Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Review

Effects of probiotic supplementation during pregnancy on metabolic outcomes: A systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 27 December 2019
Received in revised form
13 February 2020
Accepted 2 March 2020
Available online 16 March 2020

Keywords:
Probiotics
Gestational diabetes
Glycemic control
Maternal outcomes
Fetal outcomes

ABSTRACT

Aim: To perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of probiotics in pregnancy on the incidence of gestational diabetes (GDM) and fasting plasma glucose (FPG).

Methods: A MEDLINE, EMBASE, Scopus and Cochrane search (up to May 30th, 2019) was performed to identify RCTs of comparison of probiotics with placebo/active comparators in pregnant women. Principal endpoints were the incidence of GDM and the change of FPG. Other maternal and fetal outcomes were secondary endpoints. Mantel-Haenszel Odds Ratio with 95% CI (MH-OR) was calculated for dichotomous outcomes, whereas standardized differences in means was calculated for continuous variables. (PROSPERO registration CRD42019139889).

Findings: A total of 17 RCTs, all versus placebo, was identified. The overall quality of the trials was satisfactory. No effect of probiotics on incidence of GDM (MH-OR: 0.77[0.51,1.16], p = 0.21,I2:62%) was observed, with a small but significant reduction of FPG (mean difference −1.01 [−1.96, −0.06]mg/dl, p = 0.02, I^2:46%). Among secondary endpoints, a significant reduction of maternal insulin (both in women with or without diabetes) was observed in the probiotics group.

Interpretation: Probiotics during pregnancy do not reduce the incidence of GDM, with a very little (statistically but not clinically significant) reduction of fasting plasma glucose.

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https://doi.org/10.1016/j.diabres.2020.108111
0168-8227/

Contents

1. Introduction

Gestational diabetes mellitus (GDM) is a condition of glucose tolerance that is first recognized during pregnancy and that can be associated with an increased risk of several maternal and fetal complications [1]. During pregnancy, some changes occur in the gut microbiome. Some studies link maternal microbial dysbiosis to increased insulin resistance, as well as inflammatory state and oxidative stress [2]. Probiotics are living and viable micro-organisms capable of providing, when ingested in adequate quantities, specific benefits to the health of their host. Probiotic supplementation during pregnancy seems to have some benefits on metabolic health: results of some randomized controlled trials (RCTs) suggest that probiotics reduce the incidence of GDM [3,4] and reduce fasting plasma glucose (FPG) and markers of insulin resistance [5,6]; on the contrary, other RCTs showed that probiotics had no influence on the prevention of GDM [7], nor on FPG and fasting serum insulin [8–9].

The inconsistency of results could be due to several reasons: generally, trials have small sample size; they often compare treatment arms (probiotics vs placebo) in addition to confounding molecules (i.e., inulin) making the interpretation of the independent effect of probiotics problematic [10]; furthermore, the probiotics used in experimental arms vary widely among studies. The limitation of the sample size could be overcome by combining studies in meta-analyses, thus increasing statistical power and producing more reliable estimates of the effect size. Unfortunately, results of meta-analyses are also inconsistent, mainly due to heterogeneity of RCTs included. In fact, the effects of probiotics on glycemic control in GDM are reported to be either neutral [11] or beneficial [12]. A previous meta-analysis performed to evaluate the effect of probiotics in pregnancy on the risk of GDM [12] reported a significant reduction of the endpoint in the group treated with probiotics as compared with placebo: however, this meta-analysis included only 3 trials with limited sample size.

More recently, larger RCTs have been published [13–17]. The SPRING study [13] has shown that probiotics supplementation throughout pregnancy from the first half of the second trimester does not reduce the incidence of GDM in overweight and obese women. Another trial conducted in 439 overweight and obese women [15] has shown no benefits of probiotic supplementation neither on the incidence of GDM nor on glucose metabolism, nor on maternal and neonatal outcomes.

Based on the inconsistency of previous results and in consideration of the publication of recent larger trials, we performed a systematic review and meta-analysis of RCTs aimed to evaluate the health effects of probiotic supplementation in pregnant women with or without diabetes. In women without diabetes, the principal outcome was the incidence of GDM; in women with GDM, the principal outcome was the effect on FPG. We also explored the effects of probiotics supplementation on maternal outcomes, other than metabolic, and fetal outcomes.

2. Methods

The present meta-analysis of RCTs has been registered on PROSPERO website (PROSPERO CRD42019139889; https://www.crd.york.ac.uk/prospero/#recordDetails). This meta-analysis is reported following the criteria of PRISMA statement [18].

2.1. *Search strategy and selection criteria*

A MEDLINE (https://www.ncbi.nlm.nih.gov/PubMed), EMBASE (https://www.embase.com/) SCOPUS (https://www.scopus.com/), and Cochrane database (https://www.cochranelibrary.com/) search was performed to identify all clinical RCTs (with no language restriction), enrolling women in pregnancy with and without diabetes, up to May 30th, 2019 in which oral supplementation with probiotics has been compared either with placebo or active comparators. In addition, we used supplementary approaches to identify further studies (grey literature), such as hand

searching of journals, checking reference lists, and searching regulatory agency websites (Food and Drugs Administration and European Medicine Agency databases). Completed but yet unpublished trials were searched in the www.clinicaltrials.gov register. Detailed information on search string is reported in Supplementary materials (Table S1). The identification of relevant abstracts, the selection of studies, and extraction were performed independently by two of the authors (M.M. and M.M.), and conflicts resolved by a third investigator (E.V.).

For elaboration of the analysis question, the PICOS method was used: participants (pregnant women), interventions (oral probiotics supplementation), comparison (placebo or active comparison), outcomes (incidence of GDM in women without diabetes and FPG in women with or without diabetes), study design (meta-analysis of RCTs).

We included studies which met the following inclusion/exclusion criteria: (1) RCTs comparing any type of probiotic with placebo or active comparator; (2) that included pregnant women at any age and any stage of pregnancy; (3) that included women without diabetes or women with gestational diabetes; (4) evaluating any probiotic supplementation, irrespective of the dose or composition (single or multiple strains); (5) administered orally; (6) articles reporting results on the incidence of GDM, or change of FPG, insulin, homeostasis model assessment of insulin resistance (HOMA), or maternal and fetal outcomes. We excluded: (1) articles other than RCTs; (2) trials using administration route other than oral; (3) trials that compare probiotics + add-on therapy vs placebo/active comparator that not included the add-on therapy (vitamin supplementation was allowed, if it was given to both treatment arms).

2.2. Data analysis

For all published trials, results reported in published papers were used as the primary source of information, whereas results of unpublished trials were retrieved, if available, on www.clinicaltrials.gov. Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) was used for the assessment of the risk of bias. RoB 2 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. A proposed judgment about the risk of bias arising from each domain is generated by an algorithm. Judgment can be 'Low' or 'High' risk of bias or can express 'Some concerns'. The risk of bias for each study included in the present meta-analysis was reviewed independently by two of the authors (M.M. and M.M.), and conflicts resolved by a third investigator (E.V.) The following parameters/information were extracted: first author, year of publication, name of the investigational drug, form, and dosage, study design, comparator, add-on therapy, beginning of treatment and duration of treatment, number of patients in each arm, mean age, and mean prepregnancy or early pregnancy Body Mass Index (BMI).

The principal endpoints were: the incidence of GDM (diagnosed with oral glucose tolerance test at the 24-28th gestational week) in trials performed in women without diabetes and the FPG at the end of treatment in trials enrolling women with and without diabetes.

Secondary endpoints were:

(a) Mother: serum fasting insulin, HOMA index, body weight at the end of treatment, and preeclampsia and caesarean section at the end of pregnancy.
(b) Infant: macrosomia, birth weight, preterm, jaundice, neonatal hypoglycemia, Intensive Care Unit (ICU) admission; intrauterine/perinatal death.

2.3. Statistical analyses

Mantel-Haenszel odds ratio (MH-OR) with 95% Confidence Interval (95%, CI) and between-group difference-in means (mean difference: MD) with 95%, CI were calculated, on an intention-to-treat basis, for dichotomic and continuous outcomes, respectively. Heterogeneity was assessed using I^2 statistics. Even when low heterogeneity was detected, a random-effects model was applied as the primary analysis, because the validity of tests of heterogeneity can be limited with a small number of events in each component study. Fixed effect models were applied for sensitivity analysis.

All analyses were performed using Review Manager 5.3.5; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

3. Results

3.1. Trials characteristics

Fig. 1 reports the trial flow summary. The diagram follows the recommendations of PRISMA statement. A total of 17 trials (Tables 1 and 2), all versus placebo, fulfilling the inclusion criteria was identified; out of 11 trials performed in women without diabetes, only 7 reported information on incident diabetes (Table 1). All these studies reported at least one event [4,6,7,13–15,17]. A total of 6 studies enrolling women with GDM [5,8,16,19–21] and 9 studies enrolling women without GDM were included in the analysis for FPG (Table 2) [4,6,7,9,13–15,17,22]. Only 2 studies, performed in women without diabetes, did not report information on FPG but were included in the analysis for other endpoints (Table 2) [23,24].

The overall quality of trials was satisfactory for most of the items of the Rob 2 tool, apart from "other bias" (i.e. funding from industries") that was "unclear" for several trials (Fig. S1 of Supplementary Material).

The median duration of treatment with probiotics was 11.5 weeks. The mean age and BMI of the included studies were 29.4 years and 28.5 Kg/m^2, respectively (Tables 1 and 2).

3.2. Primary outcomes

Trials on women without diabetes reported 177 and 200 cases of incident GDM in probiotics and control group, respectively, showing no effect of probiotics on the incidence of diabetes (MH-OR: 0.77 [0.51, 1.16], p = 0.21, I^2: 62%; Fig. 2). Similar results were obtained in a sensitivity analysis using a fixed-effect model (0.85 [0.68, 1.07], p = 0.17) (data not shown).

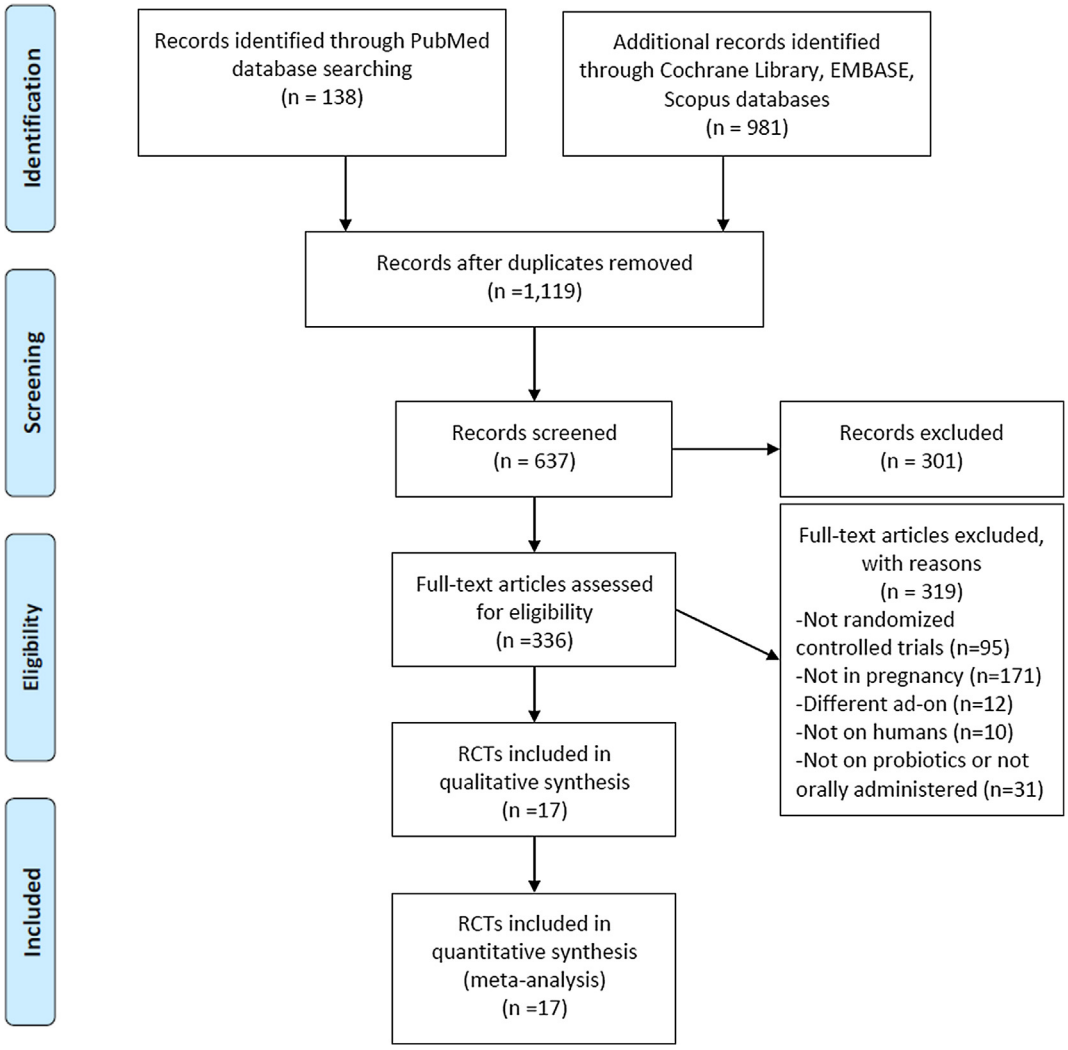

Fig. 1 – PRISMA 2009 Flow Diagram.

Information on fasting plasma glycemia at the end of treatment was reported in 15 trials (Fig. 3). Probiotics appears to produce a small but significant reduction of FPG in comparison with placebo (MD: −1.05 [−1.95, −0.16] mg/dl; p = 0.02, I^2:45%; Fig. 3). When considering separately trials enrolling women with and without diabetes, this effect did not reach the statistical significance in either group, and the difference between subgroups of trials was not statistically significant (Fig. 3). A separate analysis considering the type of probiotic scheme used revealed no significant differences (Fig. S2). In sensitivity analyses, this result did not maintain the statistical significance when using a fixed-effect model (MD, 95% CI: −0.33 [−1.09, 0.43]; p = 0.39) or excluding trials with a risk of bias uncertain or high [7,19,22] (MD, 95% CI: −0.31 [−1.14, 0.52]; p = 0.46).

3.3. *Secondary outcomes*

3.3.1. *Mother*

When analysing the effect of probiotics on fasting serum insulin in trials reporting this information (8 trials), a significant reduction was observed in comparison with placebo (MD, 95% CI: −1.63 [-2.56, −0.71] μU/ml, p < 0.001, Fig. S3), to a similar extent both in women with diabetes (n = 3 trials, MD, 95% CI: −1.83 [−4.22, 0.55] μU/ml, p = 0.13) and in women without diabetes (n = 5, MD, 95% CI: −1.74[−2.82, −0.67] μU/ml, p = 0.002). Similar results, although not reaching full statistical significance, were obtained for HOMA index (MD, 95% CI: −0.19 [−0.44, 0.05], p = 0.12, Fig. S4), with no difference between trials enrolling women with or without diabetes (data not shown). No significant difference in maternal body weight at the end of the treatment period was detected (MD, 95%CI: −1.61 [-3.83, 0.61] kg, p = 0.16, Fig. S5).

Information on preeclampsia was reported in 8 trials, with no effect of probiotics treatment in comparison with placebo (MH-OR, 95%, CI: 1.42 [0.92, 2.20], p = 0.12, Fig. S6). Similar results were obtained when separately analyzing trials in women with or without diabetes (data not shown). Caesarean section did not significantly differ between the two groups (MH-OR, 95%, CI: 0.96 [0.79, 1.16], p = 0.65, Fig. S7), with no differences when considering separately trials enrolling women with or without diabetes.

Table 1 – Principal characteristics of the trials included in the analysis for the incidence of gestational diabetes.

First author, publication year (ref)	Intervention	Study design	Form	Dosage (CFU per capsule per day)	Beginning of treatment (Gest. week)	Duration of intervention until OGTT (weeks)	# *patients Prob./Comp.*	Age (years)	Prepregnancy BMI (kg/m^2)	Primary endpoint of the study
Asgharian 2019 (17)	L. Acid., B. Lactis	Parallel	Yoghurt	5×10^{10}	22–24	4**	64/64	29.5 ± 6.2	29.2 ± 6.9	Plasma glucose during OGTT
Callaway 2019 (13)	B. Lactis, L. Ramnosus	Parallel	Capsules	$>1 \times 10^9$	0–20	12**	207/204	31.3 ± 4.7	31.9 ± 7.5	GDM incidence
Laitinen 2009 (6)	B. Lactis, L. Ramnosus	Parallel	Capsules	10^{10}	0–16	NR***	85/86	29.7 ± 4.1	NR	Mother FPG, HbA1c, insulin, HOMA, QUICKI
Lindsay 2014 (7)	L. Salivarius	Parallel	Capsules	10^9	24	4	83/82	31.4 ± 5.0	32.9 ± 2.4	Change in maternal FPG
Oksene-Gafa 2019 (14)	B. Lactis, L. Ramnosus	2x2 factorial	Capsules	$>6.5 \times 10^9$	12–17	12**	115/115	28.8 ± 5.7	38.8 ± 6.1	Maternal GWG; infant birthweight
Pellonpera 2019 (15)	B. Lactis, L. Ramnosus	Parallel	Capsules	10^{10}	0–18	12.5 ± 3.1*	219/219	30.8 ± 4.7	29.5 ± 4.3	GDM incidence
Whickens 2017 (4)	L. Ramnosus	Parallel	Capsules	$6x10^9$	14–16	13*	212/211	34.0 ± 6.0	25.5 ± 4.0	Eczema incidence in the child at 12 months

All trials enrolled women without diabetes. All trials were placebo controlled. The assessment of incident gestational diabetes was performed at the 24-28th week by 75-gr Oral Glucose Tolerance Test, with the exception of Lindsay 2014 (7) that performed a 3-h 100 gr OGTT at the 28th week.

Age and BMI are reported as mean ± standard deviation.

CFU: colony-forming units; BMI: body mass index; GDM: gestational diabetes mellitus; OGTT: Oral Glucose Tolerance Test; FPG: fasting plasma glucose; GWG: gestational weight gain; L: Lactobacillus; Acid.: Acidophilus; B.: Bifidobacterium; Gest. Gestational; Prob/Comp: Probiotics/Comparator; NR: Not Reported.

* According to the study design, the probiotics supplementation was provided from the first study visit, throughout the pregnancy, and until 6 months postpartum

** According to the study design, the probiotics supplementation was provided from enrollment until birth

*** According to the study design, the probiotics supplementation was provided from the first study visit, throughout the pregnancy, and until the end of exclusive breast-feeding

Table 2 – Principal characteristics of the trials (all placebo-controlled) included in the analysis for other endpoints.

First author, publication year (ref)	Intervention	Study design	Form	Dosage (CFU/caps. per day)	Beginning of intervention (Gest. week)	Duration of intervention (Weeks)	# patients Prob/Comp	Age (years)	Prepregnancy BMI (kg/m^2)	Primary endpoint of the study	Included in the analysis for FPG
Studies enrolling women without diabetes											
Allen 2010 (24)	L. salivarius, L. paracasei, B. Lactis, B. Bifidum	Parallel	Capsules	$1.25x10^9$	36	4	220/234	29.0 ± 5.6	NR	Maternal and fetal adverse events	No
Asemi 2013 (22)	L. Acid, B. BB12, S. Termop, L. bulgaricus	Parallel	Yoghurt	$<10^7$	Third trimester	9	37/33	24.2 ± 3.3	NR	Change in maternal FPG, insulin, insulin resistance	Yes
Asgharian 2019 (17)	L. Acid., B. Lactis	Parallel	Yoghurt	5×10^{10}	22–24	4*	64/64	29.5 ± 6.2	29.2 ± 6.9	Plasma glucose during OGTT	Yes
Callaway 2019 (13)	B. Lactis, L. Ramnosus	Parallel	Capsules	$>1 \times 10^9$	0–20	12*	207/204	31.3 ± 4.7	31.9 ± 7.5	GDM incidence	Yes
Jamilian 2016 (9)	L. Acid, L. Casei, B. Bifidus	Parallel	Capsules	2×10^9	9–12	12	30/30	28.4 ± 5.3	25.5 ± 4.1	Metabolic profile, inflammation and oxidative stress	Yes
Laitinen 2009 (6)	B. Lactis, L. Ramnosus	Parallel	Capsules	10^{10}	0–16	12**	85/86	29.7 ± 4.1	NR	Change in mother FPG, HbA1c, insulin, HOMA, QUICKI	Yes
Lindsay 2014 (7)	L. Salivarius	Parallel	Capsules	10^9	24	4	83/82	31.4 ± 5.0	32.9 ± 2.4	Change in maternal FPG	Yes
Mantaring 2018 (23)	B. Lactis, L. Ramnosus	Parallel	Capsules	$7x10^8$	24–28	Until 2 months post birth	70/70	25.5 ± 5.4	20.6 ± 2.9	Incidence of diarrhea in infants	No
Oksene-Gafa 2019 (14)	B. Lactis, L. Ramnosus	2x2	Capsules	$>6.5 \times 10^9$	12–17	12	115/115	28.8 ± 5.7	38.8 ± 6.1	Maternal excessive GWG; infant birthweight	Yes
Pellonpera 2019 (15)	B. Lactis, L. Ramnosus	Parallel	Capsules	10^{10}	0–18	14*	219/219	30.8 ± 4.7	29.5 ± 4.3	GDM incidence	Yes
Whickens 2017 (4)	L. Ramnosus	Parallel	Capsules	$6x10^9$	14–16	12***	212/211	34.0 ± 6.0	25.5 ± 4.0	Eczema incidence in the child at 12 months	Yes
Studies enrolling women with gestational diabetes											
Badehnoosh 2018 (19)	L. Acid., L. Casei, B. Bifidum	Parallel	Capsules	2×10^9	24–28	6	30/30	28.8 ± 5.4	28.3 ± 3.9	Inflammatory markers	Yes
Dolatkhah 2015 (5)	L. Acid, B. BB12, S. Termop, L. Bulgaricus	Parallel	Capsules	4×10^9	24–28	8	29/27	28.1 ± 6.2	31.4 ± 3.9	Change in maternal HOMA	Yes
Jafarnejad 2016 (21)	VSL#3 [$]	Parallel	Capsules	112.5×10^9	24–28	8	41/41	32.4 ± 3.1	26.8 ± 2.7	Inflammatory and metabolic parameters	Yes
Karamali 2016 (20)	L. Acid., L. Casei, B. Bifidum	Parallel	Capsules	$2x10^9$	24–28	6	30/30	31.8 ± 6.0	28.6 ± 4.2	Glucose homeostasis parameters	Yes
Kijmanawat 2019 (16)	L. Acid., B. Bifidus	Parallel	Capsules	10^9	24–28	4	30/30	32.5 ± 5.0	22.7 ± 3.7	Change in mother FPG, HbA1c, insulin, HOMA	Yes
Lindsay 2015 (8)	L. Salivarius	Parallel	Capsules	10^9	<34	4–6	74/75	33.5 ± 5.0	29.6 ± 6.7	Change in maternal FPG	Yes

All trials were placebo controlled. In trials enrolling women with gestational diabetes, the diagnosis was made at the 24-28th week by 75-gr Oral Glucose Tolerance Test.

Age and BMI are reported as mean ± standard deviation.

CFU: colony-forming units; BMI: body mass index; HOMA: Homeostastis Model Assessment; FPG: fasting plasma glucose; GWG: gestational weight gain; L: Lactobacillus; Acid.: Acidophilus; B.: Bifidobacterium; S.: Streptococcus; Termop.: Termophilus; Gest. Gestational; Prob/Comp: Probiotics/Comparator; NR: Not Reported.

[$] VSL#3 is a mixture of Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, and Lactobacillus delbrueckii subsp. Bulgaricus

[*] weeks of treatment, until FPG evaluation; intervention lasted until birth for all the other endpoints.

[**] weeks of treatment, until FPG evaluation; intervention lasted until the end of breastfeeding

[***] weeks of treatment, until FPG evaluation; intervention lasted until 6 months post birth

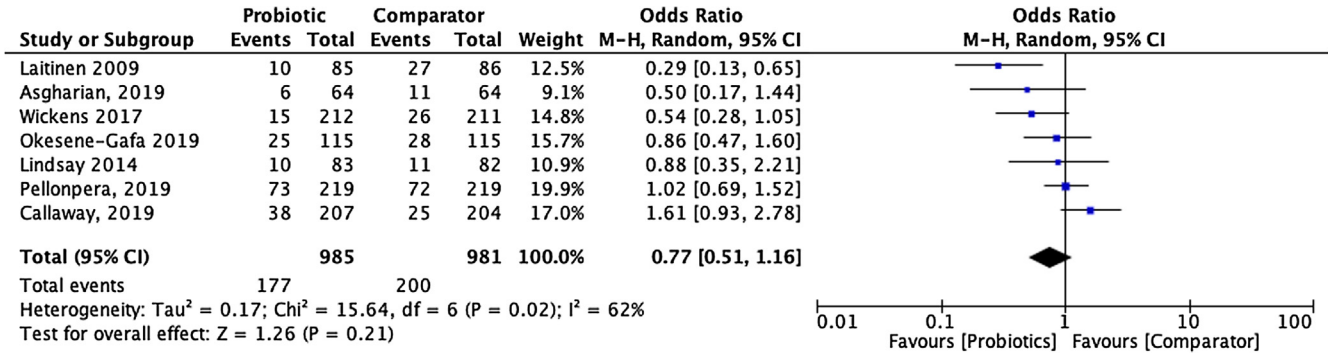

Fig. 2 – Risk of incident diabetes for probiotics versus control groups (MH-OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

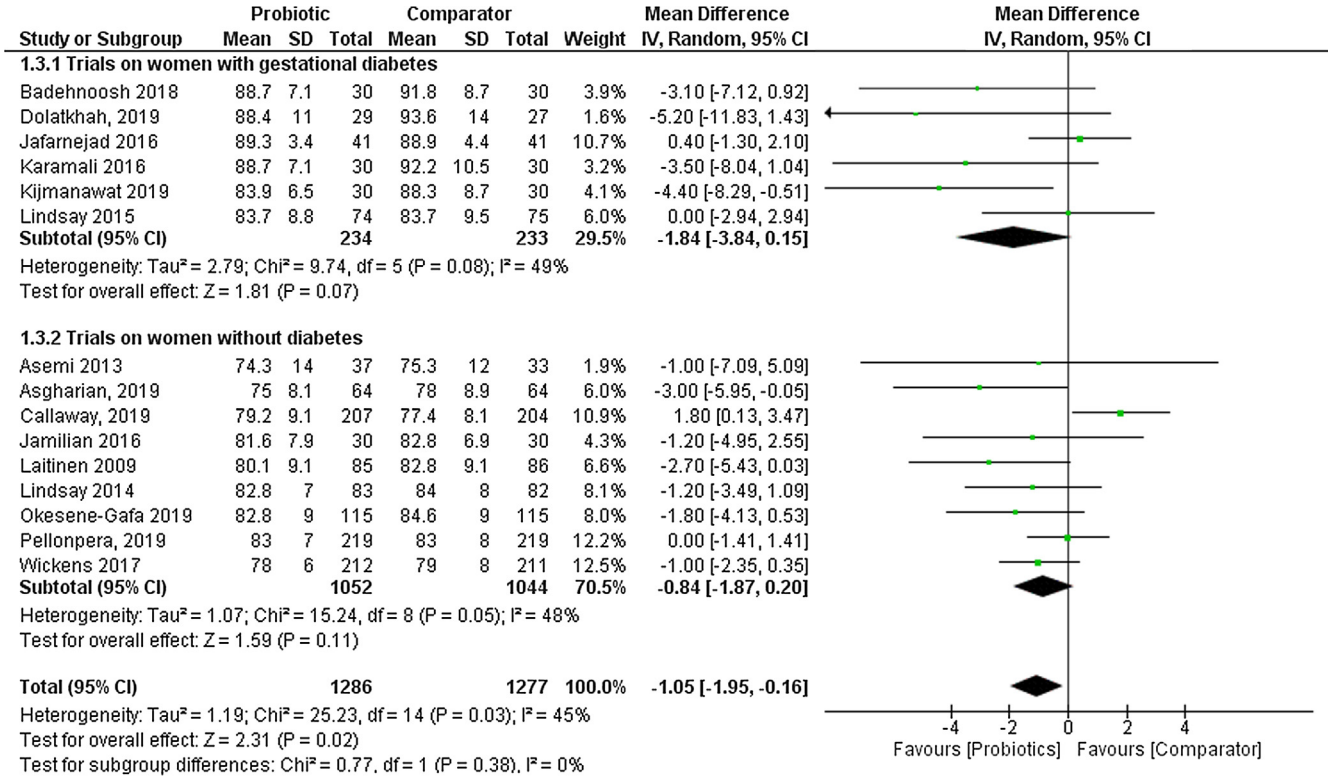

Fig. 3 – Between-group differences (probiotics versus control groups) in fasting plasma glucose (mg/dl). Results are reported for trials performed on women with and without gestational diabetes (95% CI: 95% of Confidence Intervals).

3.3.2. *Infant*

Seven trials reported information on macrosomia, showing no significant effect of probiotic treatment (MH-OR, 95% CI: 1.11 [0.84, 1.47], p = 0.47), as reported in Fig. S8.

When considering birth weight, no effect of probiotics in comparison with placebo was detected (MD, 95%CI: −11.86 [−70.51, 46.80] g, p = 0.69, Fig. S9), although a non-significant trend toward birth weight reduction was observed in trials enrolling women with GDM (n = 5, MD, 95%CI: −90.0 [−180.7, 0.7] g, p = 0.050). Information on jaundice was reported in 3 trials, showing a not significant reduction with probiotics (MH-OR, 95% CI: 0.44 [0.16, 1.18], p = 0.10, Fig. S10); notably, assessment of I^2 statistics suggests high heterogeneity (I^2: 73%). No effect of probiotic was observed on preterm birth (MH-OR, 95% CI: 1.23 [0.69, 2.20], p = 0.48, Fig. S11), as well as on admission in intensive care unit (MH-OR, 95% CI: 0.97 [0.75, 1.27], p = 0.83, Fig. S12). Moreover, probiotics did not affect the incidence of neonatal hypoglycaemia (MH-OR, 95% CI: (1.03 [0.72, 1.47], p = 0.88, Fig. S13) and intrauterine/perinatal death (MH-OR, 95% CI: 0.78 [0.37, 1.64], p = 0.51, Fig. S14).

4. Discussion

This meta-analysis shows that probiotic supplementation during pregnancy does not reduce the incidence of GDM, whereas a very little (statistically but not clinically significant) reduction of fasting plasma glucose is observed in women taking probi-

otics. This result is in line with that of a previous meta-analysis on a smaller number of trials [12]. The concurrent reduction of fasting insulinemia, and the consequent improvement of the HOMA index, suggest that this effect is attributable to an increase in insulin sensitivity, rather than to an enhancement of insulin secretion. This finding is in line with several trials conducted in pregnant women [6,15,23] and in patients with type 2 diabetes [25,26] and metabolic syndrome [27].

Despite the statistical significance of results, their clinical relevance is questionable, considering the small size of the effect. Not surprisingly, the GRADE framework provided a classification of evidence as "moderate". In order to establish the possible clinical impact of the effect of probiotics on fasting glucose, women with and without GDM should be considered separately. The reduction of fasting glucose is not significant in separate analyses performed on women either with or without GDM; however, sample sizes could be too small to detect differences in subgroup analyses.

In women without GDM, the main possible benefit of an intervention that improves insulin sensitivity should be the reduction of incident GDM. In the present metanalysis, despite the inclusion of some recent trials, the effect of probiotics in this regard is not statistically significant. However, sample sizes are still very small, resulting in a limited sensitivity of analyses. In women with GDM, a treatment producing effects on glucose metabolism is clinically useful if it determines a reduction of blood glucose enough to prevent maternal, fetal, and neonatal complications. In trials with probiotics, the observed reduction of fasting glucose in women with GDM is actually very small. Therefore, it is not surprising that those treatments fail to produce significant effects on maternal and fetal outcomes, although sample sizes could have been too small for a reliable assessment of some endpoints. On the other hand, no signal of safety issues emerged from this analysis.

Although it is uncertain exactly how probiotics might exert beneficial effects on glucose metabolism, the effect could be mediated by the gut flora [28]. Short-chain fatty acids (SCFAs) are the main product of bacterial fermentation of fiber in the gut and are significantly changed in the intestinal lumen during pregnancy [29]. It was suggested that SCFAs play an important role in the metabolism of pregnant women. Moreover, probiotics could improve insulin resistance through their anti-inflammatory effects. Probiotics decrease the levels of the inflammatory markers including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) and increase intestinal GLP-1 levels reducing glucotoxicity and increasing increase insulin sensitivity in pregnant women [30]

In addition, some limitations of the present metanalysis should be acknowledged. The reliability of the assessment of publication bias is questionable, because of the small number of available trials. For the same reason, it is not possible to explore factors that determine heterogeneity, which is relevant for both the principal outcomes. Furthermore, probiotics used differ across trials, adding uncertainty to the interpretation of results.

In conclusion, probiotic supplementation during pregnancy is associated with no benefits on the incidence of gestational diabetes but it produces a minimal improvement of fasting glucose, which appears to be determined by an increase in insulin sensitivity. Although safe, this treatment does not show, on the basis of currently available trials, sufficient clinical benefits for recommending its widespread use.

5. Role of the funding source

This research was performed with no specific funding.

Author contributions

The manuscript was drafted and revised by the authors in accordance with ICJME standards for authorship. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

MM, EV and MM were involved in each of the following points:

1. Design
2. Data Collection
3. Analysis
4. Writing manuscript

FF and GDP were involved in the following point:

1. Manuscript revision

EM was involved in each of the following points:

1. Design
2. Manuscript revision

All the authors approved the final version of this manuscript

Declaration of Competing Interest

All authors declare no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108111.

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