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[Intervention Review]

Nutritional advice for improving outcomes in multiple pregnancies

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ABSTRACT

Background

Multiple pregnancies are associated with higher rates of perinatal mortality and morbidity than singleton pregnancies, mainly due to an increased risk of preterm birth. Because fetal outcome is best at a particular range of maternal weight gain, it has been suggested that women with multiple pregnancies should take special diets (particularly high-calorie diets) designed to boost weight gain. However, 'optimal weight gain' in the mother in retrospective studies may merely reflect good growth of her babies and delivery at or near term (both associated with a good outcome) and artificially boosting weight gain by nutritional input may confer no advantage. Indeed, a high-calorie diet may be unpleasant to consume, and could lead to long-term problems of being overweight. It is therefore important to establish if specialised diets are actually of benefit to women with multiple pregnancies and their babies.

Objectives

To assess the effects of specialised diets or nutritional advice for women with multiple pregnancies (two or more fetuses).

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (15 June 2015).

Selection criteria

Randomised controlled trials, 'quasi-random' studies, and cluster-randomised trials of women with multiple pregnancies (two or more fetuses) either nulliparous or multiparous and their babies. Cross-over trials and studies reported only as abstracts were not eligible for inclusion.

Data collection and analysis

We identified no trials for inclusion in this review.

Main results

A comprehensive search of the Cochrane Pregnancy and Childbirth Group's Trials Register found no potentially eligible trial reports.

Authors' conclusions

There is no robust evidence from randomised trials to indicate whether specialised diets or nutritional advice for women with multiple pregnancies do more good than harm. There is a clear need to undertake a randomised controlled trial.

PLAIN LANGUAGE SUMMARY

Nutritional advice for improving outcomes in multiple pregnancies

In multiple pregnancies (twins, triplets and more), the metabolic rate of the mother is greater than in women who are carrying a single baby so that a high-calorie diet may also help maintain the mother's nutritional state. Multiple pregnancies have a higher risk of complications for women and their babies than do single pregnancies. In particular, poor growth of the babies in the womb, premature birth, and low birthweights are more common.

It has been suggested that a special high-calorie diet for the pregnant woman might improve the outcomes for babies. However, boosting weight gain artificially might not bring any advantage and might be unpleasant for the mother. It might even contribute to long-term problems for her of being overweight. This Cochrane review aimed to identify quality controlled studies that compared special diets with normal diets, or trials that looked at advice on special diets, but found none. That is, there is no evidence from randomised trials to advise whether specific dietary advice for women with multiple pregnancies does more good than harm.

BACKGROUND

Description of the condition

Multiple pregnancies occur when two or more fetuses are present in the uterus; this can be a result of implantation of two genetically different fertilised eggs by two different sperm (dizygotic twins), or due to the division of one fertilised egg (monozygotic). Monozygotic twins can share the same placenta (monochorionic) or have separate placentas (dichorionic) (Fox 2006).

Multiple pregnancies can be diagnosed by an ultrasound scan as early as six weeks. Women with multiple pregnancies may have more severe nausea and vomiting than those with singleton pregnancies, as a result of higher levels of human chorionic gonadotropin (hCG) (Rao 2004).

Since the 1970s there has been a steady increase in the number of twin pregnancies; from 9.6 per 1000 maternities in England and Wales (ONS 2006) in 1976 to 15.5 in 2008 (ONS 2009); in the USA, 18.8 per 1000 were twins in 1975 (Taffel 1992) rising to 32.1 per 1000 in 2006 (Martin 2009), while in Australia in 2010 multiple births accounted for 3.1% of all births (Umstad 2013). These trends have been reflected in many settings across the globe. This rise has been attributed to the increase in the use of assisted reproductive technology, and to some women deciding to have children later in life. An increase in maternal age increases the chances of multiple pregnancy. In the USA it was found that 20% of twin pregnancies from 1980 to 1997 were due to spontaneous conception, 40% due to in vitro fertilisation and 40% due to ovulation induction (Nakhuda 2005). In Europe, spontaneously conceived twins comprise 1% of all deliveries; 20% to 30% of all twins are due to assisted reproductive technology (Hansen 2009), although recent policies to restrict the number of embryos transferred during assisted conception may reverse the upward trend in multiple pregnancies (Collins 2007; Umstad 2013).

Multiple pregnancies are associated with higher rates of complications for both the mother and the fetuses. Gestational hypertension and pre-eclampsia are twice as likely to occur with twins as in singleton pregnancies with risk ratios of 2 and 2.6 respectively (Siddiqui 2007). There is a higher incidence of antepartum and postpartum haemorrhage, with the average blood loss after delivery being 500 mL higher than after a singleton birth (Rao 2004).

Multiple births have a substantial perinatal mortality rate (PMR) compared to singletons. In England and Wales, in 2006, there was an overall PMR of 8.2 per 1000 births, with twins having a rate of 27.2 per 1000, and triplets and higher order births 81.8 per 1000 (CEMACH 2008). When infants are born long before term they are functionally immature, and are usually admitted to neonatal intensive care units. They have poor thermoregulatory mechanisms, which are worsened by low brown fat levels and heat loss. Respiratory distress syndrome occurs as a result of lack of surfactant, and may be associated with chronic lung disease (bronchopulmonary dysplasia) (Keeling 2000). Multiple pregnancies have a strong association with preterm deliveries (before 37 weeks), ranging from 48.2% in Ireland to 68.4% in Austria; between 39.1% and 47.1% occur at 32 to 36 weeks, and 8.1% to 12.7% before 32 weeks (Blondel 2006).

Fifty per cent of twins are small-for-gestational age (SGA) by 39 weeks using the 1991 US singleton live birth values. Ten per cent to 15% of multiple pregnancies (twins and triplets) are SGA by 22 to 30 weeks' gestation (Alexander 1998).

Cerebral palsy is also eight times more likely to occur in twins, and has a greater prevalence when the birthweight is less than 1000 g (Pharoah 2002). When infants are below 1500 g, 30% to 65% will have neurological problems ranging from motor to cognitive/behavioural deficits. Other severe neurological concerns are intraventricular haemorrhage and periventricular leukomalacia. Necrotising enterocolitis also affects low birthweight infants, and there is a high risk of infection due to an immature immune system. Prematurity is a risk factor for retinopathy of prematurity; the retina is vascularly immature as there is insufficient vascularisation due to poor production of angiogenic factors (Keeling 2000).

Depending on the chorionicity of the twins, there are specific complications. For example, 10% to 15% of monochorionic twins have twin-twin transfusion syndrome which can result in fetal death if left untreated. This occurs as a result of anastomoses (a connection between two blood vessels) on the placenta, resulting in a compromise of blood flow to one of the twins, which results in poor growth while the other twin receives the redirected blood from the placenta (Rao 2004).

The risk to mother and fetus is increased even more when the number of fetuses increases. High order pregnancies such as triplets and quadruplets have higher rates of perinatal mortality and have an earlier gestation at delivery; the average gestation for triplets is 33.4 weeks. High order births are more likely to deliver earlier on in the pregnancy than twins; 16.9% of triplets and 29.2% of quadruplets were born before 29 weeks compared to 5.6% of twins. The risk of complications is also greatly increased for higher order births with rates of cerebral palsy of 31/1000 reported for triplets (Bromer 2011). The number of fetuses also impacts on the chances of survival for both twins, with 6.3% of triplet and 8.0% of quadruplet pregnancies having one or more fetal deaths compared to 2.4% of twins (Luke 2008).

In one series, 100% of triplets were admitted to the neonatal intensive care unit, and 54% had a major morbidity (retinopathy of the newborn, necrotising enterocolitis, ventilator support or intraventricular haemorrhage) (Luke 2006).

Description of the intervention

It has been suggested that improved diets may lead to improved outcomes in multiple pregnancies. This is based on observations that a particular range of maternal weight gain is optimally associated with good fetal outcome (Goodnight 2009). However, the converse is not necessarily true - that outcome can be improved by boosting maternal weight gain through improved diet.

Dietary input consists of many different components that may be relevant to multiple pregnancy. These include quantity of calorific intake, the source of calories such as a fat or proteins, micronutrients such as vitamin C, vitamin E, thiamine, magnesium, calcium and zinc, as well the inclusion of certain nutrients such as omega fats. The balance and amount of these components have the potential to impact on the health of the mother and fetuses.

Detailed dietary advice has been popular in the US. For example, Luke et al recommend a calorie intake of 4000 kcal for underweight

mothers (body mass index (BMI) 19.8) with a total weight gain of 50 lbs to 62 lbs (23 to 28 kg); 3500 kcal for normal weight (BMI 19.8 to 26.0) with a weight gain of 40 lbs to 54 lbs (18 to 25 kg); 3250 kcal for overweight (BMI 26.1 to 29.0) 38 lbs to 47 lbs (17 to 21 kg); and 3000 kcal for obese mothers (BMI greater than 29.0) with a weight gain of 29 lbs to 38 lbs (13 to 17 kg) (Luke 2005).

The Institute of Medicine in the US has produced guidelines recommending a weight gain of 37 lbs to 54 lbs (17 to 25 kg) for normal weight, 31 lbs to 50 lbs (14 to 23 kg) for overweight, and 25 lbs to 42 lbs (11 to 19 kg) for obese women (Rasmussen 2009).

Published work also discusses the importance of a high carbohydrate diet as it has been linked to unwanted weight gain, poor glycaemic control and poor fetal growth, whereas a diet consisting of 20% protein, 40% carbohydrate, and 40% fat was found to have better fetal growth (Luke 2005).

Haematinic supplements such as folic acid and iron will not be considered in this review, as they are assessed elsewhere (Peña-Rosas 2015a; Peña-Rosas 2015b).

How the intervention might work

In multiple pregnancies, the metabolic rate of the mother is 10% greater than in women with singleton pregnancies (Shinagawa 2005), as a result of an increasing demand on the mother's energy expenditure due to a larger placenta producing higher quantities of hormones, and two fetuses requiring a continuous nutrient supply for growth (Goodnight 2009). As a result of the increased energy use, fasting glucose levels are lower with a resulting depletion of glycogen reserves. Fats are broken down as an alternative energy source (Luke 2005).

The theoretical basis for recommending high-calorie diets is to increase the provision of nutrients to prevent the likelihood of poor fetal growth. Poor fetal growth may have a number of adverse consequences and can also be associated with preterm birth. A high-calorie diet may also help maintain the mother's nutritional state, which otherwise may be depleted by the needs of the babies, resulting in impaired maternal sense of well being. A retrospective study has shown that women with normal weights at the start of twin pregnancies are more likely to have larger neonates and less likely to deliver preterm if their weight gain during pregnancy met US Institute of Medicine recommendations (Fox 2010).

Although the focus has been on high-calorie diets, any trial of any nutritional intervention (e.g. overall better quality) specifically tailored for women with multiple pregnancies would be of interest.

Why it is important to do this review

Some recommended diets for women with multiple pregnancies have calorific contents similar or greater than those for frontline troops (e.g. 4000 kcal daily for British troops in Afghanistan; HM Forces 2011). As some women with multiple pregnancies are more sedentary than they would be when not pregnant, these diets have the potential to be associated with substantial weight gain. Excess weight gain is associated with increased complications in labour and higher rates of caesarean births, gestational diabetes, pre-eclampsia and anaesthesia-related risks (Reece 2008). Obese mothers have higher rates of fetal macrosomia, as well as increased chance of infection post surgery. By advocating a high-calorie diet and a high weight gain it is important to consider the psychological

impact this might have on the mother as well as future implications for her health. The mother will then have to face the difficulty of losing her extra weight postpartum, as obesity is linked to type 2 diabetes, cardiovascular disease, and thromboembolism (Castro 2002). It therefore needs to be established whether special diets do lead to improved outcomes for the babies and whether these cause unwanted weight gain in the mother.

In addition, a woman might experience anxiety if she were unable to follow specific nutritional advice, because of worry about resulting harm to her babies.

It is also important to consider the financial implications, as a high-calorie diet may be expensive.

OBJECTIVES

To assess the effects of special diets, or dietary advice, on the outcome of multiple pregnancies.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials; 'quasi-random' studies, and cluster-randomised trials are eligible for inclusion. We planned to exclude cross-over trials and studies presented only as abstracts.

Types of participants

Women with multiple pregnancies (two or more fetuses) either nulliparous or multiparous, and their babies.

Types of interventions

Specialised diets or specific dietary advice for multiple pregnancies, whether or not demonstrated to have an impact on weight gain during pregnancy, compared with usual care or alternative diets/advice.

Types of outcome measures

Primary outcomes

1. Early preterm births (before 34 weeks)
2. Small-for-gestational age (SGA) at birth (as defined by the trialists)

Secondary outcomes

Maternal outcomes

1. Weight gain
2. Caesarean births
3. Instrumental vaginal delivery
4. Maternal satisfaction/dissatisfaction/anxiety

Fetal outcomes

1. Preterm birth less than 37 weeks
2. Very early preterm birth less than 28 weeks
3. Respiratory distress syndrome
4. Intraventricular haemorrhage
5. Periventricular leukomalacia
6. Retinopathy of prematurity

7. Necrotising enterocolitis
8. Admission to neonatal intensive care unit
9. Perinatal death

Child outcomes

1. Learning difficulties
2. Developmental delay (as defined by the trialists)
3. Growth (weight, head circumference, height/length)
4. Cerebral palsy

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (15 June 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator 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.

Details of the 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 can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We planned to search the reference lists of retrieved articles.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see [Ballard 2011](#).

No new reports were identified as a result of the updated search.

If any relevant reports are identified in future updates of this review we will use the methods set out in [Appendix 1](#).

RESULTS

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register found no trial reports.

Risk of bias in included studies

We were unable to include any studies in this review.

Effects of interventions

We were unable to establish the effectiveness of nutritional advice as no randomised controlled studies were found.

DISCUSSION

Summary of main results

Using the above search methods and strategies, we found no trials.

AUTHORS' CONCLUSIONS

Implications for practice

This review shows that there is no evidence from randomised trials to support, or reject, special diets or special nutritional advice for women with multiple pregnancies. The optimal diet for women with multiple pregnancies is uncertain.

Implications for research

Future research should focus on designing a suitable randomised trial comparing a special high-calorie diet with usual diet. As well as assessing clinical outcomes (notably preterm birth and small-for-gestational age), such a trial should address maternal views and long-term weight profile.

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APPENDICES

Appendix 1. Methods for updates

Selection of studies

Two review authors will independently assess for inclusion all the potential studies identified as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third review author.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third review author. Data will be entered into Review Manager software ([RevMan 2014](#)) and checked for accuracy.

When information regarding any of the above is unclear, we plan 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](#)). Any disagreement will be resolved 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);
- 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 assessed 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, alternation; date of birth);
- 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 are 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 are balanced across groups or were related to outcomes. Where sufficient information is reported, or could be supplied by the trial authors, we plan to 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 investigate the possibility of selective outcome reporting bias and what we find.

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.

(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 plan to assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We plan to 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

In future updates if data become available we will assess the quality of the evidence using the GRADE approach as outlined in the [GRADE handbook](#) for the following outcomes.

1. Early preterm births (before 34 weeks)
2. Small-for-gestational age at birth (as defined by the trialists)
3. Maternal weight gain
4. Maternal satisfaction/dissatisfaction/anxiety
5. Preterm birth less than 37 weeks
6. Admission to neonatal intensive care unit (NICU)
7. Perinatal death

[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.

Continuous data

We will use the mean difference if outcomes were 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.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* 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. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both 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.

We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials

We will not include cross-over trials which are not an appropriate design for this type of intervention.

Other unit of analysis issues

Special methods are needed when carrying out analysis of outcomes for babies from multiple pregnancies (Gates 2004). Outcomes in babies from multiple pregnancies are not independent. For many outcomes there will be a higher correlation between babies from the same pregnancy than between babies from different pregnancies. The degree of non-independence of outcomes for babies from multiple pregnancies will vary considerably depending on the outcome and the type of multiple pregnancy; for some outcomes an adverse event in one twin will almost invariably be associated with the same event in the other (e.g. preterm birth); for other outcomes the degree of correlation will be lower (e.g. fetal death), but still higher than for babies from different pregnancies. In view of this non-independence, we will treat babies from the same pregnancy as clusters and adjust the data using the methods described above for cluster-randomised trials. Where possible, we will obtain ICCs from the trials, or use ICCs from similar studies. However, our experience on other reviews suggests

that published ICCs for multiple pregnancies are frequently not available. In this case we will estimate ICCs (based on clinical knowledge and data from observational studies) and carry out sensitivity analysis using a range of plausible ICC values.

Dealing with missing data

For included studies, we will note levels of attrition. In future updates, data permitting, 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, analyses will be carried out, 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. 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 τ^2 , I^2 and χ^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a τ^2 is greater than zero, or there is a low P value (less than 0.10) in the χ^2 test for heterogeneity. If we identify substantial heterogeneity (above 30%), we plan to explore it by pre-specified subgroup analysis.

Assessment of reporting biases

In future updates, 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 differs 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 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, we will present the results as the average treatment effect with 95% confidence intervals, and the estimates of τ^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.

1. Twin versus higher order multiple pregnancies.
2. Primigravid versus parous women.
3. Underweight versus normal versus overweight women.
4. Nutritional intervention starting in first trimester versus second or third trimester.

We will use the following outcomes in subgroup analysis.

1. Early preterm births (before 34 weeks).
2. Small-for-gestational age at birth (as defined by the trialists).

We will assess subgroup differences by interaction tests available within RevMan ([RevMan 2014](#)). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We plan to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result. We will restrict this to the primary outcomes only.

WHAT'S NEW

Date	Event	Description
15 June 2015	New citation required but conclusions have not changed	No included trials - conclusions remain unchanged.
15 June 2015	New search has been performed	Search updated, no trials identified.

CONTRIBUTIONS OF AUTHORS

C Ballard drafted the original protocol. JP Neilson contributed to the original draft and all subsequent versions. L Bricker, K Reed and L Wood have commented on draft versions.

DECLARATIONS OF INTEREST

Leanne Bricker: none known.

Keith Reed: I am employed by the Twins and Multiple Births Association. I receive expenses for travelling to a number of multiple birth related research projects.

Lorna Wood: none known.

James Neilson: none known.

SOURCES OF SUPPORT

Internal sources

- Liverpool Women's NHS Foundation Trust, Liverpool, UK.
- The University of Liverpool, Liverpool, UK.

External sources

- National Institute for Health Research (NIHR), UKNIHR Cochrane Programme Grant Project: 13/89/05 – Pregnancy and childbirth systematic reviews to support clinical guidelines, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods have been updated to current standard methods text for the Cochrane Pregnancy and Childbirth Group.

INDEX TERMS

Medical Subject Headings (MeSH)

*Weight Gain; Pregnancy, Multiple [*physiology]; Prenatal Nutritional Physiological Phenomena [*physiology]

MeSH check words

Female; Humans; Pregnancy