was performed in order to evaluate the specific influence of different interventions (probiotics, synbiotics) and duration of therapy (eight weeks, twelve weeks) on pooled MDs for each outcome, as long as the meta-analysis includes at least two studies per subgroup.

We aimed to assess Publication Bias with the use of Funnel plot if at least 10 studies were included in the meta-analysis, according to the Cochrane Handbook Recommendations.

Results

Study selection

The initial literature search identified 1580 records, 812 were excluded due to irrelevant content for the aim of meta-analysis or duplicated items. Among the 768 articles which were full abstract screened, a total of 20 articles were screened. After the evaluation of a full text, 11 studies were excluded because did not meet the criteria of inclusion. This happened either because of the inappropriate design, the prebiotic usage, or the lack of sufficient information on the outcomes of interest. Finally, a total number of 9 studies [13–21] were included in the present meta-analysis (Fig. 1).

Included studies

The 9 trials included a total number of 587 participants. A summary of the main characteristics of the included studies is available in Table 1.

Among all trials included, concerning the study setting and blinding, all studies were performed in Iran [17–25]. All trials were achieved in a single center. Eight studies were double-blinded, whilst one study was triple-blinded [13–16, 18–21].

Concerning the intervention, 4 studies [17, 21, 22, 24] compared the administration of synbiotic twice a day versus placebo; 5 studies [18–20, 23, 25] evaluated the effects of probiotics twice a day versus placebo; in 7 studies [17–19, 22–25] the administration was for 12 weeks, in 2 studies [20, 21] the administration was for 8 weeks. The placebo content was not clarified. *Lactobacillus acidophilus* and

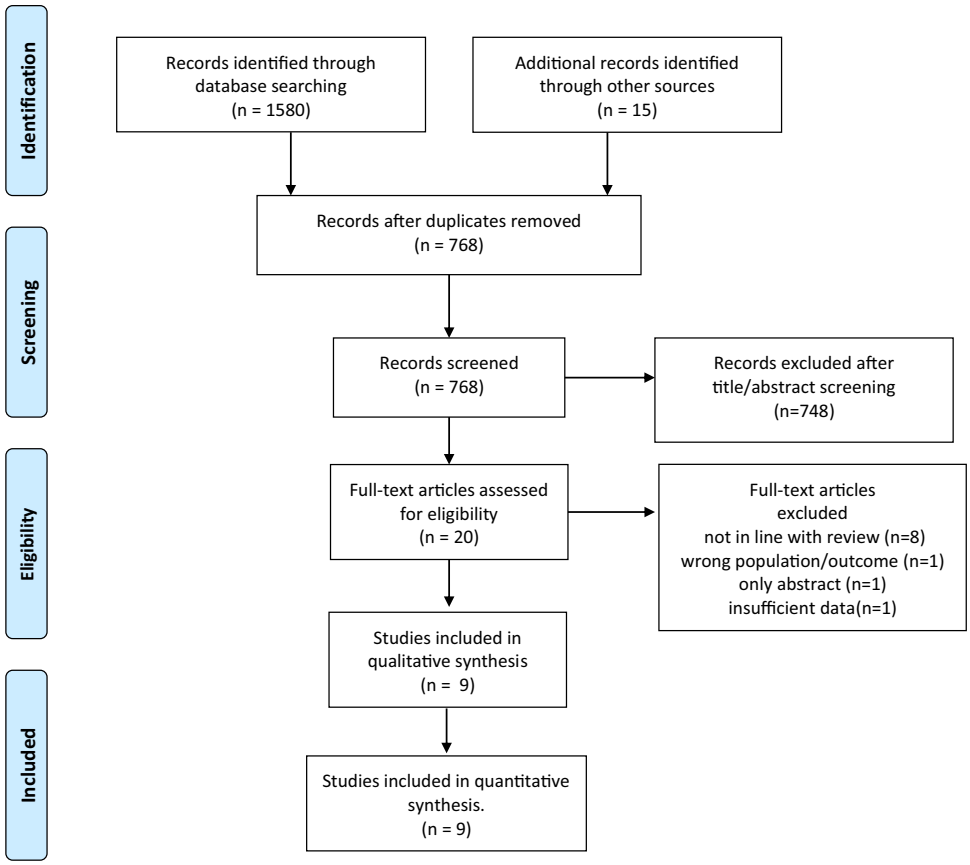


Fig. 1 PRISMA Flow-Diagram

Lactobacillus casei were the main component of the capsule administrated in every study [13–16, 18–21] with the exception of Esmaeilinezhad et al. [21] that used as principal components *Lactobacillus rhamnosus*, *Bacillus koagolans* and indices. In all studies, patients included were exclusively PCOS women [17–25]. Patient's body mass index (BMI) was < 25 (kg/m^2) in one study [17], in the other one by Ahmadi et al. BMI was > 19 [19]. In other studies, BMI was not reported. In 7 studies the age of patients was between 18 and 40 years [18–20, 22–25]. In one study the age was between 18–48 [21] and in Karimi et al. the age was between 19–37 [17]. In all studies [17–25], the diagnosis of PCOS was based according to Rotterdam criteria [1, 26]. The outcomes of every single study included in this systematic review are summarized in Table 1. Meta-analysis was not feasible for the outcomes of cholesterol VLDL, FSH, LH, ratio FSH/LH, IL-6, IL-10.

Assessment of the risk of study BIAS

Three studies [18, 20, 23] did not provide clear information on random sequence generation, on the other hand, the rest of them used an adequate method of random sequence generation with computer-generated sequence [19, 22, 24] or randomization blocks [17, 21, 25]. One study reported an adequate method of allocation concealment (sealed envelopes). We evaluated the remaining studies at unclear risk of bias.

All studies were blinded for patients and personnel (i.e. low risk of bias). In order to identify bias, the outcomes evaluated were unlikely to be influenced by the lack of blinding for outcome assessors. Therefore, all studies were considered at a low risk of bias. As dropouts did not exceed 20%, studies were judged at low risk of bias. Except one [21], all studies adhered to a recorded study protocol. Esmaelinezhad et al. (i.e. unclear risk of bias), indeed, didn't show recorded protocols for the study [21]. In all studies [17, 18, 21–24, 27] [20, 25], a power analysis was not conducted for the sample size calculation (high risk of bias) (Figure S1).

In 7 studies the analysis of the results was for intention to treat [17, 18, 21–24, 27], while in 2 studies was for protocol assigned [20, 25].

Effects of intervention

We evaluated a total number of 587 participants ($n = 294$ in Intervention Group and $n = 293$ in Control Group) from 9 studies. In the first analyses, the intervention is considered to be the total amount of probiotics and synbiotic.

Table 1 Main attributes of the studies included in the systematic review and meta-analysis

Authors and year	Country and time of realization	Participants	Main inclusion criteria	Intervention and timing	Intervention components	Intervention group	Control group	Randomization method	Main outcomes
Karimi et al. (2018) [17]	Iran From September 2015 to July 2016 (11 months)	120 patients (21 patients excluded)	Rotterdam criteria	Each synbiotic capsule 1000 mg capsule/days 12 weeks	Synbiotic *Lactobacillus acidophilus* 3×10^{10} colony-forming units (CFU)/g, Lactobacillus casei 3×10^{9} CFU/g, Lactobacillus bulgaricus 5×10^{8} CFU/g, Lactobacillus rhamnosus 7×10^{9} CFU/g, Bifidobacterium longum 1×10^{9} CFU/g, Bifidobacterium breve 2×10^{10} CFU/g and Streptococcus thermophilus 3×10^{8} CFU/g)	Group A ($n=50$)	Group B ($n=49$) placebo	Randomization list	Dietary intakes BMI FBS (fasting blood sugar) PGF-2 h (plasma glucose fasting 2-h) HbA1c (glycohaemoglobin) Fasting blood insulin Hs-CRP (high-sensitivity CRP) HOMA-IR (Homoeostatic model assessment-insulin resistence) QUICKI (Quantitative insulin sensitivity check index) Apelin 36
	Randomized Double-bind	99 randomized BMI < 25 kg/m^2 Age 19–37 years	Food records at weeks 0 and 12, and were instructed to record their daily dietary intake for 3 days, including a weekend day						

Table 1 (continued)

Authors and year	Country and time of realization	Participants	Main inclusion criteria	Intervention and timing	Intervention components	Intervention group	Control group	Randomization method	Main outcomes
Karamali et al. (2018) [18]	Iran From January 2017 to August 2017 (8 months)	71 patients (11 patients excluded) 60 randomized Age 18–40 years	Rotterdam criteria All patients completed 3-day food records and three physical activity record sas metabolic equivalents (METs) at week 0, 3, 6, 9, and 12 of intervention	2×10^9 CFU/g bacteria Produce by Tak Gen Zist Pharmaceutical Company (Tehran, Iran) 12 weeks	Probiotics *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* (2×10^9 CFU/g each)	Group A ($n=30$)	Group B ($n=30$) placebo	Computer-generated random numbers	Dietary intakes BMI Weight Total testosterone SHBG FAI mF-G score DHEAS Hs-CRP NO TAC GSH MDA
Shoaei et al. (2015) [20]	Iran From May 2013-December 2013 (8 months) Randomized Double-bind	85 patients (13 excluded) 72 randomized (7 excluded) 65 analyzed -Age 15–40 years	Rotterdam criteria Three days food records were taken (2-week days and 1-week end). Thress physical activity records were taken at 2,4,and 6 weeks	500 mg capsule /d 8 weeks	Probiotics *Lactobacillus casei 7×10 9 CFU/g, Lactobacillus acidophilus 2×10 9 CFU/g, Lactobacillus rhamnosus1.5×109CFU/g,Lactobacillus bulgaricus 2×10 8 CFU/g, Bifidobacterium breve 2×10 10 CFU/g, Bifidobacterium longum 7×10 9 CFU/g, Streptococcus thermophiles 1.5×10 9 CFU/g*	Group A (n=32)	Group B (n=33)	n/a	Dietary intakes BMI Weight FBS Insulin HOMA-IR QUICKI CRP

Table 1 (continued)

Authors and year	Country and time of realization	Participants	Main inclusion criteria	Intervention and timing	Intervention components	Intervention group	Control group	Randomization method	Main outcomes
Ahmadi et al. (2017) [19]	Iran From August 2015-November 2015 (4 months) Randomized Double-bind	85 PCOS patients (25 excluded) 60 randomized Age 18–40 years BMI greater than 19 kg/m^2	Rotterdam criteria 3-days food diaries and physical activity records	2×10^9 CFU/g bacteria 12 weeks	Probiotics *Lactobacillus acidophilus* (210^9 CFU/g), *Lactobacillus casei* ($2\ 10^9$ CFU/g) and *Bifidobacterium bifidum* (210^9 CFU/g)	Group A ($n=30$)	Group B ($n=30$)	Computer-generated random numbers	Dietary intakes BMI Weight FPG triglycerides cholesterol cholesterolV-LDL cholesterolLDL cholesterolHDL insulin HOMA-IR HOMA-B QUICKI
Samimi et al. (2018) [22]	Iran From April 2017- June 2017 (4 months) Randomized Double-bind	70 PCOS patients (10 excluded) 60 randomized Age 18–40 years	Rotterdam criteria 3-days food diaries and physical activity records	2×10^9 CFU/g bacteria 12 weeks	Synbiotic *Lactobacillus acidophilus* strain T16 (IBRC-M10785), *Lactobacillus casei strain* T2 (IBRC-M10783), and *Bifidobacterium bifidum strain* T1 (IBRC-M10771) (2×10^9 CFU/g each)	Group A ($n=30$)	Group B ($n=30$)	Randomization list	BMI Weight FPG insulin AIP (atherogenic index of plasma) triglycerides cholesterol cholesterol VLDL cholesterol LDL cholesterol HDL HOMA-IR QUICKI
Esmaeilinezhad et al. (2018) [21]	Iran From January to July 2017 (7 months) Randomized Triple-bind	125 PCOS patients 92 randomized Age 18–48 years	Rotterdam criteria	10^8 CFU/ml of each 8 weeks	Synbiotic *Lactobacillus rhamnosus* GG, *bacillus koagolans and indicous* (10^8 CFU/ml of each)	Group A synbiotic pomogranate juice ($n=22$) Group C pomogranate juice ($n=22$) Group D symbiotic beverage ($n=21$)	Group B (n=21)	n/a	BMI Weight FPG insulin HOMA-IR QUICKI Testosterone LH FSH LH/FSH

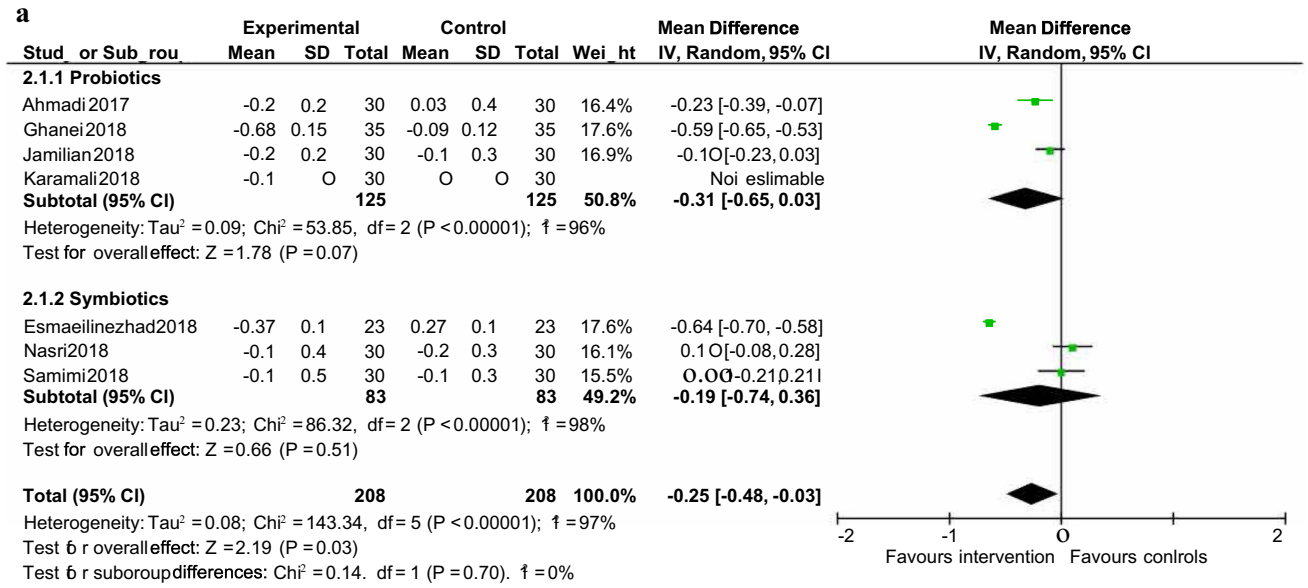
Table 1 (continued)

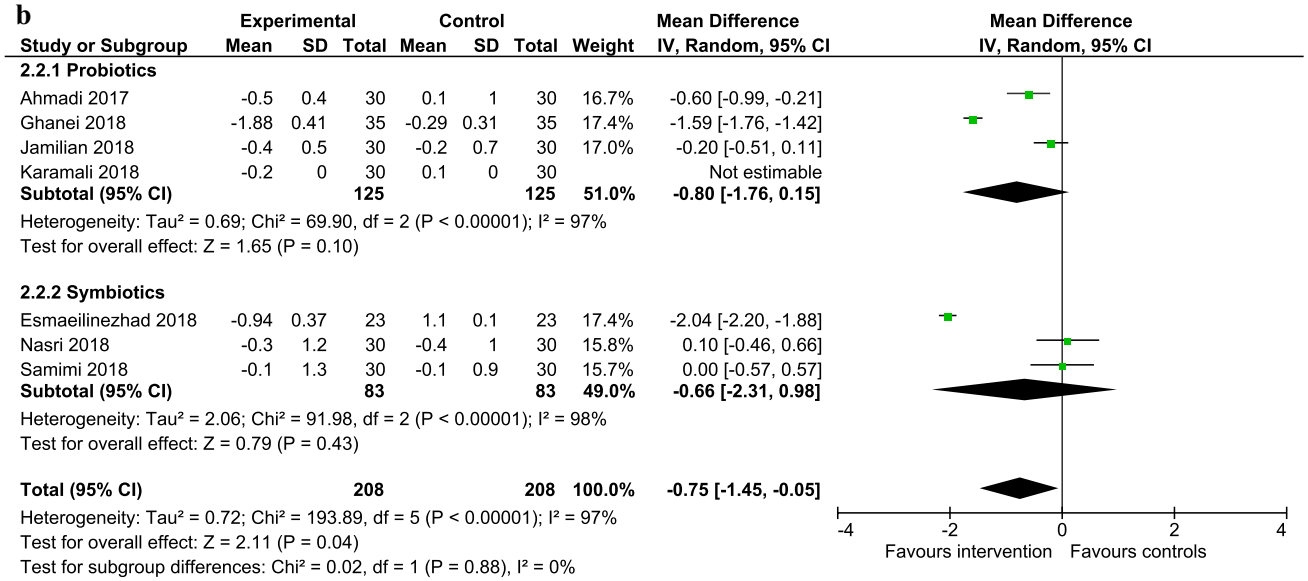
Authors and year	Country and time of realization	Participants	Main inclusion criteria	Intervention and timing	Intervention components	Intervention group	Control group	Randomization method	Main outcomes
Ghanei et al. (2018 [22]	Iran Randomizd Double-bind	90 PCOS Patients 70 randomized (4 excluded) Age 18–40 years	Rotterdam criteria	500 mg 12 weeks	Probiotics *Lactobacillus acidophilus, Lactobacillus pLantarum, Lactobacillus fermentum*, and *Lactobacillus gasseri*	Group A ($n=30$)	Group B ($n=30$)	Randomization list	Weight (kg) BMI (kg/m^2) Waist (cm) Abdominal circumference (cm) Hip circumference (cm) Menstrual cycle (days) Height (m) Diagnosis period (month) IL-6 (pg/ml) IL-10 (pg/ml) TNF-α (pg/ml) Hs-CRP (mg/l)
Jamilian et al. (2018) [23]	Iran Randomized Double-bind	68 PCOS patients 60 randomized Age 18–40 years	Rotterdam criteria	8×10^9 CFU/day 12 weeks	Probiotics *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Lactobacillus fermentum* and *Bifidobacterium bifidum* (2×109 CFU/g each) plus 200 µg/day selenium	Group A ($n=30$)	Group B ($n=30$)	Computer generated random numbers	BMI Weight Testosterone SHBG (nmol/L) mF-G scores hs-CRP NO TAC GSH MDA

Table 1 (continued)

Authors and year	Country and time of realization	Participants	Main inclusion criteria	Intervention and timing	Intervention components	Intervention group	Control group	Randomization method	Main outcomes
Nasri et al. (2018) [24]	Iran Randomized Double-bind	74 PCOS patients 60 randomized Age 18–40 years	Rotterdam criteria	12 weeks	Synbiotic 2 × 109 CFU/g each *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* plus 0.8 g inulin	Group A ($n=30$)	Group B ($n=30$)	Computer generated random numbers	BMI Height Weight MET (metabolic equivalents) Total testosterone (ng/mL) SHBG (sex hormone-binding globulin; nmol/L) FAI (free androgen index) mF-G (modified Ferriman Gallwey) DHEAS (dehydroepiandrosterone sulfate; ug/mL) hs-CRP (high-sensitivity C-reactive protein; ng/mL) NO (nitric oxide; umol/L) TAC (total antioxidant capacity; mmol/L) GSH (total glutathione; umol/L) MDA (malondialdehyde; umol/L)

Probiotics these are live bacteria found in certain foods or supplements. They can provide numerous health benefits, *Prebiotics* these substances come from types of carbohydrate (mostly fiber) that humans can't digest. The bacteria in the gut eat this fiber, *Synbiotic* is used when a product contains both probiotics and prebiotics





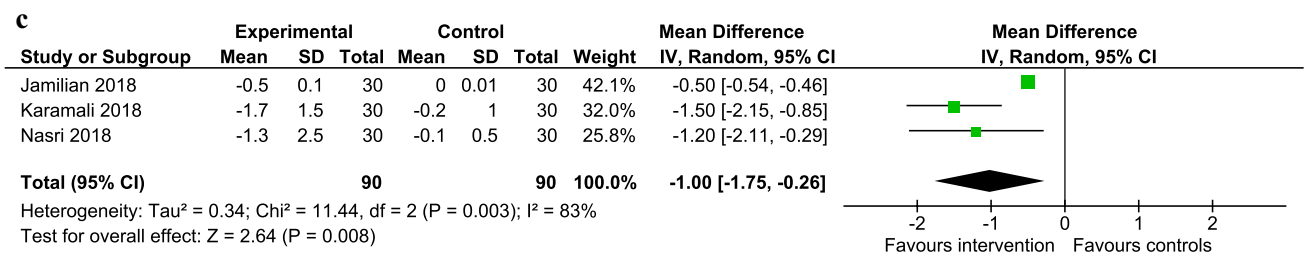
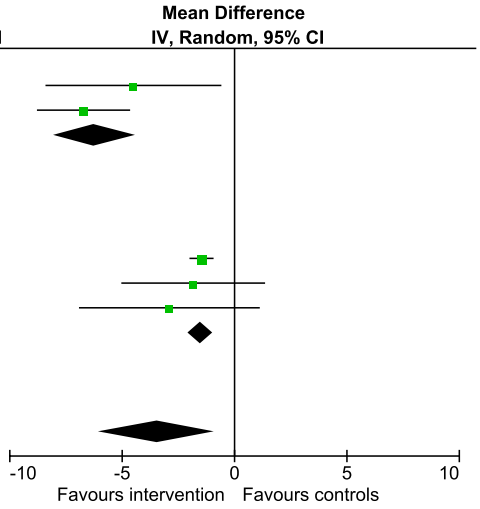


Fig. 2 **a**–**f** Probiotics/synbiotics vs placebo for polycystic ovarian syndrome: The intake of probiotic or synbiotic have a positive effect on body mass index in women with PCOS (**a**), in women with PCOS body weight was reduced after the intake of probiotic/synbiotic (**b**), The intake of probiotic/synbiotic improve the modified Ferriman–Gallway score (**c**), In women with PCOS the use of probiotic(synbiotic lead a progressive reduction of fasting plasma glucose (**d**), In women with PCOS Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), was reduced during therapy with probiotic/synbiotic (**e**), The therapy with probiotic/synbiotic have not effect on quantitative Insulin-Sensitivity Check Index (**f**)

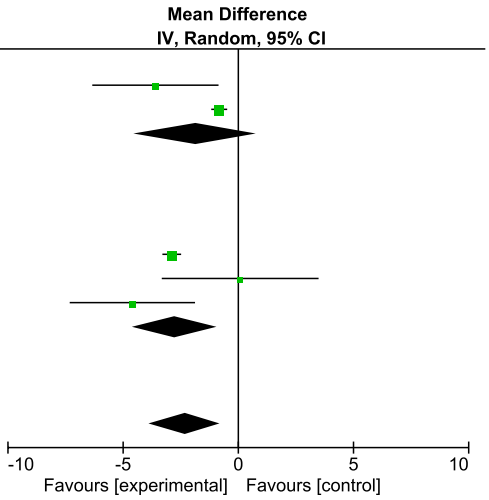
d

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 Probiotics								
Ahmadi 2017	-2.4	8.4	30	2.1	7	30	16.4%	-4.50 [-8.41, -0.59]
Shoaei 2015	-4.15	2.87	36	2.57	5.66	36	22.6%	-6.72 [-8.79, -4.65]
Subtotal (95% CI)			**66**			**66**	**39.0%**	**-6.23 [-8.07, -4.40]**
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.33); I² = 0%								
Test for overall effect: Z = 6.67 (P < 0.00001)								
2.3.2 Symbiotics								
Esmaeilinezhad 2018	-1.18	1.14	23	0.29	0.65	23	26.1%	-1.47 [-2.01, -0.93]
Karimi 2018	-0.44	7.18	50	1.4	8.94	49	18.8%	-1.84 [-5.04, 1.36]
Samimi 2018	-4.1	9.1	30	-1.2	6.6	30	16.1%	-2.90 [-6.92, 1.12]
Subtotal (95% CI)			**103**			**102**	**61.0%**	**-1.50 [-2.03, -0.98]**
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 2 (P = 0.77); I² = 0%								
Test for overall effect: Z = 5.62 (P < 0.00001)								
Total (95% CI)			**169**			**168**	**100.0%**	**-3.45 [-6.03, -0.88]**
Heterogeneity: Tau² = 6.53; Chi² = 25.15, df = 4 (P < 0.0001); I² = 84%								
Test for overall effect: Z = 2.63 (P = 0.009)								
Test for subgroup differences: Chi² = 23.66, df = 1 (P < 0.00001), I² = 95.8%								



b

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Probiotics								
Ahmadi 2017	-2	5.8	30	1.6	5	30	15.1%	-3.60 [-6.34, -0.86]
Shoaei 2015	-0.49	0.67	36	0.34	0.82	36	28.9%	-0.83 [-1.18, -0.48]
Subtotal (95% CI)			**66**			**66**	**44.0%**	**-1.87 [-4.50, 0.76]**
Heterogeneity: Tau² = 2.84; Chi² = 3.86, df = 1 (P = 0.05); I² = 74%								
Test for overall effect: Z = 1.39 (P = 0.16)								
2.4.2 Symbiotics								
Esmaeilinezhad 2018	-1.66	0.97	23	1.23	0.22	23	28.7%	-2.89 [-3.30, -2.48]
Karimi 2018	-0.1	10.27	50	-0.18	6.66	49	12.0%	0.08 [-3.32, 3.48]
Samimi 2018	-2.8	4.1	30	1.8	6.4	30	15.2%	-4.60 [-7.32, -1.88]
Subtotal (95% CI)			**103**			**102**	**56.0%**	**-2.75 [-4.56, -0.95]**
Heterogeneity: Tau² = 1.48; Chi² = 4.44, df = 2 (P = 0.11); I² = 55%								
Test for overall effect: Z = 2.99 (P = 0.003)								
Total (95% CI)			**169**			**168**	**100.0%**	**-2.31 [-3.84, -0.77]**
Heterogeneity: Tau² = 2.08; Chi² = 64.44, df = 4 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 2.95 (P = 0.003)								
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.59), I² = 0%								



c

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.5.1 Probiotics								
Ahmadi 2017	-0.5	1.4	30	0.3	1.1	30	17.3%	-0.80 [-1.44, -0.16]
Shoaei 2015	-0.25	0.18	36	-0.05	0.18	36	26.3%	-0.20 [-0.28, -0.12]
Subtotal (95% CI)			**66**			**66**	**43.6%**	**-0.41 [-0.98, 0.15]**
Heterogeneity: Tau² = 0.13; Chi² = 3.35, df = 1 (P = 0.07); I² = 70%								
Test for overall effect: Z = 1.44 (P = 0.15)								
2.5.2 Symbiotics								
Esmaeilinezhad 2018	-0.5	0.22	23	0.38	0.54	23	24.7%	-0.88 [-1.12, -0.64]
Karimi 2018	0.05	2.38	50	0.19	1.61	49	14.5%	-0.14 [-0.94, 0.66]
Samimi 2018	-0.7	1	30	0.4	1.5	30	17.2%	-1.10 [-1.75, -0.45]
Subtotal (95% CI)			**103**			**102**	**56.4%**	**-0.80 [-1.20, -0.39]**
Heterogeneity: Tau² = 0.06; Chi² = 3.67, df = 2 (P = 0.16); I² = 46%								
Test for overall effect: Z = 3.81 (P = 0.0001)								
Total (95% CI)			**169**			**168**	**100.0%**	**-0.62 [-1.07, -0.17]**
Heterogeneity: Tau² = 0.20; Chi² = 36.70, df = 4 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 2.69 (P = 0.007)								
Test for subgroup differences: Chi² = 1.16, df = 1 (P = 0.28), I² = 13.5%								

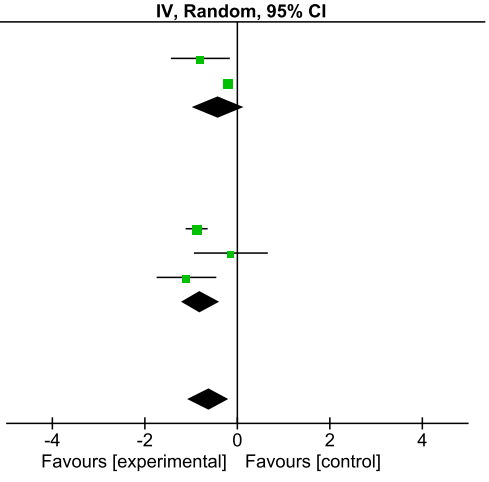
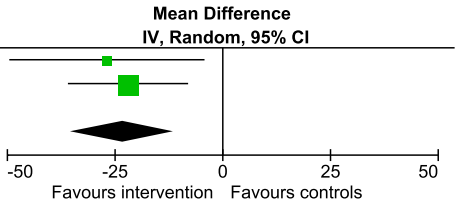


Fig. 2 (continued)

a

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ahmadi 2017	-13.3	51.3	30	13.6	37.1	30	27.5%	-26.90 [-49.55, -4.25]
Samimi 2018	-16.2	31.4	30	5.8	23.1	30	72.5%	-22.00 [-35.95, -8.05]
Total (95% CI)			**60**			**60**	**100.0%**	**-23.35 [-35.23, -11.47]**

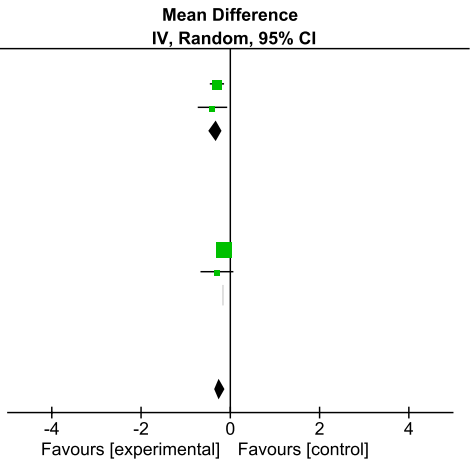
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 3.85 (P = 0.0001)



b

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.9.1 Probiotics								
Jamilian 2018	-0.3	0.32	30	0	0.31	30	27.8%	-0.30 [-0.46, -0.14]
Karamali 2018	-0.2	0.7	30	0.2	0.6	30	11.0%	-0.40 [-0.73, -0.07]
Subtotal (95% CI)			**60**			**60**	**38.7%**	**-0.32 [-0.46, -0.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%								
Test for overall effect: Z = 4.35 (P < 0.0001)								
2.9.2 Symbiotics								
Esmaeilinezhad 2018	-0.09	0.02	23	0.06	0.01	23	52.1%	-0.15 [-0.16, -0.14]
Nasri 2018	-0.4	0.9	30	-0.1	0.5	30	9.2%	-0.30 [-0.67, 0.07]
Subtotal (95% CI)			**53**			**53**	**61.3%**	**-0.15 [-0.16, -0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.43); I² = 0%								
Test for overall effect: Z = 32.20 (P < 0.00001)								
Total (95% CI)			**113**			**113**	**100.0%**	**-0.23 [-0.36, -0.11]**

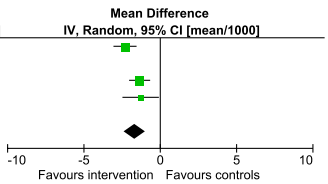
Heterogeneity: Tau² = 0.01; Chi² = 6.22, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 3.72 (P = 0.0002)
Test for subgroup differences: Chi² = 5.29, df = 1 (P = 0.02), I² = 81.1%



c

Study or Subgroup	Experimental Mean [mean/1000]	SD [mean/1000]	Total	Control Mean [mean/1000]	SD [mean/1000]	Total	Weight	Mean Difference IV, Random, 95% CI [mean/1000]
Ghanei 2018	-3.55	1.6979	30	-1.24	1.259	30	37.3%	-2.31 [-3.07, -1.55]
Jamilian 2018	-0.4	0	30	0.2	0.1	30		Not estimable
Karamali 2018	-1.15	1.295	30	0.2025	1.4263	30	40.4%	-1.35 [-2.04, -0.66]
Nasri 2018	-0.95	2.246	30	0.3353	2.466	30	22.3%	-1.29 [-2.48, -0.09]
Total (95% CI)			**120**			**120**	**100.0%**	**-1.69 [-2.38, -1.01]**

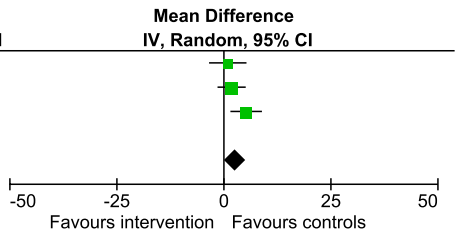
Heterogeneity: Tau² = 0.18; Chi² = 3.94, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 4.84 (P < 0.00001)



d

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jamilian 2018	1.2	12	30	0.3	2.31	30	26.2%	0.90 [-3.47, 5.27]
Karamali 2018	0.2	2.7	30	-1.6	8.8	30	39.8%	1.80 [-1.49, 5.09]
Nasri 2018	5.5	4.8	30	0.3	9.1	30	34.0%	5.20 [1.52, 8.88]
Total (95% CI)			**90**			**90**	**100.0%**	**2.72 [0.21, 5.23]**

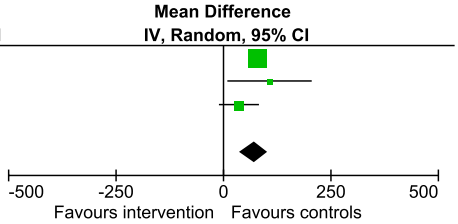
Heterogeneity: Tau² = 1.30; Chi² = 2.71, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 2.12 (P = 0.03)



e

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jamilian 2018	79.6	9.6	30	-0.5	11.9	30	63.9%	80.10 [74.63, 85.57]
Karamali 2018	8.8	120.5	30	-98.3	246.4	30	9.0%	107.10 [8.95, 205.25]
Nasri 2018	45.1	51.8	30	9.2	119.3	30	27.1%	35.90 [-10.64, 82.44]
Total (95% CI)			**90**			**90**	**100.0%**	**70.55 [38.84, 102.25]**

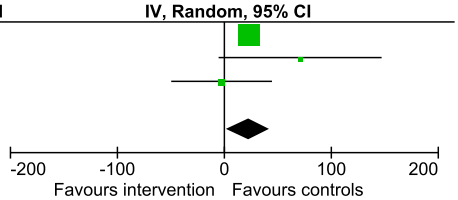
Heterogeneity: Tau² = 401.69; Chi² = 3.72, df = 2 (P = 0.16); I² = 46%
Test for overall effect: Z = 4.36 (P < 0.0001)



f

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jamilian 2018	24.6	0.2	30	1.4	5.23	30	78.4%	23.20 [21.33, 25.07]
Karamali 2018	32.8	146.1	30	-38	154.9	30	6.5%	70.80 [-5.39, 146.99]
Nasri 2018	24.7	58.7	30	27.3	117.8	30	15.1%	-2.60 [-49.70, 44.50]
Total (95% CI)			**90**			**90**	**100.0%**	**22.42 [2.08, 42.75]**

Heterogeneity: Tau² = 136.40; Chi² = 2.65, df = 2 (P = 0.27); I² = 25%
Test for overall effect: Z = 2.16 (P = 0.03)



◂**Fig. 3** **a**, **b** Probiotics/synbiotics vs placebo for polycystic ovarian syndrome have positive effect on Triglycerides (**a**), The intake of probiotic/synbiotic in women with PCOS provide a reduction in the total testosterone serum (**b**). The use of probiotics/synbiotics in women with PCOS improve all inflammatory outcomes: High sensitivity C reactive protein (**c**), Nitric oxide (**d**), Total antioxidant capacity (**e**), Total glutathione (**f**)

We found a significant decrease in BMI and a modified Ferriman-Gallway score in patients belonging to the intervention group compared to the control group (Fig. 2a–c). The intervention was associated with a significant improvement in FPG, FBI, HOMA I-R, but not in QUICK-I (Fig. 2d–f). The intervention group showed a significant reduction in serum triglycerides (Fig. 3a), but not in LDL, HDL, and total cholesterol.

The intervention was associated with a significant reduction in serum testosterone, without changes in SHBG, DEAS, and FAI (Fig. 3b).

Subgroup analysis of the type of intervention provided conflicting results. Probiotics, indeed, were associated with greater testosterone and FPG reduction, while synbiotics administration resulted in a more pronounced decrease of the FBI. However, if considered individually, each subgroup of the intervention was more effective than controls in lowering FPG, the FBI, and testosterone.

We found a significant impact of the intervention on hs-CRP, NO, TAC, GSH, and MDA, conversely, no significant effect was observed for CRP (Fig. 3c–f).

Subgroup analyses failed to detect a statistical difference between subgroups for the other outcomes. Subgroup analyses of the duration of therapy were feasible only for a few outcomes (FPG, FBI, HOMA-IR, QUICK-I). The 12-weeks therapy had a significantly greater effect on QUICK-I than the 8-weeks therapy, while no significant differences were observed in terms of the FBI, HOMA-IR, and FPG between subgroups (Figs. 2, 3).

Discussion

This systematic review and meta-analysis suggested that administration of probiotics/synbiotics improve metabolic, hormonal and systemic inflammatory factors in women with PCOS. Probiotics and synbiotics significantly reduced FPG, FBI, HOMA I-R and triglycerides. The use of probiotics and synbiotics in women with PCOS reduced the serum testosterone without effect on SHBG, DEAS, and FAI. The intake of probiotics and synbiotics by women with PCOS increased serums hs-CRP, NO, TAC, GSH, and MDA. No statistically significant effect were showed on QUICK-I, LDL, HDL, and total cholesterol. The administration of probiotics and synbiotics in women with PCOS decrease in BMI and a modified Ferriman-Gallway.

PCOS is the most common endocrinopathy among adult women. Therapy seems to be symptom-based, and include insulin-sensitizers (metformin, inositol), contraceptives and progestins [28, 29]. Studies have recently demonstrated that perturbations in bacterial communities play a role in the pathogenesis of obesity, insulin resistance and systemic inflammation in different metabolic disorders [30], considered keys factor in PCOS's pathogenesis. Insulin resistance (IR) and systemic inflammation are interrelated factors in PCOS postulating that hyperglycemia and pro-inflammatory cytokines have a synergic effect for ROS production [38]. Probiotics and synbiotics may theoretically attenuate systemic inflammation through chelating metal ion, regulating inflammatory signaling pathways, producing antioxidant metabolites and downregulating ROS. Oxidative stress biomarkers are increased in women with PCOS, including MDA, protein carbonyl, TAC, superoxide dismutase (SOD), glutathione peroxidase (GPx), and GSH. Imbalance in favor of oxidative stress, induced by several stimuli, was closely associated with the severity of inflammation in PCOS [41]. Increased oxidative damage and inflammatory cytokines are related to increased risk of hyperandrogenism, insulin resistance, cardiovascular events, and diabetes in PCOS [42, 43]. Pathophysiology of PCOS also seem to be involved with an alteration of physiological balance between microorganisms in the gut microbiome, and probiotic or symbiotic intake might restore this balance. The uptake of probiotics, prebiotics, and synbiotics balanced the colony of intestinal microbes and intestinal pH. Moreover it improved intestinal decomposition and metabolism of lipids and starch, produced inflammatory cytokines, whilst it improved intestinal digestion and absorption of nutrients. Testosterone and other androgens increased significantly in women with PCOS; probably, due to the excess androgens which, act as a stage-specific inhibitor of follicle growth in PCOS, promoting pre-antral follicle growth but suppressing later stages of follicular development [31]. Androgens induce apoptosis directly by activating an intrinsic apoptotic pathway and decreasing the production of follicular growth factors [32, 33]. Additionally, androgens exert their effects by indirect mechanisms that include the modulation of the proliferative or pro-apoptotic effects of gonadotropin and other local factors [34, 35].

Probiotics and synbiotics have an impact on anthropometric parameters in women with PCOS (BMI, body weight and modified Ferriman–Gallway score). The beneficial effects of probiotics on anthropometric parameters were potentially due to a positive modulation of energy balance, as supported by a reduction in circulating leptin levels after treatment [36]. These effects are proved by according to previous results which showed a decrease in body weight and fat after prolonged administration of probiotics (≥ 12 weeks therapy with *Lactobacillus rhamnosus* [36] *or Lactobacillus salivarius* [37]) in obese women. Conversely, in a previous

meta-analysis PCOS patients treated with probiotics/synbiotics showed a no significant changes in body weight and BMI compared to the placebo group [38]. This meta-analysis show that probiotic or synbiotics intake is associated with a reduction in FPG, FBI and HOMA I-R and a slight but not significant improvement in QUICK-I. Dysregulation of glucose metabolism could be a causal factor of PCOS and is implicated in PCOS long-term complications. The restoration of gut microbiome on glucose homeostasis using probiotics and synbiotics suggested a potential effect on the modification of the absorption of micronutrients in PCOS patients. Probiotics, indeed, seem to improve HOMA-IR after 12 weeks of therapy in women with type 2 diabetes [39]. Furthermore, previous meta-analysis showed that supplementation with probiotics could reduce blood glucose in PCOS patients, while synbiotics did not have a significant effect on FBG.

The intake of probiotics or synbiotics seem to reduce inflammatory cytokines, lipid peroxidation (i.e. reducing the generation of hydrogen peroxide radicals) and oxidative damage via producing short-chain fatty acid in the intestine [40]. The previous meta-analysis showed a significant decrease in serum testosterone SHBG, DEAS, and FAI in women with intake of probiotic/synbiotic a [41]. Nevertheless, our results confirmed only a significant reduction in testosterone.

Finally, we found an improvement of the triglyceride levels after the intake of probiotics/synbiotics compared to the control group, with no change in LDL, HDL, VDRL, and total cholesterol. Hypertriglyceridemia and low apolipoprotein A-I represent the most common lipid abnormalities in women with PCOS. Triglycerides levels were constantly assessed across studies, while, HDL different subtypes were not measured. Therefore, we cannot exclude that probiotics/synbiotics may have a different impact on different HDL subtypes, without modifying the total levels of HDL. The intake of probiotics could improve the gut microbiome in a dietary lipid content-dependent manner [42]. However, the modulation of the genes that control appetite is not solely attributable to the presumable enhancement of fatty acids produced by microbiota (*e.g*. *Lactobacillus* spp. and other lactic acid bacteria], but could be also due to the probiotic's capability of inducing entero-endocrine cell proliferation, thus increment and decrement gut metabolic peptide production and secretion [6, 43].

Although there was not a limitation on country, searching results should be considered carefully since all studies were performed in Iran. This fact could, potentially limit the generalizability of our findings to other ethnic groups. None of the studies provided a methodological flaws and a power-analysis for the sample size calculation. Secondly, studies that included drugs were more likely to be published than studies with negative results, another reason for a careful interpretation of the results. Third, the small sample size included in a pooled analysis, as well as heterogeneity in the interventions administered might represent additional sources of bias. Those factors contribut to this heterogeneity included, different ovarian patterns between hyperandrogenic or hyperinsulinemic and the bacterial species were not the same in most of the studies. Finally in the studies considered the unit measurement for each outcomes were not always comparable for all studies included.

Conclusions

Available evidence suggests that ≥ 12 weeks of administration of probiotics/synbiotics may improve metabolism, reduce serum testosterone and decrease systemic inflammation in women with PCOS. There is a clear need to structure a well-driven RCT with previous power analysis that analyze pregnancy-related outcomes in PCOS women being treated with probiotic or synbiotic to demonstrate possible fertility-related effects. This is due to the previously available evidence that points to recommend the use of probiotic/synbiotic in the clinical practice. A robust RCT should demonstrate if these treatments could improve the fertile potential of women with PCOS. Moreover, future studies in different settings will also assess the potential application of the intervention to other ethnic groups. Many questions are still unsolved in the field of PCOS, representing a strong stimulus for further studies in this intriguing area of reproductive biology and endocrinology.

Authors contributions MC designed the study, performed the literature search, defined inclusion criteria and selected studies for inclusion, participated in data extraction, performed the risk of bias assessment, performed the statistical analysis, and wrote the first and final drafts of the manuscript; AV designed the study, performed the literature search, performed the risk of bias assessment, performed the statistical analysis, and wrote final drafts of the manuscript; LP performed the literature search, selected studies for inclusion; MC performed the literature search; AA participated in the statistical analysis; GA critically revised the manuscript; NC critically revised the manuscript, participated in assessing the risk of bias within studies and the grading of evidence.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

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