

REVIEW ARTICLE

Probiotics in pregnancy and maternal outcomes: a systematic review

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Abstract

Objectives: To systematically review the literature on the use of probiotics in pregnancy and their impact on maternal outcomes.

Methods: Online databases were searched in April 2012 using the following terms to identify eligible studies: "probiotics", "pregnancy", "maternal outcomes" and "metabolism". Primary outcomes of selected studies were maternal fasting glucose during pregnancy and rates of gestational diabetes mellitus (GDM). Secondary outcomes were rates of pre-eclampsia, maternal inflammatory markers and lipid profiles and gestational weight gain. Studies whose primary outcomes were bacterial vaginosis, pre-term delivery and infant atopy were excluded. Only English-language articles were included. The limited number of eligible studies and varying outcomes precluded formal meta-analysis of these data.

Results: Initially, 189 articles were identified and screened. Seven articles met inclusion criteria and are included in the present review. Results demonstrated that probiotic use in pregnancy could significantly reduce maternal fasting glucose, incidence of GDM and pre-eclampsia rates and levels of C-reactive protein.

Conclusions: Probiotics hold potential as a safe therapeutic tool for the prevention of pregnancy complications and adverse outcomes related to maternal metabolism. Further randomised controlled trials are urgently required, particularly among those at high risk of metabolic disorders, such as overweight and obese pregnant women.

Keywords

Maternal outcomes, metabolism, pregnancy, probiotics

History

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Introduction

Probiotics are defined as live microorganisms, which when administered in adequate amounts, confer a health benefit on the host [1]. The human gastrointestinal tract is host to a vast ecosystem of microbes which are necessary for health, however, specific alterations in the microbiota composition or activity also has the potential to influence disease [2,3]. The use of probiotics is one method by which the gut microbiota activity may be manipulated to benefit health [4].

The therapeutic role of probiotics on mucosal immunity, intestinal disorders and allergies has been well established [2,5,6]. Evidence is also emerging that gut microbiota play an important role in energy homeostasis, inflammation and glucose metabolism [7,8]. Furthermore, recent data suggests that manipulation of the maternal gut microbiota during pregnancy may have important benefits in terms of improving maternal metabolic profile [9,10] and pregnancy outcomes [11,12].

Pregnancy is a critical period of development during which particular events or stimuli and maternal nutritional status may 'program' the long-term function and health of the offspring [13]. On this basis, the maternal gut microbiota is thought to contribute towards the microbial, metabolic and immunological programming of the child [14]. The use of probiotics in pregnancy to influence offspring immunity and prevent atopic disorders has been the topic of numerous studies, which were recently reviewed in a meta-analysis [15]. Similarly, the effect of probiotic use in pregnancy on bacterial vaginosis and subsequent pre-term labour was recently reviewed [16]. However, studies have also emerged which are investigating probiotic use in pregnancy and subsequent maternal metabolic outcomes, including glucose metabolism [10] and gestational diabetes mellitus (GDM) [11], pre-eclampsia [12], gestational weight gain [17], lipid profile [18] and levels of inflammatory markers [9]. Such maternal outcomes can hold serious implications for the future health of both mother and offspring. For example, GDM increases the future risk of type-2 diabetes for the mother and birth of a macrosomic infant, with later implications for childhood obesity and diabetes [19]. Thus, probiotics hold potential as an important and safe therapeutic tool during pregnancy, which may have far-reaching beneficial effects beyond that of controlling atopic disorders and vaginal infections.

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The aim of this paper is to systematically review all studies reporting maternal metabolic outcomes associated with probiotic use in pregnancy.

Methods

This systematic review was conducted according to recommendations of the PRISMA statement [20]. The PubMed, MEDLINE, EMBASE and Cochrane Databases were searched in April 2012 for eligible human-based studies. Only English-language articles, without time restrictions, were included. Combinations of the search terms “probiotics”, “pregnancy”, “maternal outcomes” and “metabolism” were used to identify eligible studies. Only randomised controlled trials (RCTs) and prospective cohort studies were included. Abstracts of the publications identified by the primary search were reviewed and the references of included manuscripts were also searched for additional, potentially important publications. Multiple abstracts from the same authors/dataset were identified to avoid duplication. In addition, online trial registries (www.controlled-trials.com and www.clinicaltrials.gov) were searched for eligible studies.

The primary outcomes were maternal fasting glucose during pregnancy and incidence of GDM. Secondary outcomes included incidence of pre-eclampsia, maternal inflammatory markers and lipid profiles, gestational weight gain, vaginal infections, pre-term birth, neonatal morbidity or mortality, infant growth, infant atopy, breast milk composition and infant gut microbiota composition. Studies of probiotic use in pregnancy whose primary outcomes were pre-term birth, vaginal infections or infant atopy were excluded as they have been recently reviewed by other publications.

Results

Figure 1 presents the search strategy for included studies. A total of six randomised trials [9–11,17,18,21] and one prospective cohort study [12] involving probiotic use in pregnancy and maternal metabolic outcomes were identified. Among the six RCTs, there were only two individual research groups/datasets, each having three publications on various maternal metabolic endpoints. The first of these research groups is based in Finland and randomised 256 women in their 1st trimester to one of three interventions. The second research group is based in Iran and randomised 70 women in their third trimester to a probiotic or placebo intervention.

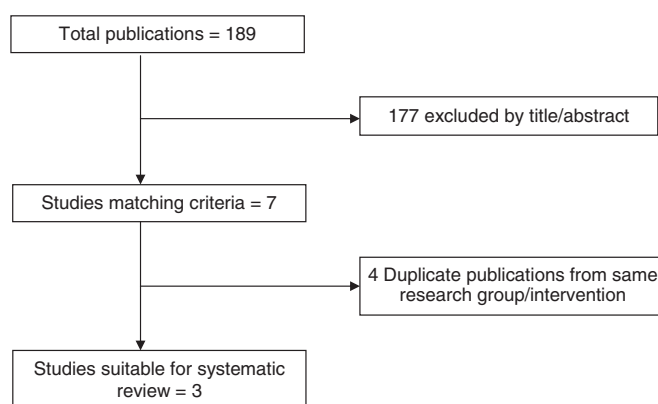


Figure 1. Search strategy.

A total of 33 399 primiparous women who consumed probiotics in pregnancy were followed in the prospective cohort study. Details of each of the included studies' outcomes and methodology are presented in Table 1 and results are presented in Table 2.

Brantsaeter et al. [12] reported that intake of probiotic milk-based products is associated with a reduced risk of pre-eclampsia, particularly severe pre-eclampsia (OR = 0.79, 95% CI: 0.66–0.96). Daily probiotic intake offered the lowest pre-eclampsia risk for all sub-types (OR = 0.80, 95% CI: 0.66–0.96) but particularly for the more severe cases (OR = 0.61, 95% CI: 0.43–0.89). Results from Luoto and colleagues report significant effects of a probiotic-supplemented dietary counselling intervention on maternal blood glucose (baseline-adjusted means 4.45, 4.60 and 4.56 mmol/l in diet/probiotics, diet/placebo and control/placebo groups respectively; $p = 0.025$) [10], insulin concentration (adjusted means 7.55, 9.32 and 9.27 mU/l for diet/probiotic, diet/placebo and control/placebo groups respectively; $p = 0.032$) [10], GDM incidence (13%, 36% and 34% in the diet/probiotic, diet/placebo and control/placebo groups respectively; $p = 0.003$) [11] and central adiposity at six months post-partum (OR 0.30, 95% CI 0.11–0.85, $p = 0.023$ adjusted for baseline body mass index [BMI]) [17]. In a separate study, Asemi and colleagues reported a significant reduction in maternal levels of high sensitivity C-reactive protein (hs-CRP) among consumers of probiotic yoghurt (10.44 ± 1.56 to 7.44 ± 1.03 $\mu\text{g/ml}$; $p = 0.041$), which was also significantly different from the conventional yoghurt group ($p = 0.001$) [9]. There was no significant change in tumour necrosis factor (TNF)- α levels in either yoghurt group in this study ($p = 0.633$ for probiotic yoghurt, $p = 0.134$ for conventional yoghurt) and the effects on lipid profiles [18] and biomarkers of oxidative stress [21] were inconclusive, with no significant differences between the probiotic and conventional yoghurt groups reported.

Discussion

Although, there is a substantive body of literature on the use of probiotics in pregnancy, research into the effects of probiotics on maternal metabolism and pregnancy outcomes is in its infancy. The limited number of studies to date on this topic has identified a variety of pregnancy outcomes that may be affected. The suggested mechanisms of these effects are thought to be similar, with the metabolic activities of the gut microbiota playing a central role.

Evidence for a link between the gut microbiota and obesity and associated metabolic disorders first emerged when differences in the gut microbiota composition were observed between obese and lean individuals [22]. Obesity is often characterised by reduced numbers of Bacteroidetes, while an increased ratio of the Bacteroidetes phylum (predominantly the Gram-negative *Bacteroides*) to Firmicutes phylum (which includes the Gram-positive *Clostridium* group) is associated with metabolic health [4,8]. Alterations in gut microbial composition according to weight status have also been reported among pregnant women [23,24]. Santacruz et al. [23] reported increased numbers of *Staphylococcus*, *Enterobacteriaceae* and *Escherichia coli* species and reduced

Table 1. Summary of methodology of included studies.

References	Primary outcome	Secondary outcomes	Study design	N	Mean age (years)	Mean BMI (kg/m ²)	Probiotic type	Placebo	Intervention	Intake from/until
Brantsaeter et al. [12]	Pre-eclampsia	None	Prospective cohort	33 399	Not stated, but 59% aged 20–29 years	Not stated, but 66% in normal range	Lactobacillus acidophilus and Lactobacillus rhamnosus from milk and yoghurt based products	N/A	Assessment of milk-based probiotic intake and observation of pre-eclampsia incidence among consumers/non-consumers	Self-reported habitual intake during pregnancy
Luoto et al. [11]; Laitinen et al. [10]; Ilmonen et al. [17]	Maternal anthropometry over 12 month post-partum period	Maternal glucose metabolism, incidence of GDM, adverse pregnancy outcomes, foetal and infant growth	Double-blind placebo-controlled randomised trial	256	30	23.6	Lactobacillus rhamnosus GG (10 ¹⁰ cfu) and Bifidobacterium lactis Bb12 (10 ¹⁰ cfu) in a single capsule	Matching appearance, taste, smell and level of intake (1/ day)	Randomisation to 1 of 3 groups: dietary counselling and probiotic; dietary counselling and placebo; no dietary counselling and placebo	First trimester until end of exclusive breast-feeding
Asemi et al. [9]; Asemi et al. [18]; Asemi et al. [21]	Maternal inflammatory markers and biomarkers of oxidative stress	Maternal lipid profiles, insulin resistance, serum calcium, iron, AST and ALT	Single-blind placebo-controlled randomised trial	70	24.95	24.9 in probiotic group, 25.5 in placebo group ($p > 0.05$)	Lactobacillus acidophilus LA5 and Bifidobacterium animalis BB12 (10 ⁷ cfu in total) in 200 g yoghurt form	Matching appearance, taste, smell, portion size and level of intake (1/ day)	Randomisation to a daily probiotic or placebo yoghurt	Third trimester for nine week period

N/A, not applicable; cfu, colony forming units; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2. Summary of results of included studies.

References	Maternal outcomes	Foetal outcomes	Mean gestational weight gain	Dietary intakes
Brantsaeter et al. [12]	Reduced risk of severe pre-eclampsia associated with intake of probiotic milk products (OR = 0.79), lowest risk observed at highest level of intakes (OR = 0.61)	Not reported	Not recorded	Lower intakes of protein and dietary fibre among women that developed pre-eclampsia.
Laitinen et al. [10]	Reduced plasma glucose ($p = 0.025$) and improved insulin sensitivity ($p = 0.028$) in diet/probiotic group, during pregnancy and post-partum.	Normal birth weight, gestational age and post-natal growth in all study groups. No differences in adverse events between the groups.	15 kg in diet/probiotic group, 14.8 kg in diet/placebo and control/placebo groups ($p > 0.05$).	No difference in energy intakes between groups. Significantly higher intakes of MUFA and PUFA and lower intake of SFA in the diet/probiotic and diet/placebo groups compared to the control/placebo group. No significant differences in macronutrient intakes between the diet/probiotic and diet/placebo groups.
Luoto et al. [11]	Reduced GDM frequency in diet/probiotic group (13%) compared to diet/placebo (36%) and control/placebo (34%) groups ($p = 0.03$).			
Ilmonen et al. [17]	Reduced risk of central adiposity in the diet/probiotics group (OR 0.3, $p = 0.023$)			
Asemi et al. [9]	Reduced serum hs-CRP in the probiotic group ($p = 0.041$). No effect of probiotic or conventional yoghurt on TNF- α .	No adverse events associated with either group.	9.4 kg in probiotic yoghurt group, 9.34 kg in conventional yoghurt group ($p > 0.05$)	No significant changes in dietary intakes between the study groups or within groups during the intervention period.
Asemi et al. [18]	Reduced serum total, HDL, LDL cholesterol and reduced serum triglycerides in both probiotic and conventional yoghurt groups. No significant differences between the groups.			
Asemi et al. [21]	Significant effect on erythrocyte GR but no effect on other markers of oxidative stress			

OR, odds ratio; GDM, gestational diabetes mellitus; HDL, high density lipoprotein; LDL, low density lipoprotein; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

numbers of *Bifidobacterium* and *Bacterioides* in overweight compared to normal-weight pregnant women, which is in agreement with findings from studies in non-pregnant women. However, Collado et al. [24] reported somewhat conflicting results, with significantly higher levels of *Bacterioides* and *Staphylococcus* in overweight pregnant women and a significant association between high *Bacterioides* concentrations and excessive gestational weight gain. It has been acknowledged that confounding factors, such as age and dietary intakes, may influence the gut microbiota among overweight and obese individuals [8], which may explain the discrepancies between these two studies of pregnant women.

Various mechanisms have been proposed by which the gut microbiota may influence obesity and metabolism. These include increased energy harvest from the diet to generate short-chain fatty acids (SCFA) [25], microbial regulation of serum lipids and cholesterol [4] and of carbohydrate metabolism [25] and increased bacterial lipopolysaccharide (LPS) expression which triggers pro-inflammatory cytokine production and subsequent low-grade chronic inflammation [26]. The use of probiotics is one way in which the gut microbiota may be altered to improve metabolic health [4]. Although the current review presents a variety of positive and null effects of probiotic consumption in pregnancy on maternal outcomes, no adverse effects of their use in this population group have been identified to date [27,28].

As part of the large Norwegian observational study ‘‘The Mother and Child Cohort Study’’, Brantsaeter et al. [12] observed the incidence of pre-eclampsia among pregnant women who reportedly consumed milk-based probiotics containing *Lactobacillus* bacteria. The protective effects appear to be most prominent in cases of severe pre-eclampsia and with daily probiotic product intakes. Pre-eclampsia is a serious condition associated with poor pregnancy outcomes, including maternal and perinatal mortality [29]. During early pregnancy, successful implantation occurs in a pro-inflammatory microenvironment mediated by a Th1-type response. This is then followed by a shift to Th2 to control endocrine and immune interactions. Additionally, progesterone stimulates a Th2-type response, which acts to reduce inflammatory cytokines and represses allogeneic responses, which are thought to confer survival advantage to the foetus [30]. However, evidence suggests that an excessive maternal inflammatory response to pregnancy is responsible for the development of pre-eclampsia [31]. Thus, the reported intake of *Lactobacillus* probiotics among women in this study may have suppressed the Gram-negative bacterial LPS expression to reduce inflammation. This mechanism would be in agreement with the findings of Yeganegi et al. [32] in which supernatant fluid of *L. rhamnosus* GR-1 influenced the LPS response in placental trophoblast cells to reduce overall systemic inflammation levels. Furthermore, clinical trials in non-pregnant individuals involving the use of milk-based probiotics have reported reduced blood pressure effects [33,34]. Although this study is limited by its observational design and once-off assessment of probiotic intakes in pregnancy, the researchers did control for various confounding factors including pre-pregnancy BMI, educational

attainment, smoking status, dietary supplement use, total energy intake and dietary fibre intake [12]. This appears to be the first study to examine the relationship between probiotic intake and pre-eclampsia and clinical trials are warranted to further examine the potential beneficial effects and exact mechanisms involved.

A recent RCT conducted by Asemi and colleagues (Table 1) investigated the anti-inflammatory effects of probiotics during pregnancy [9]. Pregnancy is associated with an increased production of pro-inflammatory factors due to increased adipose tissue, especially in the third trimester [35]. This in turn is associated with various pregnancy complications including insulin resistance and GDM [36], preterm delivery [37] and pre-eclampsia and intrauterine growth restriction [38]. In this single-blind RCT, daily consumption of a probiotic yoghurt containing *Lactobacillus* and *Bifidobacterium* species from 28 to 37 weeks gestation significantly lowered serum levels of hs-CRP from 10.44 ± 1.56 to 7.44 ± 1.03 $\mu\text{g/ml}$ ($p = 0.041$), while consumption of the conventional yoghurt had no significant effect [9]. The authors suggested that the SCFA produced by the probiotic bacteria were responsible for lowering serum hs-CRP via enzymatic blocking of its hepatic synthesis [9]. However, these anti-inflammatory effects may be limited as no significant change was observed in TNF- α levels for either yoghurt group.

Another outcome examined by Asemi et al. were indices of oxidative stress, including plasma total antioxidant capacity, erythrocyte glutathione reductase (GR), glutathione peroxidase and plasma glutathione (GSH) [21]. Oxidative stress in pregnancy is associated with various adverse outcomes including pre-eclampsia [39], low birth weight [40] and premature delivery [41]. Asemi et al. [21] reported that consumption of the probiotic yoghurt significantly increased GR and this effect was significantly different from that of the conventional yoghurt on GR levels ($p = 0.01$). GR is responsible for catalysing the production of glutathione (GSH), an important anti-oxidant. Although the probiotic yoghurt also significantly increased levels of GSH ($p = 0.01$) and affected other indices of oxidative stress, changes in these parameters were not significantly different from the conventional yoghurt group [21]. Therefore, this study yielded inconclusive results on the ability of probiotic yoghurts to reduce oxidative stress in pregnancy.

Asemi et al. have also published results on the effect of the probiotic versus conventional yoghurt on maternal lipid profiles in pregnancy [18]. The probiotic yoghurt significantly reduced total ($p = 0.001$), HDL (0.002) and LDL (0.006) cholesterol, as well as triglyceride levels ($p = 0.02$), although changes in these parameters were not significantly different from the conventional yoghurt group. Therefore, there is currently no evidence for a positive effect of probiotics in pregnancy on oxidative stress or lipid metabolism. However, studies in non-pregnant individuals have reported beneficial effects of various probiotics on such parameters [42,43]. Asemi et al. [18] acknowledged several limitations of their RCT which may have contributed to their negative findings, including the use of a single-blinded randomised design and short intervention period (nine weeks) due to budget restrictions.

The Nutrition, Allergy, Mucosal immunology and Intestinal microbiota (NAMI) programme in Finland appear to be the first researchers to publish results on the effects of probiotics in pregnancy on maternal insulin resistance and GDM. This programme involves probiotic administration combined with balanced maternal nutrition during pregnancy and lactation. The overall objective is “to provide a new direction in the search for scientifically validated means of reducing the risk of Western lifestyle disease” [11]. The study population for this programme’s on-going prospective, randomised trial included 256 mother-baby pairs, the mothers being recruited early in pregnancy at their first antenatal visits. The intervention involved randomisation to receive either individualised dietary counselling or routine standard care. The diet group was further randomised to receive a daily probiotic capsule (diet/probiotic group), containing *Lactobacillus Rhamnosus GG*, ATCC 53 103 and *Bifidobacterium lactis* Bb12 at a dose of 10^{10} colony-forming units/day of each, or placebo (diet/placebo group). These were continued until six months postpartum while mothers were lactating. The standard care group received a placebo (control/placebo group).

As a component of the NAMI programme, Laitinen et al. [10] (Table 2) reported that blood glucose concentrations during pregnancy were lowest in the diet/probiotic group and this group also had better glucose tolerance, as evidenced by a reduced risk of elevated glucose concentration compared to the control/placebo group ($p = 0.013$) and the lowest insulin concentration out of all treatment groups. The authors suggested that the observed pronounced effect of probiotics on glucose metabolism is most likely attributable to their immune-regulatory properties, which reduce inflammation, a factor which plays a fundamental role in insulin resistance [44].

Also in the NAMI programme, Luoto et al. [11] reported promising results of the probiotic-supplemented dietary counselling intervention on the incidence of GDM (Table 2) with the lowest rates occurring in the diet/probiotic group. The risk of GDM was not significantly different between the diet/placebo and control/placebo groups ($p = 0.823$), indicating that probiotics, rather than dietary changes, were responsible for the protective effect seen in the group receiving probiotics and dietary counselling. However, the dietary intervention, with or without probiotics, was reported to have a modifying effect on GDM among affected women, through a significant reduction in birth weight ($p = 0.035$) and length ($p = 0.028$) compared to babies born to GDM affected women in the control group. The dietary intervention in this RCT resulted in an increased fibre intake and improved quality of dietary fat [10]. Such dietary changes can modify the gut microbiota composition and thereby diminish the risk of GDM-associated foetal overgrowth [11]. Furthermore, this study attests the safety of an early probiotic intervention in pregnancy. No adverse events in mothers or children occurred and no significant differences in prenatal or postnatal growth rates among the study groups were detected.

Beneficial effects of the probiotic intervention in the NAMI programme on weight management for the mother have recently been reported by Ilmonen et al. [17]. The diet/probiotic intervention significantly reduced the risk of central

adiposity, defined as waist circumference ≥ 80 cm, at six months postpartum compared to the diet/placebo and control/placebo groups. These results are of particular importance given that central abdominal adiposity is a key risk factor for metabolic disorders, such as diabetes and cardiovascular disease, in women during the postpartum period [17]. The authors suggest that the reduced adiposity may be attributed to a probiotic-induced increase in intestinal permeability. Alternatively, the probiotics may be responsible for immune regulation through their production of anti-inflammatory cytokines, which have the capacity to dampen local and systemic inflammation associated with obesity [45].

In conclusion, the studies included in this systematic review demonstrate several beneficial effects of probiotic consumption in pregnancy, indicating their potential use as a safe therapeutic tool to improve maternal outcomes. However, discrepancies remain to be clarified on the effects of probiotics on maternal oxidative stress in pregnancy, while there appears to be no significant beneficial effect of probiotics on maternal lipid profiles.

It should be noted that the pre-pregnancy BMI of women recruited for these interventions were primarily in the normal weight category ($20.0\text{--}24.9\text{ kg/m}^2$). Thus, the effect of similar probiotic interventions among obese pregnant populations has not been determined, despite the fact that obesity significantly increases the risk of obstetric complications and poor birth outcomes [46]. Further controlled trials of probiotics in pregnancy are required to fully establish their effects on maternal metabolic outcomes and inclusion of overweight and obese women in future studies is likely to be of significant benefit from a public health perspective.

Declaration of interest

The authors report no conflicts of interest.

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