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# Probiotics for treating women with gestational diabetes for improving maternal and fetal health and well-being (Protocol)

Okesene-Gafa KAM, Brown J, McCowan L, Crowther CA

Okesene-Gafa KAM, Brown J, McCowan L, Crowther CA.
Probiotics for treating women with gestational diabetes for improving maternal and fetal health and well-being.
*Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD012970.
DOI: 10.1002/14651858.CD012970.

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## TABLE OF CONTENTS

[Intervention Protocol]

# Probiotics for treating women with gestational diabetes for improving maternal and fetal health and well-being

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**Editorial group:** Cochrane Pregnancy and Childbirth Group.
**Publication status and date:** New, published in Issue 2, 2018.

**Citation:** Okesene-Gafa KAM, Brown J, McCowan L, Crowther CA. Probiotics for treating women with gestational diabetes for improving maternal and fetal health and well-being. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD012970. DOI: 10.1002/14651858.CD012970.



## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the safety and effectiveness of probiotics in treating pregnant women with gestational diabetes mellitus (GDM) on maternal and infant outcomes.

## BACKGROUND

### Description of the condition

Gestational diabetes (GDM) is defined as "carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy" (Alberti 1998). The prevalence of GDM is thought to vary from 1.5% to 14% worldwide and varies between ethnic groups (ACOG 2001; Dablea 2005; Ekeroma 2015; Ferrara 2007; Poston 2013), and countries or institutions depending on the diagnostic criteria for GDM being used (ADA 2010; Diabetes Care 2010; Ekeroma 2015; NICE 2015). The global epidemic of obesity (a risk factor for GDM) is continuing to rise in developed and developing countries (Swinburn 2011), with the concomitant increase in rates of pregnancy complications (WHO 2016), including GDM. Health risks for women with GDM include pre-eclampsia, induction of labour (Crowther 2005), caesarean section, and over half of women with GDM will develop type 2 diabetes within 10 years of the birth (Kim 2002). The risks for their infants include macrosomia, respiratory distress syndrome, birth injuries such as nerve palsy, bone fracture and shoulder dystocia, jaundice, and hypoglycaemia, that if prolonged or severe can cause brain injury (Crowther 2005; Landon 2009). In addition, there is increasing recognition of the association between intrauterine fetal programming effects with adverse long-term health consequences for the infant, creating a vicious intergenerational cycle of obesity, diabetes, and metabolic syndrome (Boney 2005; Dablea 2005).

### Description of the intervention

Probiotics are micro-organisms that naturally occur in foods and when consumed in adequate amounts may confer health benefits for the host (FAO 2001). Probiotics are usually found in fer-

mented milk products, yoghurts or dietary supplements as well as in capsules. There are many different types of probiotics and the two most widely used genera are *Lactobacillus* and *Bifidobacterium* (Laitinen 2009; Luoto 2010).

The gut microbiome (micro-organisms that colonise the gut) is thought to influence obesity and type 2 diabetes through modification of energy extraction, inflammation, hunger and satiety, as well as lipid and glucose metabolism (Flint 2012; Nieuwdorp 2014; Turnbaugh 2006). Type 2 diabetes has been associated with changes in the gut microbiome (Larsen 2010). Obese women have also been identified to have a different gut microbiome compared to lean women (Nieuwdorp 2014; Turnbaugh 2006). Gut microbiome differences also exist between pregnant overweight and normal weight women (Collado 2008), as well as in the third trimester of pregnancy compared to the first trimester, with the third trimester microbiome being similar to those with metabolic syndrome (Koren 2012). Supplementation with probiotics has been shown to improve glycaemic control in men and women with type 2 diabetes (Andreasen 2010; Ejtahed 2012), and prevent worsening insulin resistance in late pregnancy (Asemi 2013). Probiotics have been shown to prevent GDM in a sample of pregnant women in a general population (Luoto 2010), and probiotics with dietary counselling reduced mean plasma glucose concentrations and improved insulin sensitivity in another study of healthy pregnant women both antenatally and postpartum (Laitinen 2009). Probiotics reduced pre-eclampsia in a large Norwegian cohort study (Braentsaeter 2011) and are considered safe to use in pregnancy (Allen 2010; Elias 2011). Probiotics capsules (*Lactobacillus rhamnosus*) in a double-blind randomised controlled trial showed significant and sustainable weight loss in obese women (Sanchez 2014). There is a larger randomised controlled trial of probiotics or placebo in pregnant women currently underway in Australia to detect whether probiotics can prevent GDM in obese and overweight women (Nitert 2013). A systematic review and meta-analysis looking at the effect of treatment of GDM on pregnancy outcomes showed that treatment significantly reduced the risks of fetal macrosomia, large-for-gestational-age births, shoulder dystocia and gestational hypertension, as well as a tendency to reduction of perinatal/neonatal mortality and birth trauma (Poolsup 2014). GDM treatment to date has mostly comprised of dietary and glucose-lowering agents either insulin and or tablets (biguanides or second-generation sulphonylureas) (Coustan 2013). The role of probiotics in treating pregnant women with GDM has yet to be clearly established.

## How the intervention might work

Probiotics in the 1960s were hypothesised to have the beneficial effects of producing substances that may promote the growth of other micro-organisms and was further revised in the 1980s as a microbial feed supplement that improves the intestinal balance of the host (FAO 2001). The discovery of the gut microbiome and its relationship to health and disease, together with DNA sequencing technology meant easier identification of the host genome and host micro-organisms or microbiome (Solt 2015). Microbiome changes influence gut content by allowing the predominance of some organisms over others, which in turn can cause a generalised increase in inflammatory markers in the host and increasing risks of diseases (Solt 2015). Modification of the gut microbiome (Flint 2012) by probiotics may be used as an intervention to prevent or treat metabolic diseases through various complex intracellular metabolic pathways within the gut (Nieuwdorp 2014; Turpin 2010). The mechanisms are complex from probiotics actively competing with pathological bacteria to dampening their inflammatory effect possibly by producing more butyrate; to improving the bile acid pool to reduce insulin resistance; or binding to mucosal receptors in the gut altering metabolic pathways responsible for the metabolic syndrome and satiety (Nieuwdorp 2014). Furthermore, probiotics have an anti-obesity action by influencing energy extraction in humans through increased lipolysis and reduction in lipoprotein lipase, which may reduce excess energy storage (Turpin 2010). The microbiomes of obese people have been found to have the ability to convert non digestible carbohydrates to digestible short-chain fatty acids, with increased uptake in the gut increasing energy harvest, storage and consequently increasing adiposity (Flint 2012). High adiposity in human and animal studies has been associated with increased systemic inflammation, which impacts adversely on pregnancy outcomes especially increasing risks of pre-eclampsia (Braentsaeter 2011) and increased insulin resistance. Probiotics have been shown to reduce the rates of severe pre-eclampsia (Braentsaeter 2011), reduce insulin resistance (Asemi 2013) and improve insulin sensitivity (Laitinen 2009). Other beneficial effects of probiotics include reduction of psychological distress in healthy volunteers (Messaoudi 2011) and consumption of probiotic yoghurt improved mood (Benton 2007) possibly by reducing systemic inflammatory markers (Dinan 2011). Futhermore, individuals with depression have been shown to have a different microbiome to healthy individuals (Jiang 2015) as well as high levels of inflammatory cytokines (Dinan 2011), with probiotics predicted to dampen the negative effects of inflammation causing depression. Other benefits of probiotics have been their use in neonates to prevent necrotising enterocolitis and mortality in preterm infants through similar mechanisms as described and establishing a healthy microbiome within the neonate (AlFaleh 2009).

## Why it is important to do this review

We anticipate an increase in the numbers of women diagnosed with GDM with the more widespread application of the International Association of Diabetes and Pregnancy Study Group diagnostic criteria (Cundy 2014), (Ekeroma 2015). The majority of women will be treated with lifestyle modification alone (Metzger 2007). All women with GDM may receive lifestyle advice and for

some women this may be an effective treatment to maintain glycaemic control without the addition of pharmacotherapy (Brown 2017). The use of probiotics may prove a useful adjunct to lifestyle interventions and reduce the need for pharmacotherapy. This review will establish the effectiveness of such an intervention in particular for women with mild GDM.

# OBJECTIVES

To evaluate the safety and effectiveness of probiotics in treating pregnant women with gestational diabetes mellitus (GDM) on maternal and infant outcomes.

# METHODS

## Criteria for considering studies for this review

### Types of studies

We will include randomised or cluster-randomised trials (published or unpublished). We will exclude quasi-randomised and cross-over trials. We will not restrict language or year of publication. We will include conference proceedings.

### Types of participants

We will include trials of pregnant women diagnosed with gestational diabetes (diagnosis as defined by the individual trial). Trials of women with type 1 or type 2 diabetes diagnosed prior to pregnancy will be excluded.

### Types of interventions

We will include trials where the intervention is a probiotic (any type) administered by any route given during pregnancy to treat women with gestational diabetes and where the control group received placebo or standard care (as defined by trialist).

### Types of outcome measures

#### Primary outcomes

**Maternal**

- Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia)
- Subsequent development of type 2 diabetes (as defined by trialist)
- Mode of birth

**Infant**

- Perinatal (fetal and neonatal) mortality
- Large-for-gestational age (birthweight greater than the $90^{th}$ centile; or as defined by individual trial)
- Composite of serious neonatal outcomes (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy
- Neurosensory disability (defined by trialists)

#### Secondary outcomes

**Maternal**

- Induction of labour
- Perineal trauma
- Placental abruption
- Postpartum haemorrhage
- Postpartum infection
- Weight gain during pregnancy
- Adherence to the intervention
- Behaviour changes associated with the intervention
- Relevant biomarker changes associated with the intervention (e.g. adiponectin, free-fatty acids, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), insulin)
- Sense of well-being and quality of life
- Views of the intervention
- Breastfeeding (e.g. at discharge, six weeks postpartum)
- Use of additional pharmacotherapy
- Glycaemic control during/end of treatment (as defined by trialists)
- Maternal hypoglycaemia
- Maternal mortality

**Long-term maternal outcomes**

- Postnatal depression
- Postnatal weight retention or return to pre-pregnancy weight
- Body mass index (BMI)
- GDM in a subsequent pregnancy
- Type I diabetes
- Type 2 diabetes
- Impaired glucose tolerance
- Cardiovascular health (as defined by trialists, including blood pressure (BP), hypertension, cardiovascular disease, metabolic syndrome)

**Infant**

- Stillbirth
- Neonatal mortality
- Gestational age at birth
- Preterm birth (less than 37 weeks' gestation and less than 32 weeks' gestation)
- Apgar score (less than seven at five minutes)
- Macrosomia
- Small-for-gestational age
- Birthweight and z-score
- Head circumference and z-score
- Length and z-score
- Ponderal index
- Adiposity
- Shoulder dystocia
- Bone fracture
- Nerve palsy
- Respiratory distress syndrome
- Hypoglycaemia requiring (variously defined)
- Hyperbilirubinaemia
- Neonatal hypocalcaemia
- Polycythaemia
- Relevant biomarker changes associated with the intervention (e.g. cord c peptide, cord insulin)

**Later childhood**

- Weight and z score
- Height and z score
- Head circumference and z score
- Adiposity (including BMI, skinfold thickness)
- BP
- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Impaired glucose tolerance
- Dyslipidaemia or metabolic syndrome
- Educational achievement

**Adulthood outcomes**

- Weight
- Height
- Adiposity (including skin folds, fat mass)
- Cardiovascular health (as defined by trialists, including BP, hypertension, cardiovascular disease, metabolic syndrome)
- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Impaired glucose tolerance
- Dyslipidaemia or metabolic syndrome
- Employment, education and social status/achievement

**Health services**

- Number of antenatal visits or admissions
- Number of hospital or health professional visits (including midwife, obstetrician, physician, dietician, diabetic nurse)
- Admission to neonatal intensive care unit/nursery
- Length of antenatal stay
- Length of postnatal stay (maternal)
- Length of postnatal stay (baby)
- Cost of maternal care
- Cost of offspring care (including neonatal intensive care unit admission)
- Costs associated with the intervention
- Costs to families associated with the management provided

## Search methods for identification of studies

The following methods section of this protocol is based on a standard template used by the Cochrane Pregnancy and Childbirth.

### Electronic searches

We will search Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist.

The Trials Register is a database containing over 24,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than

keywords. This results in a more specific search set that will be fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).
In addition, we will search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using the keywords identified in Appendix 1.

### Searching other resources

We will search the reference lists of retrieved studies.
We will not apply any language or date restrictions.

## Data collection and analysis

The following methods section of this protocol is based on a standard template used by the Cochrane Pregnancy and Childbirth.

### Selection of studies

Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion. We will create a study flow diagram to map out the number of records identified, included and excluded.

### Data extraction and management

We will design a form to extract data based on the Cochrane Pregnancy and Childbirth Group's data extraction form. We will collect information relating to the type of intervention, frequency and route of administration. This will include sources of funding, trialists' declarations of interest and trial dates. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion. We will enter data into Review Manager software (RevMan 2014) and check for accuracy. If information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

### Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

#### (1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); studies judged to be of high risk of bias will be excluded.
- unclear risk of bias.

#### (2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes);
- unclear risk of bias.

#### (3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

#### (3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

#### (4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition

and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

#### (5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

#### (6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

#### (7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

### Assessment of the quality of the evidence using the GRADE approach

For the main comparison or probiotic versus placebo, the quality of the evidence will be assessed using the GRADE approach, outlined in the GRADE handbook and Chapters 11 and 12 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011), for the outcomes listed below.

**Maternal**

- Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia)
- Subsequent development of type 2 diabetes (as defined by trialist)
- Mode of birth
- Induction of labour
- Perineal trauma
- Postnatal weight retention or return to pre-pregnancy weight
- Postnatal depression

**Neonatal/child/adult**

- Perinatal (fetal and neonatal) mortality
- Large-for-gestational age (birthweight greater than the 90th centile; or as defined by individual trial)
- Composite of serious neonatal outcomes (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy
- Neurosensory disability (defined by trialists)
- Neonatal hypoglycaemia
- Adiposity (neonatal/child/adult)
- Diabetes (type 1or type 2) or impaired glucose tolerance (child/adult)

The GRADEpro Guideline Development tool will be used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

### Measures of treatment effect

#### Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals (CI).

#### Continuous data

For continuous data, we will use the mean difference with 95% CIs if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods; these will also be presented with 95% CIs.

### Unit of analysis issues

#### Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will make adjustments using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. We will consider it reasonable to combine the results from both cluster-randomised trials and individually-randomised trials if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

#### Multiple pregnancy

There may be unit of analysis issues that arise when the women randomised have a multiple pregnancy. We will present maternal data as per woman randomised and neonatal data per infant.

#### Multiple-arm studies

Where a trial has multiple intervention arms we will avoid 'double counting' of participants by combining groups to create a single pair-wise comparison if possible. Where this is not possible, we will split the 'shared' group into two or more groups with smaller sample size and include two or more (reasonably independent) comparisons.

### Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

### Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the $Tau^2$, $I^2$ and $Chi^2$ statistics. We will regard heterogeneity as substantial if the $I^2$ is greater than 30% and either a $Tau^2$ is greater than zero, or there is a low P value (less than 0.10) in the $Chi^2$ test for heterogeneity.

### Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

### Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% CIs, and the estimates of $Tau^2$ and $I^2$.

### Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

- Different types of probiotic (probiotic A versus probiotic B)
- Mode of administration of probiotic (capsule versus yoghurt versus nutritional supplement)
- Dosage (high versus low dose)

- Diagnostic criteria used for GDM (IADPSG, American College of Obstetrics and Gynaecology, World Health Organization, Carpenter and Coustan, Australian Diabetes in Pregnancy Society, other criteria not specified above, diagnostic criteria not specified)

Subgroup analysis will be restricted to the review's primary outcomes.
We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the $Chi^2$ statistic and P value, and the interaction test $I^2$ value.

### Sensitivity analysis

If there is evidence of significant heterogeneity, we will explore this by using the quality of the included trials for the primary outcomes. We will compare trials that have low risk of bias for allocation concealment with those judged to be of unclear or high risk of bias. Where there is substantial heterogeneity we will also explore whether this can be explained by type of publication (conference proceeding or full-text paper) and also by study size (small n $\leq$ 300 or large n > 300). We will also carry out sensitivity analysis to investigate the effect of the randomisation unit in instances where we include cluster-RCTS along with the individually-randomised trials.

## ACKNOWLEDGEMENTS

Portions of the methods section of this protocol are based on a standard template used by the Cochrane Pregnancy and Childbirth Review Group. Outcomes may be similar to other Cochrane reviews on treatment for gestational diabetes due to the attempt to have consistency across all protocols and reviews on this condition.

We acknowledge the support from the Cochrane Pregnancy and Childbirth Review Group editorial team in Liverpool, the Australian and New Zealand Satellite of the Cochrane Pregnancy and Childbirth Review Group (funded by NHMRC) and the Liggins Institute, University of Auckland, New Zealand.

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* *Indicates the major publication for the study*

# APPENDICES

## Appendix 1. Keywords for searching trials registries

probiotics AND gestational diabetes

# CONTRIBUTIONS OF AUTHORS

Julie Brown guarantees this protocol. Kara Okesene-Gafa prepared the original draft of this review protocol. Julie Brown, Caroline Crowther and Lesley McCowan have all contributed by providing input and feedback in the preparation of the protocol.

# DECLARATIONS OF INTEREST

Kara Okesene-Gafa - is currently involved with the Healthy Mums and Babies (HUMBA) randomised controlled demonstration trial. The HUMBA RCT will not be eligible for inclusion in this review. In kind we have been provided with probiotics (Lactobacillus Rhamnosus GG and Bifidobacterium Lactis BB12) and placebo capsules free of charge from Christian Hansen Denmark (http://www.chr-hansen.com/en) for our HUMBA trial (http://humba.ac.nz/). In this randomised controlled double blind trial, women are randomised to receive probiotics or placebo capsules with the main aim of reducing pregnancy weight gain and infant birth weight (ANZCTR registration number 12615000400561). In kind: Roche International- equipment & consumables for HBA1c for the HUMBA trial. National Heart Foundation assisted by letting us use some of their resources for the study and development of some of the content in the text messages as part of HUMBA trial. Public interest funding for the Healthy Mums and Babies (HUMBA) trial was received from Cure Kids, Counties Manukau Health, Mercia Barnes Trust Fund, University of Auckland Faculty Research Development Fund and Lottery Health Research Fund.

Caroline Crowther - is also currently involved with the Healthy Mums and Babies (HUMBA) randomised controlled demonstration trial. The HUMBA RCT will not be eligible for inclusion in this review. In kind we have been provided with probiotics (Lactobacillus Rhamnosus GG and Bifidobacterium Lactis BB12) and placebo capsules free of charge from Christian Hansen Denmark (http://www.chr-hansen.com/en) for our HUMBA trial (http://humba.ac.nz/). In this randomised controlled double blind trial, women are randomised to receive probiotics or placebo capsules with the main aim of reducing pregnancy weight gain and infant birth weight (ANZCTR registration number 12615000400561). In kind: Roche International- equipment & consumables for HBA1c for the HUMBA trial. National Heart Foundation assisted by letting us use some of their resources for the study and development of some of the content in the text messages as part of HUMBA trial.

Lesley McCowan - is also currently involved with the Healthy Mums and Babies (HUMBA) randomised controlled demonstration trial. The HUMBA RCT will not be eligible for inclusion in this review. In kind we have been provided with probiotics (Lactobacillus Rhamnosus GG and Bifidobacterium Lactis BB12) and placebo capsules free of charge from Christian Hansen Denmark (http://www.chr-hansen.com/en) for our HUMBA trial (http://humba.ac.nz/). In this randomised controlled double blind trial, women are randomised to receive probiotics or placebo capsules with the main aim of reducing pregnancy weight gain and infant birth weight (ANZCTR registration number 12615000400561). In kind: Roche International- equipment & consumables for HBA1c for the HUMBA trial. National Heart Foundation assisted by letting us use some of their resources for the study and development of some of the content in the text messages as part of HUMBA trial.

Julie Brown - has received an institutional grant to provide research assistant support to produce and update Cochrane systematic reviews on treating women with GDM to be included in a Cochrane Overview. This review is one of the included reviews.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- Liggins Institute, University of Auckland, New Zealand.

Infrastructure support for Cochrane authors has been provided by the Liggins Institute, University of Auckland.

- Cochrane Pregnancy and Chidbirth Australasian Satellite, New Zealand.

We acknowledge the infrastructure support of the Pregnancy and Childbirth Australian Satellite (funded by NHMRC).