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Review Article

The Effect of Probiotics or Synbiotics on the Hypertensive Disorders of Pregnant Women with Gestational Diabetes: A Systematic Review and Meta-analysis

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Abstract

Introduction: Antioxidants and anti-inflammatory drugs have been suggested to treat preeclampsia. This systematic review and meta-analysis was conducted to investigate the efficacy of probiotic or synbiotic supplementation on hypertensive disorders in women with gestational diabetes mellitus (GDM).

Methods: The databases including Cochrane, Embase, Ovid, ProQuest, Scopus, Web of Science, and PubMed were systematically searched for collecting the randomized controlled trials (RCTs) investigating the efficacy of probiotic or synbiotic supplementation versus placebo on hypertensive disorders and pregnancy outcomes in GDM until July 2020.

Results: Five RCTs with a total sample size of 402 women were included in the meta-analysis. There was no significant decline in systolic blood pressure (standardized mean difference [SMD] = -3.41, 95% confidence interval [CI] = -8.32 to 1.50, P = 0.17), diastolic blood pressure (SMD = -5.11, 95% CI = -14.20 to -3.98, P = 0.27), preeclampsia (odds ratio [OR] = 1.56, 95% CI = 0.61 to 3.98, P = 0.35), cesarean section (OR = 0.52, 95% CI = 0.18 to 1.50, P = 0.23), and macrosomia (OR = 0.81, 95% CI = 0.41 to 1.57, P = 0.53). No significant increase was observed in terms of 5-minute Apgar (SMD = 0.16, 95% CI = -0.06 to 0.39, P = 0.15, I^2 = 0%), birth weight (SMD = -0.18, 95% CI = -0.43 to 0.06, P = 0.13, I^2 = 0%), and gestational age (SMD = 0.13, 95% CI = -0.11 to 0.37, P = 0.28, I^2 = 0%).

Conclusion: Probiotic or synbiotic supplements are not associated with significant effects on pregnancy outcomes in GDM. However, due to the limited number of studies in this regard and heterogeneity between studies, future high-quality RCTs are recommended.

Introduction

Pregnancy is a critical period for the manifestation of complications such as hypertensive disorders, especially preeclampsia. Hypertension (HTN) is among the three leading causes of maternal and fetal mortality across the world,[1] and affects 2-8% of pregnancies.[2] HTN without symptoms of proteinuria is considered as the high blood pressure in pregnancy, leading to preeclampsia in almost half of cases. Preeclampsia can delay intrauterine growth and increase perinatal mortality. According to the World Health Organization (WHO) data, preeclampsia and eclampsia cases have been increasing in developed and especially in developing countries since 1990.[3]

Despite the medical importance of preeclampsia, the underlying causes of this disease remain unknown.[4] Termination of pregnancy to prevent maternal morbidity in early preeclampsia is associated with severe neonatal morbidity.[5]

The most common complication of diabetes in pregnant women has been shown to be cesarean section, HTN, and preeclampsia.[6] In women with HTN, hyperinsulinemia has been shown to be more than normotensive controls in the oral glucose tolerance testing.[7]

Evidence suggests that the maternal over-inflammatory response, which may be due to oxidative stress,[8] is responsible for the occurrence of preeclampsia.[9] Various treatments, including antioxidants and anti-inflammatory drugs, have been suggested to treat preeclampsia.[4] Probiotics can be recommended as a treatment due to the anti-inflammatory and antioxidant properties[10,11] and free

radical scavenging,[12] which is increased in preeclampsia and diabetes.[13] A slight decrease in HTN may have public health benefits and positive cardiovascular consequences.[14]

Prebiotics are as the nutrient fibers of probiotics and indigestible carbohydrate components that selectively promote the growth and activity of beneficial bacterial species (probiotics) in the gut.[15] Prebiotics are food ingredients or nutrients that escape the digestion in the upper gastrointestinal tract and then selectively fermented by bacteria, thereby altering the activity and/or composition of the intestinal microbiota.[16]

The combination use of probiotics and prebiotics, is generally termed as synbiotics. The use of synbiotics during pregnancy as a supplementary treatment with the aim of controlling plasma glucose and other metabolic indices may be helpful for the management of gestational diabetes mellitus (GDM).[7]

Synbiotic interventions can significantly improve systolic blood pressure (SBP) levels in adults.[17] Given the increased incidence of preeclampsia and pregnancy HTN, and because of its significant negative consequences on mothers and babies, probiotic or synbiotic supplementation could be considered as one of the inexpensive and available therapeutic approaches to reduce HTN and its complications. Therefore, this meta-analysis aimed to investigate the effect of probiotic or synbiotic supplementation on preeclampsia and gestational HTN in diabetic pregnant women.

Materials and Methods

Initially, the Cochrane database of systematic reviews (CDSR) was searched to find the review studies investigating the effect of probiotics or synbiotics on HTN and preeclampsia in pregnant women with GDM until July 2020.

In the second stage, English databases including Cochrane, Embase, Ovid, ProQuest, Scopus, Web of Science, and PubMed as well as Magiran, SID, Iranmedex, and Irandoc, for Persian literature review were searched until July 2020 with the keywords mentioned above. Reference list of review articles and papers published at conferences were also reviewed. Was also evaluated as further references. Two researchers (RM and KHH) independently evaluated the title and summary of the studies obtained from the search strategy. The entire study was read out if the study was eligible or the information provided was not sufficient to make a decision. If needed, discussion or consultation was conducted with third and fourth parties (MSH, AFKH) to ensure that the studies were appropriate for selection.

The search strategy was performed in various databases with the following details: 1- "GDM" or "gestational diabetes" or "diabetes pregnancy" or "diabetic mother" or "insulin gestation" or "Pregnancy-Induced Diabetes", 2- "Preeclampsia" or "Pre-Eclampsia" or "Gestational Hypertension" or "Hypertension of pregnancy" or "Pregnancy-Induced Hypertension" or "PIH", 3- "Probiotic" or "Synbiotic", 4- "Randomized controlled trial" or "randomized trial" or "randomized clinical trial" or "randomized controlled", 5- #1 AND #2 AND #3 AND #4. However, no review study was found in this regard.

The present study was designed in accordance with the guidelines in the Cochrane manual and preferred reporting items for systematic reviews and meta-analyses (PRISMA) Statement. In this study, all randomized controlled trials (RCTs) comparing the effect of probiotics or synbiotics on SBP and diastolic blood pressure (DBP) or preeclampsia were compared with placebo. The PICOS criteria (participants, interventions, comparators, outcome, and study design) for determining the eligibility criteria of the study were as follow: Participants (P): Pregnant women over 24 weeks diagnosed with GDM, Intervention (I): Probiotic capsules, synbiotic capsules, Comparator (C): Placebo capsules, Outcomes (O): Primary outcomes (SBP, DBP, preeclampsia) and Secondary outcomes (Cesarean delivery, 5-minute Apgar, macrosomia, birth weight and gestational age), and Study design (S): RCTs.

The first and second authors independently used the designed form to extract data from eligible studies (Figure 1). Any disagreement was resolved in consultation with the third and fourth authors. The risk of bias for each study was evaluated independently by the first and second authors for each study using Cochrane handbook for systematic reviews (Table 1). Data were analyzed using Review Manager (RevMan), version 5.3 statistical software. In three studies, the incidence of preeclampsia was evaluated as a qualitative variable; thus, the results were extracted in number (percentage). Both SBP and DBP were evaluated quantitatively in two studies and the mean and standard deviation of their values were extracted after the intervention.

The primary outcomes in this study included pregnancy HTN and preeclampsia, and secondary outcomes included cesarean delivery, 5-minute Apgar, macrosomia, birth weight, and gestational age.

Out of 5094 papers retrieved, 3124 were identified as duplicates after inclusion in the EndNote X7.8 software. Of the remaining 1970 papers, 1914 papers were not related to the study subject, 27 studies were related to disease prevention, and 23 studies had been conducted on unintended outcomes. Furthermore, we could not have full access to one of the studies. Finally, the remaining five studies were evaluated for inclusion criteria and included in the meta-analysis (Figure 1). The characteristics of the studies are summarized in Table 2.

The quality of the included articles was assessed using the Cochrane collaboration's tool for assessing risk of bias in randomized trials. The biases were divided into six categories, including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias),

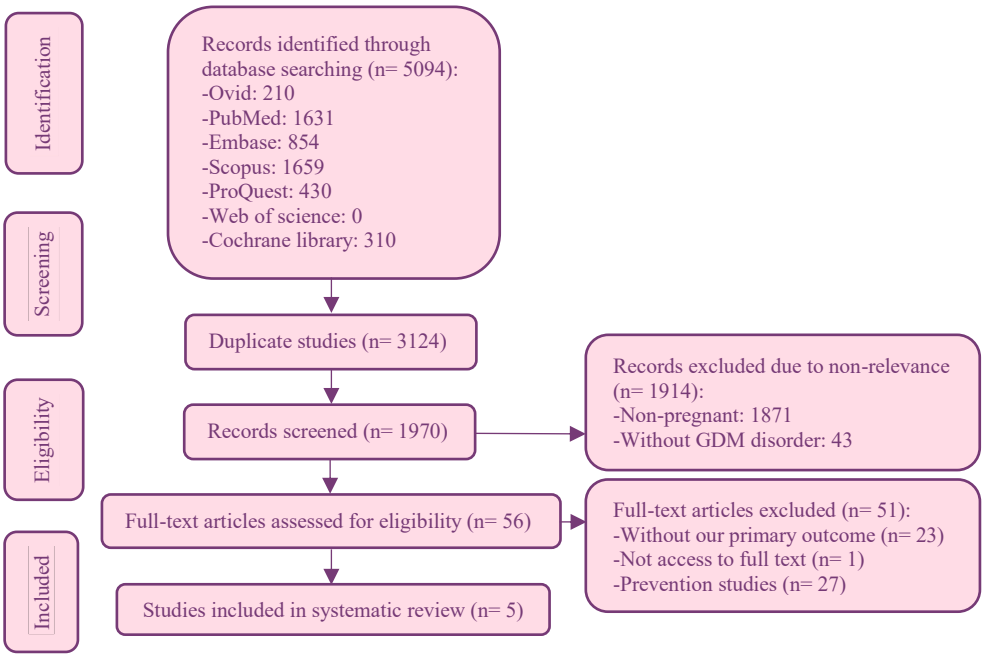

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart

incomplete outcome data (attrition bias), and selective reporting (reporting bias), each of which were evaluated in the triple risks consisting of high, unclear, and low risk (Table 2, Figures 2 and 3). Three studies had a low-risk bias in the all evaluated components. The risk of bias was unclear in one component in two studies. All articles included in this meta-analysis were low-risk in terms of random sequencing, random allocation, and participant blindness.

The inclusion criteria of the retrieved studies were: a randomized, placebo-controlled trial, using probiotic or synbiotic supplements with any strain used in the supplement in the participants; mother age above 18 years old; pregnancy over 24 weeks with diagnosis of GDM; and published in English and Persian language.

The exclusion criteria were: all review studies, animal studies, observational studies, retrospective studies, and study protocols.

Results

Primary Outcomes

The Effect of Probiotics or Synbiotics in Comparison with Placebo Group on SBP

Two RCTs[7,10] with a total sample size of 146 participants evaluated the effect of probiotic or synbiotic supplementation on SBP compared with placebo. I^2 index showed significant heterogeneity between studies ($I^2 = 98\%$, $P < 0.00001$); hence, a random effect model was used to collect data. The overall estimated effect of these studies did not show a significant effect on SBP in women with GDM after supplementation by probiotic or synbiotic in comparison with the control (SMD = -3.41, 95% CI = -8.32 to 1.50, $P = 0.17$). The results of the analysis showed that probiotic or synbiotic supplementation had no effect on SBP (Figure 4A).

The Effect of Probiotics or Synbiotics in Comparison with Placebo Group on DBP

Two RCTs[7,10] with a total sample size of 146 participants evaluated the effect of probiotic or synbiotic supplementation on DBP compared with placebo. I^2 index showed significant heterogeneity between studies ($I^2 = 99\%$, $P < 0.00001$); hence, a random effects model was used to collect data. The overall estimated effect of these studies did not illustrate a significant effect of probiotics or synbiotics on DBP in women with GDM compared to the control group (SMD = -5.11, 95% CI = -14.20 to 3.98, $P = 0.27$). The results of the analysis showed that probiotic or synbiotic supplementation had no effect on SBP (Figure 4B).

The Effect of Probiotics or Synbiotics in Comparison with placebo Group on the Incidence of Preeclampsia

Three RCTs[18,19] with a total sample size of 256 participants evaluated the effect of probiotic or synbiotic supplementation on the incidence of preeclampsia compared with placebo. I^2 index did not indicate significant heterogeneity between studies ($I^2 = 0\%$, $P = 0.53$); hence, a fixed effect model was used to collect data. The overall estimated effect of these studies did not show a significant effect on the incidence of preeclampsia in women with GDM after using the probiotic or synbiotic supplements compared with the control group (OR = 1.56, 95% CI = 0.61 to 3.98, $P = 0.35$). The results of the analysis

Table 1. Risk of bias in the studies included

Risk of bias	Author's comment	Reason for judgment
Nabhani et al[7]		
Random sequence generation (selection bias)	Low risk	Participants were divided into groups of 47 and 48 using computer-generated random sequencing.
Allocation concealment (selection bias)	Low risk	The placement of individuals in the intervention or control group was randomized. In this trial, the envelopes were coded as "A" or "B".
Blinding of participants and personnel (performance bias)	Low risk	Participants and researchers were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessment was done.
Incomplete outcome data (attrition bias)	Low risk	Three of the 48 members of the synbiotic group and two of the 47 members of the placebo group discontinued intervention.
Selective reporting (reporting bias)	Low risk	All the predetermined outcomes in the study method were reported.
Hajifaraji et al[10]		
Random sequence generation (selection bias)	Low risk	Participants were divided into two groups of 32 using computer-generated random sequence blocking by computer software.
Allocation concealment (selection bias)	Low risk	The placement of individuals in the intervention or control group was randomized. In this trial, the envelopes were coded as "A" or "B".
Blinding of participants and personnel (performance bias)	Low risk	Participants and researchers were blinded.
Blinding of outcome assessment (detection bias)	Unclear	Not enough explanation was given in the method in this case.
Incomplete outcome data (attrition bias)	Low risk	Two of the 32 members of the probiotic group and one of the 32 members of the placebo group discontinued intervention. Two of each group needed drug therapy. One of the placebo group occurred preterm pregnancy
Selective reporting (reporting bias)	Low risk	All the predetermined outcomes in the study method were reported.
Badehnoosh et al[18]		
Random sequence generation (selection bias)	Low risk	Participants were divided into two groups of 30 using computer-generated random sequence blocking by computer software.
Allocation concealment (selection bias)	Low risk	The placement of individuals in the intervention or control group was randomized.
Blinding of participants and personnel (performance bias)	Low risk	Participants and researchers were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessment was done.
Incomplete outcome data (attrition bias)	Low risk	All of 60 women in the study continued the intervention.
Selective reporting (reporting bias)	Low risk	All the predetermined outcomes in the study method were reported.
Karamali et al[19]		
Random sequence generation (selection bias)	Low risk	Participants were divided into two groups of 30 using computer-generated random sequence blocking by computer software.
Allocation concealment (selection bias)	Low risk	The placement of individuals in the intervention or control group was randomized.
Blinding of participants and personnel (performance bias)	Low risk	Participants and researchers were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessment was done.
Incomplete outcome data (attrition bias)	Low risk	All of 60 women in the study continued the intervention.
Selective reporting (reporting bias)	Low risk	All the predetermined outcomes in the study method were reported.
Lindsay et al[20]		
Random sequence generation (selection bias)	Low risk	Participants were divided into groups of 74 and 75 using computer-generated random sequencing.
Allocation concealment (selection bias)	Low risk	The placement of individuals in the intervention or control group was randomized. In this trial, the envelopes were coded as "A" or "B".
Blinding of participants and personnel (performance bias)	Low risk	Participants and researchers were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessment was done.
Incomplete outcome data (attrition bias)	Low risk	Nine members of each group lost to follow out. And four of each group discontinued intervention.
Selective reporting (reporting bias)	Unclear	Not enough explanation was given in the method in this case.

Table 2. Characteristics of studies included in the review

Authers, (Year)	Study type	Intervention	Control	Sample size Intervention/ Control	The length of the intervention	Probiotic species	Total dose of probiotic (CFU)
Nabhani et al[7] (2018)	RCT	Synbiotic	Placebo	48/ 47	6 weeks	*Lactobacillus acidophilus*	5×10^{10}
						L. plantarum	1.5×10^{10}
						L. fermentum	$7\ 10^{9}$
						L. gasseri	2×10^{10}
						FOS as prebiotic substance	38.5 (mg)
Hajifaraji et al[10] (2017)	RCT	Probiotic	Placebo	32/ 32	8 weeks	*Lactobacillus acidophilus LA-5*	$>4\times10^{9}$
						Bifidobacterium BB-12	
						Streptococcus thermophilus STY-31	
						Lactobacillus delbrueckii bulgaricus LBY-27 plus	
Badehnoosh et al[18] (2018)	RCT	Probiotic	Placebo	30/ 30	6 weeks	*Lactobacillus acidophilus*	2×10^{9}
						Lactobacillus casei	
						Bifidobacterium bifidum	
Karamali et al[19] (2018)	RCT	Synbiotic	Placebo	30/ 30	6 weeks	*Lactobacillus acidophilus strain T16*	2×10^{9}
						L. casei strain T2	
						Bifidobacterium bifidum strain T1	
						Inulin	800 (mg)
Lindsay et al[20] (2015)	RCT	Probiotic	Placebo	74/ 75	6 weeks	*Lactobacillus salivarius*	1×10^{9}

CFU: Colony-forming unit, FOS: Fructooligosaccharide.

showed that probiotic or synbiotic supplementation had no effect on the incidence of preeclampsia (Figure 4C).

Secondary Outcomes

The Effect of Probiotics or Synbiotics in Comparison with Placebo Group on the Rate of Cesarean Section

Three RCTs[18,19] with a total sample size of 267 participants evaluated the effect of probiotics or synbiotics in comparison with placebo group on the rate of cesarean delivery in pregnant women with GDM. The overall estimated effect did not indicate a significant reduction in cesarean delivery rate in the intervention group compared with placebo (OR = 0.52, 95% CI = 0.18 to 1.50, $P = 0.23$). There was a significant heterogeneity between studies ($I^2 = 70\%$, $P = 0.03$); hence, a random effect model was used to collect data (Figure 4D).

The Effect of Probiotics or Synbiotics in Comparison with Placebo Group on the Rate of Macrosomia

Three RCTs[18,19] with a total sample size of 267 participants evaluated the effect of probiotics or synbiotics on the rate of macrosomia in pregnant women with GDM compared with placebo. The overall estimated effect did not show a significant decrease in macrosomia rate in the intervention group compared to placebo (OR = 0.81, 95% CI = 0.41 to 1.57, $P = 0.53$). There was no significant heterogeneity between studies ($I^2 = 48\%$, $P = 0.15$); hence, the fixed effect model was used to collect data (Figure 4E).

The Effect of Probiotics or Synbiotics in Comparison with Placebo Group on Infant 5-Minute Apgar Score

Three RCTs[18,19] with a total sample size of 267 participants evaluated the effect of probiotics or synbiotics in the 5-minute neonatal Apgar score of pregnant women with GDM compared with the placebo group. The overall estimated effect did not indicate a significant decrease in the score of 5-minute Apgar in the intervention group compared to placebo (SMD = 0.16, 95% CI = -0.06 to 0.39, $P = 0.15$). There was no significant heterogeneity between studies ($I^2 = 0\%$, $P = 0.41$); hence, the fixed effect model was used to collect data (Figure 4F).

The Effect of Probiotics or Synbiotics in Comparison with Placebo Group on Newborn's Birth Weight

Three RCTs[18,19] with a total sample size of 267 participants evaluated the effect of probiotics or synbiotics on newborn's birth weight in pregnant women with GDM compared with placebo. The overall estimated effect did not show a significant decrease on birth weight in the intervention group compared to placebo (SMD = -0.18, 95% CI = -0.43 to 0.06, $P = 0.13$). There was no significant heterogeneity between studies ($I^2 = 0\%$, $P = 0.43$); hence, the fixed effect model was used to collect data (Figure 4G).

The Effect of Probiotics or Synbiotics in Comparison with Placebo Group on Gestational Age

Three RCTs[18,19] with a total sample size of 267 participants evaluated the effect of probiotics or synbiotics on

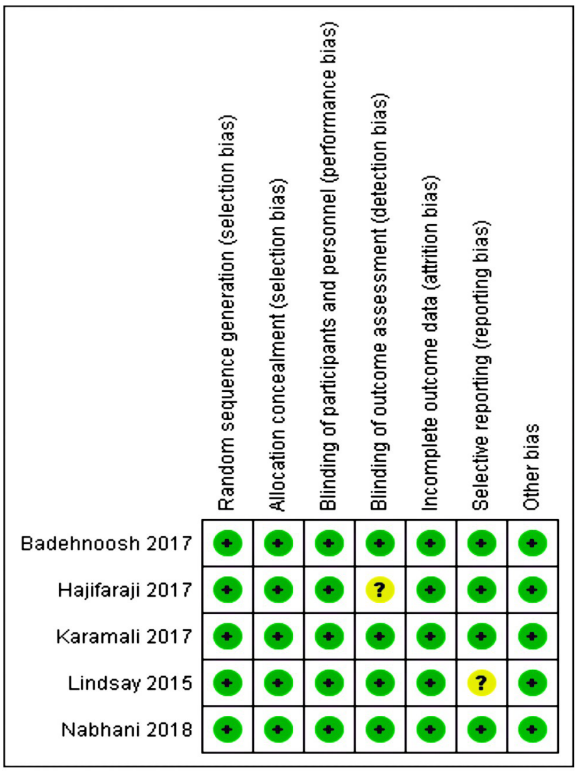

Figure 2. Risk of bias summary: Review authors' judgments about each risk of bias item for each included study

gestational age in pregnant women with GDM compared to placebo. The overall estimated effect did not indicate a significant decrease in gestational age in the intervention group compared to placebo (SMD = 0.13, 95% CI = -0.11 to 0.37, $P = 0.28$). There was no significant heterogeneity between studies ($I^2 = 0\%$, $P = 0.71$); hence, the fixed effect model was used to collect data (Figure 4H).

Discussion

This systematic review included five RCTs. Two articles evaluated the effect of probiotic or synbiotic supplements on blood pressure for 6 to 8 weeks, and three articles investigated the effect of the mentioned supplements on preeclampsia and other pregnancy outcomes. According to the pooling data of meta-analysis, there was no significant difference between the two groups of probiotic or synbiotic supplementation and placebo regarding blood pressure, preeclampsia, and other pregnancy outcomes.

Evidence suggests that pathologic changes in the maternal vascular endothelium lead to a variety of manifestations of preeclampsia such as changes in vascular responses, vasospasm, and abnormalities in some body systems.[21] These endothelial changes can also be due to oxidative stress.[8]

The gut microbiota plays an important role in lowering blood pressure,[22] reducing inflammation,[23] hemostasis, glucose metabolism,[24] and body mass index.[25] These supplements play a positive role in reducing oxidative stress and systemic inflammation.[26] They are also useful in the physiological processes involved in diabetes, HTN, inflammation, and kidney function.[13]

Lately, clinical studies have suggested that the role of pharmacological therapy along with dietary supplementation is of paramount importance in the management of HTN during pregnancy.[27]

The anti-inflammatory response mechanism of probiotics, like the mechanism of anti-inflammatory drugs, is modulating the expression of genes responsible for inflammation in the gut and HTN.[28] These supplements also reduce inflammation created in human placental trophoblast cells.[29,30] Probiotic bacteria produce and regulate short-chain fatty acids, which prevents the production of inflammatory enzymes and improves the antioxidant status.[31]

Probiotics may also be involved in controlling and improving blood pressure through several different mechanisms. For example, it may improve cholesterol and blood lipids,[32] and regulate the renin-angiotensin production system through producing angiotensin-converting enzyme inhibitory peptides.[33] Other mechanisms, such as increased nutrient and

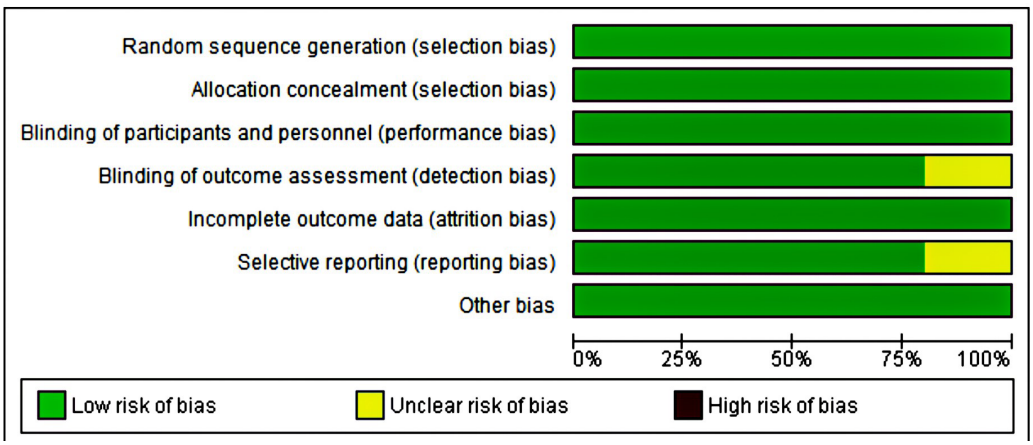

Figure 3. Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies

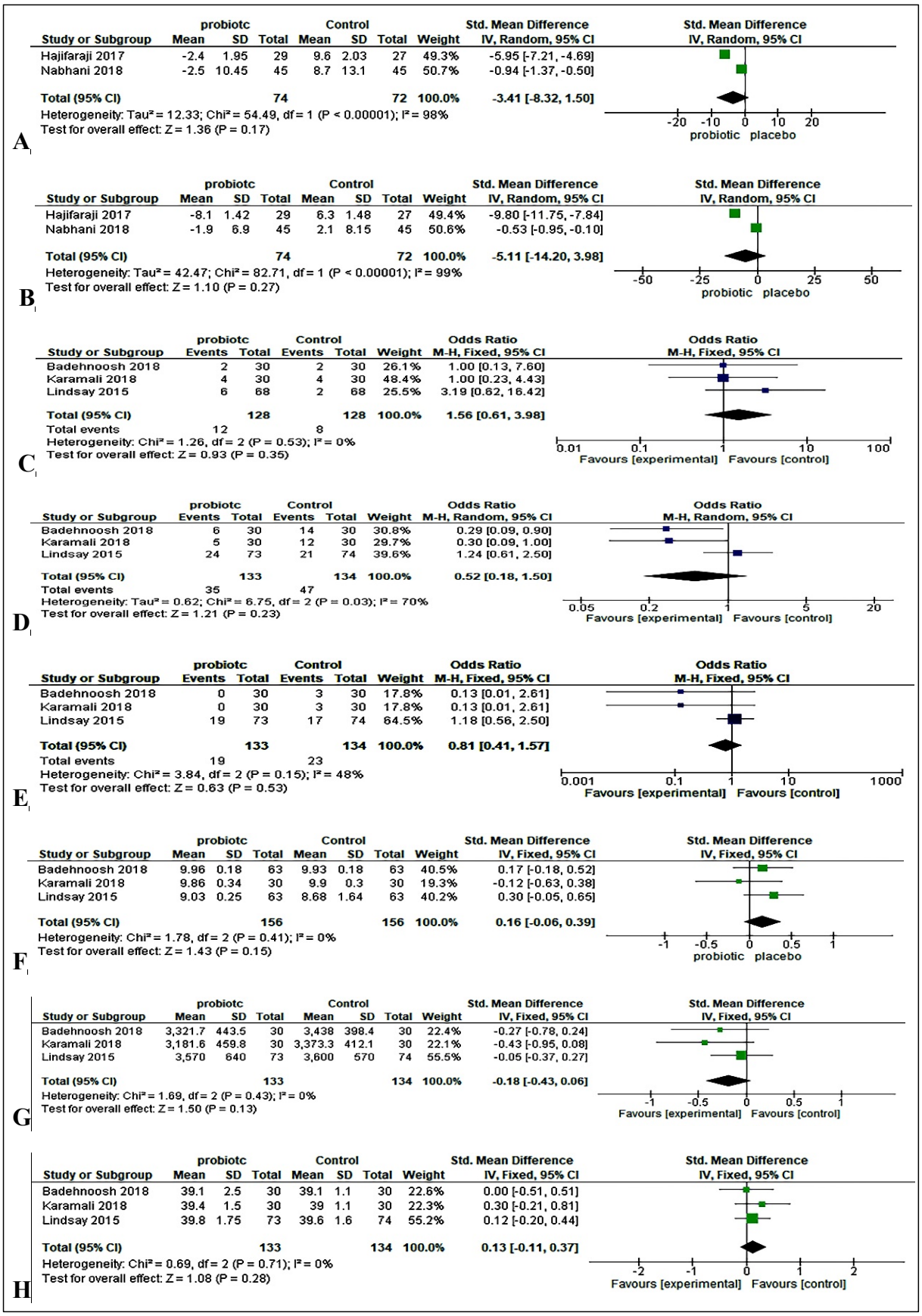

Figure 4. Primary outcomes: Forest plot of included study- Effect of probiotic or synbiotic compared with placebo on **A:** Systolic blood pressure, **B:** Diastolic blood pressure **C:** Preeclampsia. **Secondary outcomes:** Forest plot of included study- Effect of probiotic or synbiotic compared with placebo on **D:** Cesarean section rate, **E:** Macrosomia, **F:** 5-min Apgar score, **G:** Birth weigh, **H:** Gestational age

phytoestrogens uptake, and reduced blood sugar and inflammatory GDM may be one of the mechanisms of the effect of probiotics on blood pressure.[34]

The most important factors affecting the potential of probiotics on inflammation, oxidative stress, and metabolism are species and strains of probiotics.[35] Lactic acid bacteria, especially *Lactobacillus* and *Bifidobacterium* species, provide conditions for improving nutritional values and vitamin content of food products.[36]

The results of a meta-analysis by Zhang et al[37] showed that probiotic supplementation could reduce the risk of hyperbilirubinemia in newborn and improve glycemic control, glycaemia, lipid profile, inflammation, and oxidative stress in pregnant women with GDM and reduce triglycerides. Nevertheless, similar to this study, probiotic effect was not significant in gestational age and macrocosmic variables. The results of another meta-analysis by Peng et al[38] showed that probiotic supplementation resulted in a significant decrease in fasting blood glucose, insulin resistance, and insulin concentration in pregnant women. However, the probiotic effect on gestational age and birth weight was not significant as in this study.

In the study conducted by Badehnoosh et al[18] the probiotic supplementation in women with GDM for 6 weeks had beneficial effects on Fasting Plasma Glucose (FPG), inflammatory factors, oxidative stress index, neonatal hyperbilirubinemia, neonatal hospitalization, and cesarean section.

In the present study, the effect of probiotics on the blood presser and incidence of preeclampsia was not significant. In a systematic review by Lindsay et al[20] the use of probiotics had a protective effect on the incidence of preeclampsia. Probiotics have also been shown to be a safe and reliable therapeutic tool to improve maternal outcomes. According to one of the included articles by Brantsaeter et al[39] the consumption of probiotic-containing dairy products was associated with a reduced risk of preeclampsia, especially severe preeclampsia.

In a cohort study conducted by Nordqvist et al[40] consumption of probiotic-containing milk in late pregnancy was associated with a low risk of preeclampsia, especially severe preeclampsia. However, no association was found between probiotic use in pre-pregnancy and early pregnancy with preeclampsia.

In the study by Safavi et al[41] synbiotic supplementation reduced inflammatory factors, fasting blood sugar and insulin resistance. Moreover, in the study by Nikniaz et al[42] synbiotic supplementation increased the total antioxidant capacity of breast milk. In another study by Nabhani et al[7] synbiotic supplementation significantly reduced both SBP and DBP. Although Karamali et al[19] concluded that synbiotic supplementation can have a positive effect on pregnancy outcomes, Taghizadeh et al[43] showed that consumption of synbiotics among pregnant women does not affect pregnancy outcomes.

Contradiction between studies may also be due to the presence of GDM underlying disease in the studies reviewed in this systematic review. Also the heterogeneity of the results of different studies can be related to the applied probiotic species and the duration of the intervention. *Lactobacillus* species had been used in all studies.

It seems that the studies that used more species such as *Lactobacillus* in combination with Bifidobacterium reported more favorable results. For example, the SBP and DBP results in pregnant women with GDM in the study by Hajifaraji et al[10] that used both probiotic strains were more significant than the study by Nabhani et al[7] that used only one *Lactobacillus* species. In the study by Hajifaraji et al[10] which evaluated the results every two weeks, until the fourth week, there was no significant difference in SBP and DBP between the two groups. From week 6, the probiotic effect on the control group was significant and from week 8, the statistical significance was very high.

In line with the study by Hajifaraji et al[10] a meta-analysis by Khalesi et al[34] reported the important benefits of probiotics on improving blood pressure. In this article, studies that used probiotics for more than 8 weeks showed a greater reduction in SBP and DBP than studies that used this supplement for less than 8 weeks. Moreover, studies that used several types of these supplements had a favorable effect on SBP or DBP.

According to the previous studies, it seems that probiotic or synbiotic supplements can have a better effect on disorders such as high blood pressure and preeclampsia if used prophylactically and for a long time. This could be due to the possible gradual effects of probiotics on intestinal microbiota and correction of existing conditions.

In current study, the results of each of the RCTs which evaluated the blood pressure of women with GDM showed significant effects, though there was a high heterogeneity among them. The number RCTs carried out in this field is very limited, and both studies are related to Iran.

The results of this systematic review and meta-analysis should be considered with the following limitations: First, there was heterogeneity in some types of intervention, including differences in species, strain, and probiotic dose. Second, the number of RCTs in this field is very limited, and this may be a reason for the insignificance of the effect of probiotics on HTN. Moreover, most of the studies had been conducted in Iran, which might undermine the generalizability of the results. Hence, further RCTs on different ethnicities and a larger sample size are needed. Third, the duration of intervention with these supplements should be longer than 8 weeks to obtain the desired results from probiotic or synbiotic use.

Conclusion

There was no significant difference in HTN, preeclampsia, cesarean delivery, 5 minute Apgar, macrosomia, birth weight, and gestational age between the two groups

Research Highlights

What is the current knowledge?

- Probiotics can have anti-inflammatory and antioxidant effects if used for a long time.
- If different species and strains are used, they will have a better effect.
- These types of supplements have a better effect if used as a prevention than when used as a treatment.

What is new here?

To achieve better results, many studies with long interventions, from different complementary strains in different areas are needed.

receiving probiotic supplement and the control group. Conducting more studies among different races to better generalize the results and homogenize them in terms of the type of intervention probiotic can be helpful in the achievement of more conclusive results.

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Authors' Contributions

RM, AFKH, MSH, MEM: Study concept and design; RM, AFKH, MSH, KHH, MEM: Acquisition, analysis, and interpretation of data; RM, AFKH, KHH, MEM: Drafting of the manuscript; RM, AFKH, MSH, KHH, MEM: Critical revision of the manuscript for important intellectual content; RM, AFKH, MSH, KHH: Statistical analysis. All authors have read and approved the manuscript.

Conflict of Interests

The authors declare that they have no competing interests.

Data Accessibility

The datasets are available from the corresponding author on reasonable request.

Ethical Issues

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Iran (Code: IR.TBZMED.REC.1398.556).

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Not applicable.

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