Effects of weight management interventions on maternal and fetal outcomes in pregnancy: Individual patient data (IPD) meta-analysis of randomised trials and model based economic evaluation

1. Background

Weight management in pregnancy has the potential to improve maternal and fetal outcomes. Weight management interventions found to significantly reduce weight gain in pregnancy compared to standard care. Based on aggregate data meta-analysis, dietary interventions appeared to be more effective in reducing gestational weight gain and improving obstetric outcomes compared to those based on lifestyle modification. Weight gain in pregnancy varies with age, ethnicity and parity. Meta-analysis of individual participant data IPD,[1] where the raw patient-level data are obtained and synthesised across trials will substantially increase the power to detect baseline factors that truly modify intervention effect, and will enable intervention effects to be quantified for clinically relevant groups. It will also allow the magnitude of benefit due to weight change in pregnancy to be quantified for both the mother and baby.

2 Objectives

Primary objective

1. To determine, using IPD meta-analysis of randomised trials, the differential effects of weight management interventions in pregnancy by i) BMI ii) age iii) ethnicity iv) parity and v) medical conditions like diabetes on a) maternal weight and b) composite pregnancy outcome of maternal and fetal complications

Secondary objectives

2. To validate weight change as an outcome measure by quantifying the relationship between the amount of weight gained in pregnancy and the risk of adverse maternal and fetal outcomes for a) normal weight b) overweight and c) obese women
3. To assess if adherence in pregnancy to IOM weight gain recommendations minimises risk of adverse pregnancy outcomes in a) normal weight b) overweight and c) obese women
4. To identify the predictors of gestational weight gain in pregnancy based on patient characteristics such as parity, pre pregnancy BMI, ethnicity, smoking, diet and lifestyle and socioeconomic status
5. To undertake network meta-analysis to produce a rank order of interventions
6. To assess cost effectiveness of the interventions in pregnancy using model based full economic evaluation with VOI (Value of Information) analysis.

3 Research Methods

Our IPD meta-analytical approach will follow existing guidelines and our output will comply as a minimum with the PRISMA statement,[4] and adhere to recent reporting guidelines for IPD meta-analysis.[1] Our methods will be as follows:

Updating literature searches

The following databases will be searched: MEDLINE, EMBASE, BIOSIS, LILACS, Pascal, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA). In addition, information on studies in progress, from commercial providers like Weight Watchers, Slimming world and unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including the Inside Conferences, Systems for Information in Grey Literature (SIGLE), Dissertation Abstracts and Clinical Trials.gov. Internet searches will also be carried out using specialist search gateways (such as OMNI: http://www.omni.ac.uk/), general search engines (such as Google: http://www.google.co.uk/) and meta-search engines (such as Copernic: http://www.copernic.com/). Language restrictions will not be applied to electronic searches. **Contact with authors and establishment of a collaborative group**
We have established the i-WIP collaborative group that includes representatives from all the groups which have published trials of a) diet versus standard care b) physical activity versus standard care and c) comprehensive weight management versus standard care to evaluate the effectiveness of weight management interventions in pregnancy on maternal and fetal outcomes.
A related website will be developed to improve visibility and communication. The provision of data by the principal investigators of the individual trials will be covered by a memorandum of understanding and any publication of the IPD meta-analysis section of this project will be in the name of the collaborative group, with all contributors listed.

Data collection, entry and checking, and study quality

The minimum data to be collected for IPD meta-analysis will be agreed at the first collaborator's workshop. All variables recorded, even those not reported in the published studies, will be considered for collection and for planning subgroup analyses with sufficient statistical power. A bespoke database will be set up and authors will be allowed to supply data in whatever way convenient to them. This project will take responsibility for converting the data to the required format. There will be flexibility in the format and method of transfer of primary data. All data supplied will be subjected to range and consistency checks. This will ensure that all randomised

patients are included, avoid inclusion of non-randomised patients, improved accuracy of data and ensure intention to treat analysis. Any missing data, obvious errors, inconsistencies between variables or outlying values will be queried and rectified as necessary through input from the original authors. In addition, due to poverty of reporting it has not been possible to obtain information on all the features of methodological quality of individual studies in the published reports. The quality of each trial will be also be assessed at this stage, for example to evaluate the integrity of the randomisation and follow up procedure. We will use the Risk of Bias tool developed by the Cochrane Collaboration, and use this to score the quality of each study.[5] In subsequent meta-analysis, sensitivity analyses will be used to examine the robustness of statistical and clinical conclusions to the inclusion / exclusion of trials deemed at high risk of

Data synthesis

Summarising overall effect of[1] weight management interventions

We will include all patients ever randomised and will base analysis on the intention to treat principle. Initially, all studies will be reanalysed separately and the original authors asked to confirm accuracy of the individual study results, with any discrepancies resolved. Then, for each intervention type and outcome separately, we will perform either a one-step or a two-step IPD meta-analysis to obtain the pooled intervention effect. The one-step approach analyses the IPD from all studies simultaneously, whilst accounting for the clustering of patients within studies. In contrast, the two-step approach first estimates the intervention effect from the IPD in each study separately, and then pools them using a conventional meta-analysis of the intervention effect estimates obtained. We will use a random effects meta-analysis approach, which allows for between-study heterogeneity in intervention effect. If no between-study heterogeneity is found to exist, this model suitably reverts to a fixed effect model. Heterogeneity will be summarised using the I^2 statistic (which provides the proportion of total variability that is due to between-study heterogeneity) and the estimated between-study variance ('tau-squared').

For continuous outcomes, we will aim to synthesise mean differences (potentially standardised if outcome scales differ substantially) and adjust for baseline values using analysis of covariance, as recommended.[6] For binary outcomes, we will aim to synthesise relative risks or odds ratios, with the binomial nature suitably modelled using, for example, a one-step logistic regression adjusting for clustering.

Examining heterogeneity and potential subgroup effects

To consider the causes of heterogeneity and factors that may modify intervention effect, for each weight management intervention we will meet the primary objectives of our project by performing the pre-specified subgroup analyses by:

- Body mass index in early pregnancy - normal weight (BMI 20-24.9 kg/rrT), overweight (BMI 25-29.9 kg/ m^2) and obese (BMI > 30 kg/ m^2)
- Age (less than or more than 20 years)
- Ethnicity (Caucasian, Asian, Black African, Black Caribbean, Oriental, Middle eastern)
- Parity (no previous children, one or more children)
- Risk status of medical co morbidities in pregnancy like diabetes - low risk vs high risk
- Type of intervention
- Examining optimal levels of[1]weight gain in pregnancy that minimises adverse maternal and fetal outcomes

As a secondary analysis, we will also consider three groups of patients (normal weight, overweight, and obese) and examine how weight gain during pregnancy is associated with maternal and fetal outcomes. For each group separately and each outcome, we will fit a suitable regression model that accounts for clustering of patient within studies and quantifies how each 1- unit increase in weight gain changes the risk of a poor outcome. As the relationship is likely to be non-linear, we will consider non-linear trends between weight gain and outcome using fractional polynomial terms. This will help estimate what weight gain value minimises the risk of a poor outcome.

Evaluation ofpredictors of-weight change in pregnancy

We will evaluate those variables that may have an effect on gestational weight gain including age, ethnicity, underlying medical conditions like diabetes, parity, type and duration of intervention and socioeconomic status. For all candidate predictors, we will perform separate analyses in each BMI cohort (normal, overweight and obese) and analyse on the whole metaanalysis database, adjusting again for the clustering of patients within studies. Multivariable models will be built using backward elimination of variables according to likelihood ratio criteria, starting with all variables with P <0.1 in univariate models, in order to examine which predictors have independent prognostic value.

Indirect comparison

All trials identified in our review compare interventions to a control group. We will perform a meta-analysis separately for each intervention option, such as diet based and physical activity interventions. Under the assumption that the sets of trials in each meta-analysis are comparable, an indirect comparison will be carried out by calculating the difference in treatment effect sizes for all interventions (to get say A vs B using A vs C minus B vs C), and ranking those that appear to be the most effective. This is essentially a network meta-analysis approach, but there are no trials with direct comparisons of treatments to be included in the network.[19,20] Within-trial randomised comparisons of each study will be preserved. The indirect comparison will be treated with caution, recognising that the main assumption - i.e. there are no systematic differences between the sets of trials that could bias the indirect measurements - is difficult to verify, though we will compare the types of patients and the amount of heterogeneity in the different sets of trials to help establish if they are similar. Where indirect comparisons have been compared to direct comparisons, over 95% concordance has been found.

Exploration of sources of bias

For each analysis containing 10 or more studies the likelihood of publication bias will be investigated through the construction of contour-enhanced funnel plots and appropriate statistical tests for 'small-study effects';[9] that is, the tendency for smaller studies to provide more positive findings. We will recognise that, especially where heterogeneity exists, publication bias may be one of a number of reasons for any small study effects identified. The restriction of 10 studies is due to the low power of identifying small study effects with few studies.[10]

4 Health economic evaluation and decision analytic modelling

The aim of health economic evaluation is to conduct a model based economic evaluation to assess the cost effectiveness of the interventions to manage weight gain in pregnancy and to carry out a value of information analysis to inform future research. This project will involve the development of a decision analytic simulation model as a framework for conducting cost-effectiveness and cost-utility analyses (as far as possible) and associated value of information analyses. The model development process will use, as a starting point, the recently published report on Weight Management in Pregnancy: Economic Modelling.11 That model, from researchers at the University of Sheffield, was recently commissioned by the National Institute for Health & Care Excellence (NICE).

Assuming that a Markov model is found to be appropriate, it will be constructed using TreeAge Pro software. This is a widely-used and highly user-friendly software package ideally suited to the

construction and analysis of decision tree and Markov models.

The principal clinical data to be used in populating the model will be drawn from other aspects of our research work, namely the individual patient meta analyses and existing randomised controlled trials (as detailed earlier in this proposal). Economic outcomes are not likely to be directly available from any of the trials included in the meta-analysis. Hence the cost and health-related quality of life implications of the interventions will be assessed using other relevant data in the published literature. Quality of life and health care cost implications of weight-related conditions will be obtained from the NICE CPHE-sponsored economic evaluation of weight management in pregnancy 11 as well as a survey of published literature.

Resource use will be estimated from the existing published evidence (such as the NICE guidance document on obesity) and additional cost data will be sought from other sources such as the annual review of unit health and social care costs (by the University of Kent) and national schedule for reference costs.

The economic evaluation will attempt to adopt a broad perspective as far as possible and seek to include consideration of costs incurred by the health sector, by patients and by the economy more broadly in terms of productivity issues. However, the primary base case analysis will adopt the health care provider perspective and the societal perspective will be explored as part of a secondary sensitivity analysis. The relative cost-effectiveness of weight management interventions in pregnancy will be evaluated using effect size estimates for these interventions obtained from the IPD meta-analysis.

The main objective of the evaluation will be to determine the characteristics of the weight management intervention(s) that are the most cost-effective. Hence the range of options (in terms of duration, frequency and intensity) for which trial data exist will be investigated.

An incremental approach will be adopted with a focus on additional costs and gain in benefits associated with a move away from current practice to alternative treatment strategies. The cost-effectiveness component of the work will report results in terms of an incremental cost-effectiveness ratio (ICER) of cost per unit of benefit gained, measured in appropriate clinical and economically relevant outcome measures.

The IPD meta-analysis (described in an earlier section) will be based on composite weight related outcomes that include maternal weight gain in pregnancy and composite pregnancy outcomes which include maternal and fetal complications. However, an economic analysis based on composite outcomes will not be meaningful as the full extent of cost implications based on such an outcome will be lost. We will therefore look at the primary outcomes individually; for example, we will present results in terms of cost per case of GDM avoided; and cost per case of pre-eclampsia avoided; etc (according to the defined primary outcome lists). If possible, results will be presented in terms of cost per major outcome averted,

where major outcome will be pre-defined to include one or more of the complications such as GDM, Pre-eclampsia and so on.

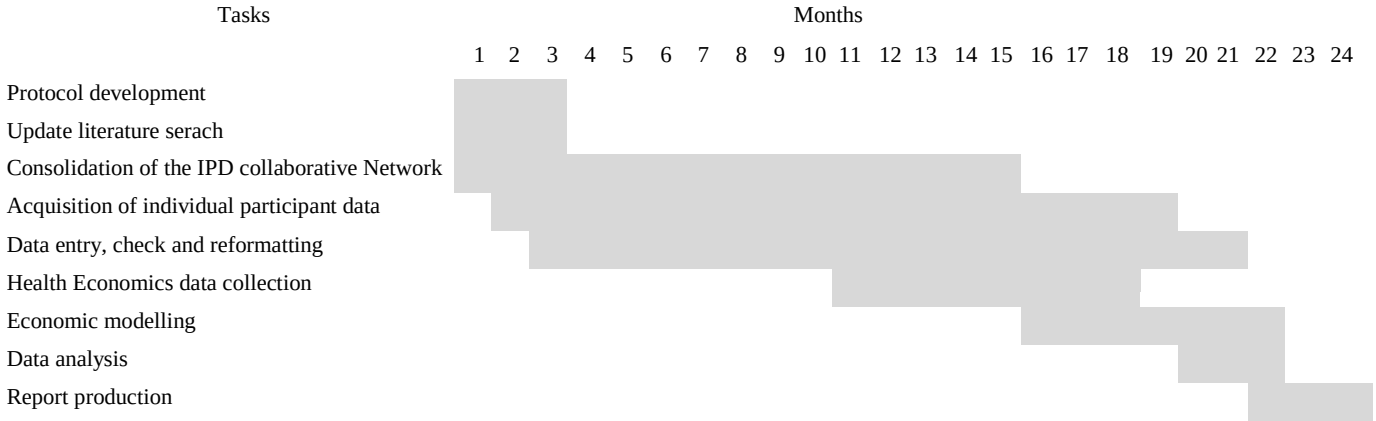
Some limited quality of life data potentially suitable for use in a cost-utility framework are available from published sources (for example Madan and Chilcott) [11] and so the economic evaluation will attempt additionally to present results in terms of incremental cost per quality-adjusted life year (QALY) gained. However, appropriate data for this outcome are likely to be sparse and subject to significant uncertainty.[11] Furthermore, it is not anticipated that the intervention is likely to show any direct impact on infant or maternal mortality.

The results will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also include a value of information analysis to quantify the total uncertainty in terms of the value of removing that uncertainty. As appropriate, we shall include partial value of information analysis calculations. In addition to this probabilistic sensitivity analysis on our base-case model, we shall include a range of alternative analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalizability of the results.

If possible (if available data allow), separate sub group analyses will be performed for women who enter the pregnancy as normal weight, overweight and obese. If data permit, analyses will also be performed for particular risk groups (ethnic minorities, teenage pregnancies, low socioeconomic status, multiparous, high risk pregnancy complicated by medical conditions).

5 Project timetable

Fig. shows the project timetable and milestones for IPD meta-analysis and economic modelling.



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