

BMJ Open Effect of simple, targeted diet in pregnant women with metabolic risk factors on maternal and fetal outcomes (ESTEEM): study protocol for a pragmatic multicentre randomised trial

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ABSTRACT

Introduction: Women with metabolic risk factors are at higher risk of adverse pregnancy outcomes. Mediterranean-based dietary interventions have the potential to minimise these risks. We aim to evaluate the effectiveness of a simple, targeted intervention modelled on Mediterranean diet in preventing maternal and fetal complications in pregnant women with metabolic risk factors.

Methods and analysis: Pregnant women with a singleton pregnancy <18 weeks gestation, and without pre-existing diabetes, chronic renal disease and autoimmune diseases will be recruited. Women with metabolic risk factors will be randomised to receive a dietary intervention based on a Mediterranean pattern, supplemented with extra virgin olive oil and mixed nuts until delivery. The intervention will be delivered through a series of one to one and group sessions. The primary outcome is a composite maternal outcome of pre-eclampsia or gestational diabetes and a composite fetal outcome of stillbirth, small for gestational age fetus or admission to the neonatal intensive care unit. Secondary outcomes include maternal, fetal, dietary and laboratory outcomes. We aim to randomise 1230 eligible women with metabolic risk factors. We will also compare the outcomes in women with and without these risk factors. The sample size will provide us with 80% power at 5% significance, assuming a 20% loss to follow-up to detect a 30% reduction in maternal and fetal complications.

Ethics and dissemination: The ESTEEM trial is designed to provide a definitive estimate of the effects of Mediterranean dietary pattern in pregnancy on maternal and fetal outcomes. The pragmatic nature of ESTEEM ensures the applicability of its findings into clinical practice. The findings of the study will be published in peer-reviewed journals and presented at national and international scientific meetings and congresses. Ethical approval was granted by the NHS Research Ethics Committees (14/EE/1048).

Trial registration number: NCT02218931; Pre-results.

Strengths and limitations of this study

- Large sample size to provide adequate power to detect a reduction in composite maternal and fetal outcomes.
- Pragmatic design to facilitate the translation of findings into clinical practice.
- Advocating healthy lifestyle changes.
- Objective assessment of adherence.
- Unblinded intervention.
- Variations in care provision for the control group.

INTRODUCTION

Obesity is rapidly increasing worldwide adversely affecting public health.¹ Pregnant women with metabolic risk factors such as increased adiposity and dyslipidaemia are at high risk of adverse pregnancy outcomes.² About one in five women currently enter pregnancy as obese in the UK, leading to complications such as gestational diabetes, pre-eclampsia, stillbirth and neonatal death.³ High levels of triglycerides and cholesterol are independent risk factors for pre-eclampsia and diabetes in pregnancy.^{4 5} Poor dietary habits, sedentary lifestyle and underlying genetic predisposition all contribute to this phenomenon. Diet and physical activity based interventions have shown a beneficial effect on gestational weight gain, with varied effect on pregnancy outcomes.⁶

The Mediterranean dietary pattern has demonstrated a beneficial effect in reducing metabolic risk factors such as adiposity, hypertension and dyslipidemia.⁷ In non-pregnant individuals with metabolic risk factors, a Mediterranean diet-based intervention supplemented with extra virgin olive oil



and nuts was shown to reduce cardiovascular mortality and morbidity.⁸ Observational studies in pregnancy have reported a reduction in the risk of pre-eclampsia, gestational diabetes and fetal growth restriction in women with high compliance to a Mediterranean-based diet compared to those with low compliance.^{9–11} However, the existing studies in this population are non-randomised, of poor quality, or focus on specific components of the diet, rather than modifying the overall dietary pattern.⁶

There is a need for an adequately powered pragmatic randomised trial to evaluate the beneficial effect of a Mediterranean diet in pregnancy that is simple, feasible and targeting women at most risk of complications.

OBJECTIVES

We aim to assess the effects of Mediterranean diet-based intervention in high-risk pregnant women to minimise maternal and fetal complications.

Our primary objective is to compare, in pregnant women with metabolic risk factors, the effect of a simple, targeted Mediterranean-based diet, supplemented with extra virgin olive oil and nuts, composed within culturally appropriate recipes and food options, on a composite maternal (pre-eclampsia or gestational diabetes) and fetal outcome (stillbirth, small for gestational age fetus or admission to neonatal intensive care unit), to current care.

The secondary objectives are to assess the effect of the dietary intervention on different individual maternal and fetal complications and on the participants' lipid profile in the two randomised groups. We will also evaluate the risk of complications in women with and without metabolic risk factors in the recruited cohort. Furthermore, we will study the effect of the dietary intervention on the risk of composite maternal and fetal outcomes in the following subgroups: obese women, women with raised triglycerides and women with chronic hypertension.

METHODS AND ANALYSIS

Study design

ESTEEM is a parallel group randomised trial embedded in a cohort study.

Setting

Secondary and tertiary care maternity units in England from September 2014 to September 2016.

Participants

Eligibility for recruitment

Women are eligible to participate in the ESTEEM study if they are pregnant with singleton fetus of <18 weeks gestation, are 16 years old or more, have a body mass index (BMI) between 18.5 and 40 kg/m², are able to consume nuts and olive oil, follow a Mediterranean dietary pattern and have a good understanding of

written and spoken English. Participants are excluded if they have a history of pre-existing diabetes, chronic renal disease and autoimmune disease or if they are on any lipid-altering drugs, for example, statins

Eligibility for randomisation

Women will be randomised to the trial if they have any of the following risk factors: obesity (BMI ≥ 30 kg/m²), raised serum triglycerides (≥ 1.7 mmol/L) or chronic hypertension (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic blood pressure).

Study conduct

Pregnant women will be provided with the ESTEEM Patient Information Sheet (PIS) at least 24 hours prior to the hospital booking visit to ensure that they have adequate time to consider the trial. If a participant has not read or received the PIS beforehand, the research team will explain the PIS in person. If the participant fully understands the study and is keen to join, a written consent form will be obtained. An additional written consent form will be completed prospectively to collect and store umbilical cord blood samples for use in future studies investigating the link between the maternal diet and the cord blood nutrients. Participants can still join the study if they decline the cord blood collection. Examples of both consent forms are submitted as supporting information (see online supplementary appendix 1).

Following consent, baseline information will be obtained from the participants, blood pressure will be measured, and an additional lipid profile test will be carried out to assess the participant's suitability for randomisation.

Women who fulfil the criteria for randomisation will be randomly allocated to the intervention group (Group A) or the control group (Group B). The randomisation and sequence allocation will be performed by the trial research staff via a password-protected internet-based data management system in a ratio of (1:1). Minimisation (with a random element to ensure allocation concealment) will be used to ensure balanced groups for maternal weight, gravidity and ethnicity. Women with no metabolic risk factors will be followed up as a non-randomised cohort and maternal and fetal outcomes will be obtained (Group C) ([figure 1](#)).

Women randomised to the intervention will be invited to the ESTEEM antenatal clinic to meet the study dietitian or a trained allied health professional before 18 weeks, who will deliver the dietary intervention on a 1-1 basis. Women will be invited to two further sessions at 20 and 28 weeks gestation for delivery of the intervention in a group setting. Two follow-up phone calls will be made to the participants in the intervention group at 24 and 32 weeks gestation to check on their well-being, assess their compliance using the ESTEEM questionnaire and check for any adverse events (AEs).

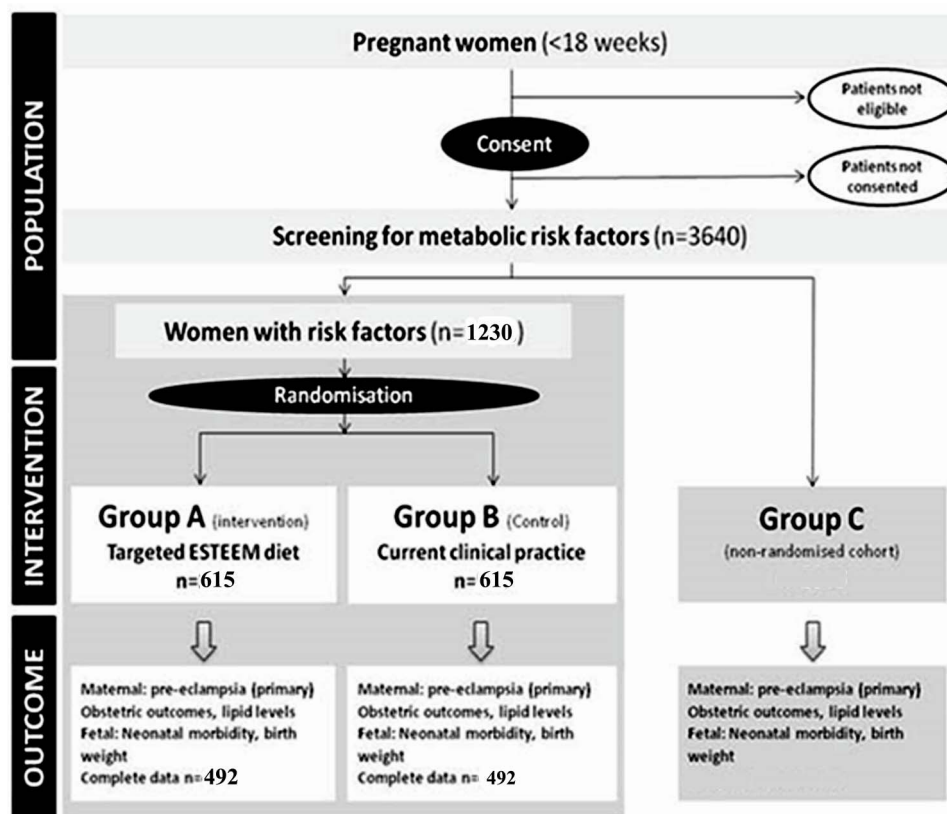


Figure 1 ESTEEM study design including the screening, recruitment and randomisation process.

Participants in the intervention group who miss the first appointment in which intervention is delivered will be given another appointment at 20 weeks of gestation. Any participant who fails to attend subsequent group sessions will be kept in the intervention group, if they continue to collect the nuts and olive oil and adhere to the intervention. Group sessions and telephone follow-ups will have a 2-week window for completion of tasks. Failure to complete the follow-up in time will be recorded as a deviation of protocol, and records will be updated accordingly.

Baseline information, as well as ESTEEM Q, IPAQ and EQ5D questionnaires, will be completed in person, over the telephone or posted to all participants in the intervention and the control groups. A final 1-1 follow-up session will be offered between 36 weeks gestation and delivery to women in both groups. The aim of this session is to assess dietary intake, physical activity, quality of life, repeat the serum lipids profile blood test and measure their weight and blood pressure (figure 2).

Health technology assessed

The ESTEEM dietary intervention is based on Mediterranean diet, with education to modify lifestyle choices. The key components of the diet include high intake of fruit and vegetables, non-refined grains, legumes, moderate to high consumption of fish, small to moderate intake of poultry and dairy products such as

yoghurt and cheese, low consumption of red meat and processed meat and avoidance of sugary drinks, fast food and food rich in animal fat. In particular, ESTEEM advocates high intake of nuts (including walnuts, hazelnuts and almonds estimated at 30 g/day) and high intake of extra virgin olive oil as the main source of fat (estimated at 0.5 L/week). The intervention will include dietary education sessions, grocery shopping advice, cooking recipes for a healthy diet and advice for appropriate meal choices at restaurants.

At the first visit, the dietician or a trained allied health professional will assess the participant's dietary habits using 24 hours food recall followed by focused questions to estimate their basal dietary intake and identify elements for change towards a Mediterranean diet. Participants will be encouraged to set and record personalised goals following the SMART model (specific, measurable, achievable, relevant and time-specific) to implement the highlighted changes to their diet.¹² Women will also be asked to complete the ESTEEM questionnaire (a 12 items short dietary questionnaire specifically designed to assess the intake of Mediterranean food groups) to provide a baseline record. The participants' physical activity will be assessed using the IPAQ questionnaire,¹³ and their quality of life will be assessed using the EQ-5D questionnaire.¹⁴ The dietician or a trained allied health professional will also provide standardised education material on the benefits

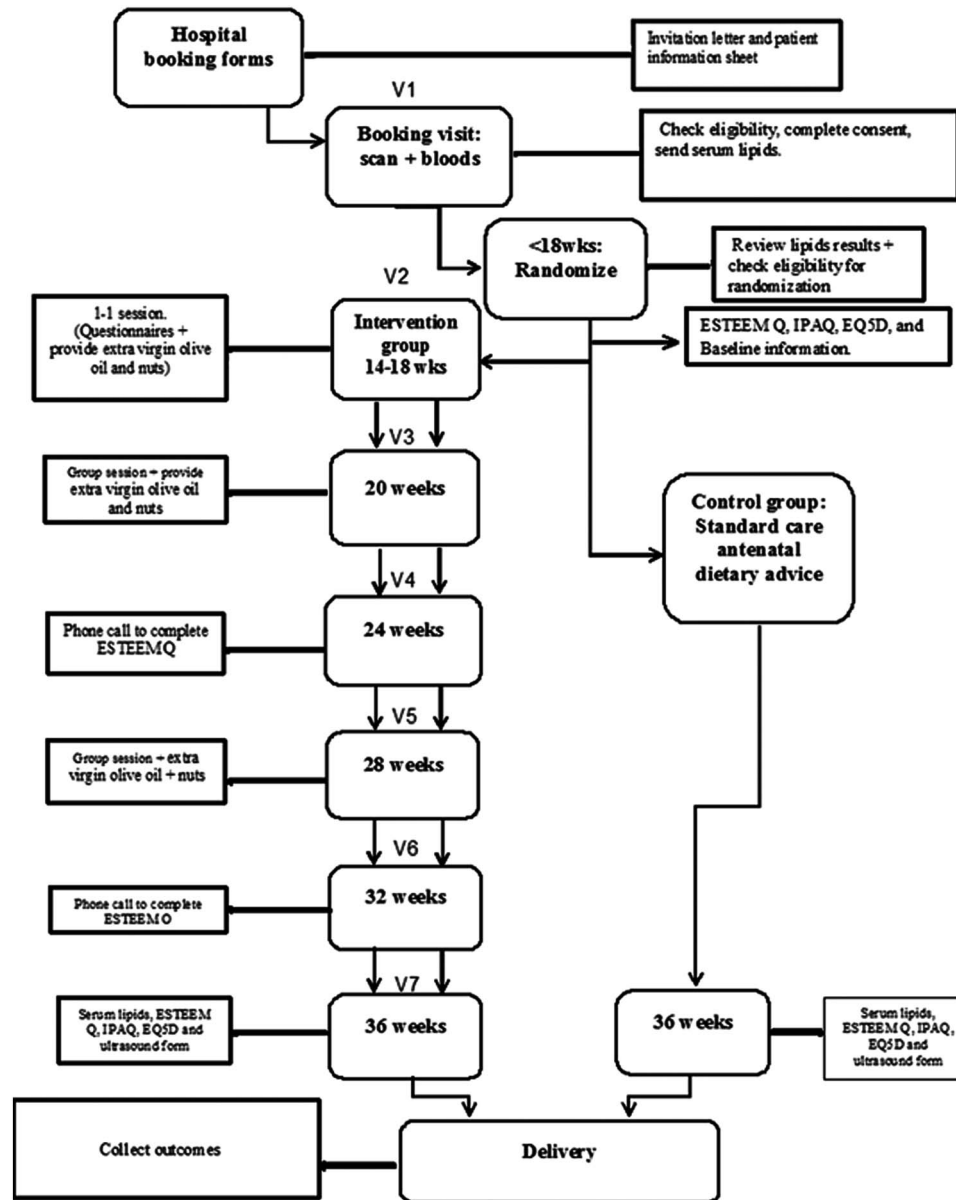


Figure 2 Flow chart of the ESTEEM study conduct.

of Mediterranean diet in pregnancy and supportive fact sheets on the benefits of nuts and extra virgin olive oil.

In the group sessions, mothers will be encouraged to involve their partners and the whole family in the dietary changes. Culturally adaptable recipes and grocery list for foods will be provided to promote intake of a Mediterranean lifestyle diet. Women will be advised to modify their current diet with a healthier option where possible, such as reducing the saturated fat and added sugar intake. Adherence to the intervention will be assessed primarily against the number of sessions attended, and if needed supplemented with dietary information collected using the ESTEEM Questionnaire at 20, 24, 28, 32 and 36 weeks gestation.

The control group will be provided with the usual antenatal dietary advice as per NICE guidelines on antenatal care, weight management in pregnancy and

hypertension in pregnancy.^{15–17} Folic acid and vitamin D supplementation will be provided as per national recommendations for all participants.

Umbilical cord blood samples collection and storage

Umbilical cord blood samples will be collected from all consented participants on delivery of the baby for use in future studies. Blood will be collected from the umbilical cord and the placenta using a syringe and a needle and saved in a 10 mL ethylenediaminetetraacetic acid (EDTA) dry tubes. All samples will be stored at an accredited Human Tissue Resource Centre (Barts and the London NHS Trust) and will be stored for a maximum of 72 hours at the site of collection. Samples will be then transferred to an accredited tissue bank facility (The Blizard Institute—Queen Mary University of London) to be stored in a -80°C freezer. All samples will be coded

anonymously with no information identifying the study participants. Samples will be stored in accordance with the institutional Data Protection Policy for the lifetime of the study and 10 years after its completion.

Proposed outcome measures

The primary outcome is a composite maternal outcome defined as pre-eclampsia (new onset or superimposed) or gestational diabetes; and a fetal composite outcome defined as stillbirth, small for gestational age fetus (birth weight less than 10th centile) or admission to the neonatal intensive care unit. The definitions are provided in online supplementary appendix.²

The secondary outcomes are as follows: maternal: pre-eclampsia, gestational diabetes, preterm delivery, gestational weight gain, antepartum haemorrhage, mode of delivery, anaemia and admission to high dependency unit or intensive care unit; fetal and neonatal: stillbirths, neonatal deaths, hypoxic ischaemic encephalopathy, birth weight (in kg using customised and population centiles) small for gestational age (<10th centile) and admission to neonatal intensive care units; dietary: nutrients and food intakes, food groups, including olive oil, vegetables, fruits, red meat, butter/margarine, sugary drinks, pulses, fish intake and commercial sweets; laboratory: levels of triglycerides, high-density lipoproteins, ratio of triglycerides and levels of non-high-density lipoprotein cholesterol.

Food frequency and ESTEEM questionnaires

The ESTEEM food frequency questionnaire (FFQ) is designed to assess habitual dietary intake over a specific reference period in a pregnant population. It was adapted from a validated FFQ specifically designed to assess the dietary intake in a pregnant Mediterranean population.¹⁸ We adapted the ESTEEM FFQ to capture cultural foods commonly consumed in the study's multi-ethnic population. We obtained nutrients values from the McCance and Widdowson's Composition of foods integrated data set¹⁹ and portion sizes from the Food Standards Agency UK portion sizes.²⁰ We will use the methodology reported in the EPIC FFQ design²¹ to estimate dietary intake by capturing frequency data of the different nutrients and food groups.

We also developed a short food questionnaire of 12 items to assess the participants' adherence to the dietary intervention (The ESTEEM Q). The questionnaire was developed based on a similar 14 items questionnaire used in the PREDIMED trial to assess the adherence to a Mediterranean-based dietary intervention and was adopted to be used in a pregnant population.²² We will collect both questionnaires at baseline and 36 weeks from the control and the intervention groups.

The FFQ will be validated in the pilot phase against multiple 24-hour food recalls using the multipass method in a subsample of 65 randomised participants. The agreement between daily intake of food groups, energy, macronutrients and micronutrients estimated,

respectively, from the FFQ and from the 24-hour recalls will be evaluated using intraclass correlation coefficients. To graphically check the agreement between the two methods, we will use the analysis proposed by Bland and Altman,²³ using a plot of the differences between the measurements against their means. Evidence of consistent disagreement between the nutrients and food intakes will be investigated using paired t-tests. We will also identify the quintiles of intakes according to the 24-hour food recall data and the degree of gross misclassification (the proportion classified into opposite quintiles) and complete or adjacent agreement (the proportion classified into the same or an adjacent quintile) using the FFQ and 24-hour food recall data as additional indices of validity.

The FFQ will be also used to validate the ESTEEM questionnaire (ESTEEM Q) in the subsample of 65 participants. We will use reported food intakes from the FFQ to generate a response to each question on the ESTEEM. The resulting FFQ-generated ESTEEM Q total score will be compared against the actual ESTEEM Q total score.²² The agreement between the two ESTEEM Q total scores will be evaluated using intraclass correlation coefficients. To assess the convergent validity of the ESTEEM Q total score, we will calculate the Pearson product moment correlations between the actual ESTEEM Q total score and nutrient intakes estimated from the FFQ. We will use Kappa statistics to determine the agreement between the scores for each of the 14 questions of the ESTEEM Q. We will also use the Bland-Altman method to illustrate the agreement between the scores of the FFQ and the ESTEEM Q total scores. We will use a paired t-test to investigate any consistent disagreement between the two scores.

Sample size

We expect the prevalence of the composite maternal outcome of pre-eclampsia or gestational diabetes to be 24% and expect the ESTEEM dietary intervention to reduce it by 30%. We will need 982 women to detect a 30% reduction in the primary outcome rate. After allowing for a 20% dropout, we will need to randomise 1230 eligible women to ensure an 80% power at the 5% significance level. We expect the above sample size to have an 80% power to detect a similar reduction in the composite fetal outcome rate at the 5% significance level, while allowing for a 20% loss to follow-up and a similar prevalence of 24%.

Statistical analysis

The effect of the treatment on the risk of composite maternal and fetal outcomes will be estimated as an OR with 95% CI, using a multivariable logistic regression. We will adjust for the minimisation factors, as well as age, history of previous gestational diabetes, family history of hypertensive disorders (hypertension and/or pre-eclampsia), family history of diabetes and history of stillbirth. These covariates have been selected based on prior



evidence. Secondary outcomes will be analysed using a multivariable logistic regression for binary outcomes and a linear regression for continuous outcomes, with a normalising transformation where necessary. Where a continuous outcome is also assessed at baseline, this will be adjusted for as an additional covariate. Analyses will be on an intention-to-treat basis. We do not anticipate any missing primary outcome data, as the selected outcomes should be recorded for all women and newborn infants. However, should any primary outcome data be missing, we will analyse participants with complete outcome data only. This approach is unbiased if data are 'Missing at Random'. If the primary outcome is missing for more than 5% of participants, then a sensitivity analysis will be conducted to explore the 'Missing at Random' assumption. Minimisation factors must also be non-missing for participants to be randomised.

Subgroup and secondary analysis

The primary analysis of the treatment effect on the risk of composite maternal and fetal outcomes will be repeated separately within three subgroups: obese women, women with raised triglycerides and women with chronic hypertension. These subgroups will be analysed by statistically testing for an interaction term. Subgroup-specific ORs will be reported with 95% CIs. These analyses will be secondary and given less weight in our conclusions than the primary analysis. Secondary to the intention-to-treat analysis we will perform analyses of the treatment effect which takes into account the participants' compliance with the intervention using a complier-averaged causal effect (CACE) analysis.

Internal pilot

We will dedicate the first 3 months of the study for an internal pilot to evaluate the rates of recruitment to the trial and test the trial's procedures. During the first 3 months of study's setup phase, we will obtain feedback from service users on the design of the patient information materials. During this period, we will also assess the number of pregnant women screened for recruitment, proportion of screened population who are eligible with metabolic risk factors, the adherence to the protocol, the fidelity of the follow-up, the reasons for exclusion from the trial, the proportion of eligible women participating in the trial and the reasons for which eligible women declined participation in the trial.

If more than half of eligible women are not recruited as anticipated by the end of the pilot phase, we will survey the clinical staff early to identify any issues that can be resolved to promote recruitment. Failure to recruit more than 50% of the target population over the first 6 months of recruitment will lead to a review of trial feasibility.

Data monitoring and confidential interim analysis

ESTEEM has a Trial Steering Committee (TSC) of four independent members, including a representative from

APEC (Action on Pre-eclampsia), a charity dedicated to the well-being of women diagnosed to have pre-eclampsia and a service user with a history of pre-eclampsia. There are also three independent members on the Data Monitoring Committee (DMC). At the end of the pilot phase, all data will be presented to the DMC for confidential review. Recommendations of the DMC will be discussed with the TSC. There will be no gaps in recruitment to continue the momentum built-up during the pilot phase. All planned protocol amendments will be discussed and approved by the TSC, Main REC and the sponsor before taking action.

Data handling and confidentiality

The chief investigator has the overall responsibility to ensure that the participants' anonymity is protected and maintained at all times in the study. All information collected on the study participants will be kept confidential and managed in accordance with the Data Protection Act (1998-UK), NHS Caldicott Guardian (Health Service Circular: HSC 1999/012), The Research Governance Framework for Health and Social Care and the Research Ethics Committee Approval.

All data collected in the study will be entered onto a dedicated password-protected electronic database using a secure computer and internet connection. Paper case report forms (CRF) will be used as a backup if required. Data will be monitored centrally for consistency, viability, quality and screened for out-of-range errors. We will cross-check for conflicting data within and between the CRF using computerised logic checking screens. In the event of missing items or uncertainty in the records, data will be referred back to the relevant centre for clarification. Paper CRFs will be verified and processed on site by the trial coordinators or other delegated team members. Any data to be processed will be anonymised prospectively. All personal information obtained for the trial will be held securely and treated as strictly confidential. All staff members, at each hospital or the trials unit, share the same duty of care to prevent unauthorised disclosure of personal information to any unauthorised body. We will not publish any data that could lead to the identification of any study participants.

During the course of study, all records are the responsibility of the chief investigator and will be kept in secure conditions. On completion of the study, all records will be kept securely by the sponsor for a further 20 years.

Quality assurance and auditing

The chief investigator will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, good clinical practice (GCP), Trust and Research Office policies and procedures and any subsequent amendments.

Non-compliance may be captured from a variety of different sources including monitoring visits, CRFs,

communications and updates. The sponsor will maintain a log of any non-compliance to ascertain if there are any trends developing or escalating. The sponsor will assess the non-compliances and resolve it within a fixed time frame.

The study sites will perform remote trial monitoring as determined by the sponsor to verify the validity of source data. A random sample of cases will be monitored at source when site visits are performed. The documents to be verified will be randomly selected. Any major discrepancies found at a site visit would trigger a more extensive audit of trial data at the site involved.

Adverse events

Any AEs, defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities, will be recorded in the participant's individual study file, the medical notes and the CRF with appropriate follow-up by the research team.

Any serious adverse event (SAE), defined as an untoward occurrence of death, life-threatening condition, hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, congenital anomaly or birth defect or any condition judged as medically significant by the investigator, will be reported to the study sponsor within 24 hours of learning of the event and to the main research ethics committee within 15 days.

ETHICS AND DISSEMINATION

NHS Research Ethics Committee approval was obtained in all centres (UK IRAS integrated research application system; reference 14/EE/1048). ESTEEM is registered online with clinicaltrials.gov (NCT02218931).

The study collaborators will hold a meeting on completing the study to discuss and evaluate the main results. The success of the study depends on the collaboration of a large number of stakeholders including doctors, nurses, midwives, nutritionists and others. Thus, the main credit for publishing the study's results will be dedicated to all collaborators equally. The trial management committee will be responsible for publishing the ESTEEM findings in high impact peer-reviewed journals. Open access publications will be sought where possible to maximise impact. All ESTEEM publications will follow the ICMJE authorship guidelines. Oral and poster presentations will be sought in national and international conferences of interest to the study topic to maximise dissemination. Individual study centres will not be permitted to publish partial data obtained from participants in the ESTEEM study without discussion with the chief investigator and/or the TSC.

DISCUSSION

Pregnancy offers an optimal period to motivate women to adhere to healthier diet and lifestyle changes.²⁴ The

role of behavioural and dietary-based interventions has been increasingly evaluated to assess its benefit in preventing pregnancy complications. To date, no intervention has been shown to be significantly beneficial.²⁵

The ESTEEM study is specifically designed to test the beneficial role of a Mediterranean-based dietary intervention in reducing metabolic risk factors in a high-risk pregnant population.

The high intake of beneficial food such as vegetables, fruits, non-refined grains, fish, extra virgin olive oil and nuts and the reduced intake of high-fat food and red meat characteristic of a Mediterranean diet have been shown to improve lipid profiles, insulin sensitivity and blood pressure.⁸ This protective effect is linked to the increased intake of poly and mono-unsaturated fatty acids readily available in a Mediterranean diet compared to a modern Western diet.²⁶ A low ratio of unsaturated to saturated fatty acid in the diet has been linked to adverse outcomes in pregnancy such as pre-eclampsia and fetal growth restriction.²⁷ However, available studies are of poor quality and not sufficiently powered for specific pregnancy outcomes.⁶

The planned large study sample will provide ESTEEM with adequate power to detect a reduction in primary and secondary outcomes. The choice of the primary composite outcomes was agreed with the TSC based on input from multistakeholders in research on obesity in pregnancy.²⁸ Delivering the intervention via interactive educational sessions coupled with dedicated grocery lists and cooking recipes is aimed to improve the participants' adherence to the intervention.²⁹ Inducing and maintaining dietary changes in pregnancy and beyond could be challenging.³⁰

Advocating a Mediterranean-based diet through educational intervention might not be sufficient to introduce a permanent change. Our strategy of providing cooking recipes specially developed to adopt local food culture and implement a Mediterranean cooking style could help the participants to better understand and comply with the intervention. The cost of acquiring nuts and olive oil is relatively high in the UK which could present a burden on the study participants. To improve adherence, we opted to provide the participants with extra virgin olive oil and mixed nuts throughout the study. This will also ensure the continuous availability of these nutrients throughout the lifetime of the study. The group sessions are aimed to reinforce the knowledge and the education on the benefits of Mediterranean diet, promote healthy eating habits, healthy shopping and sharing experiences among participants and will provide opportunities to explore obstacles and potential solutions.

Assessing adherence to the intervention is crucial to accurately interpret dietary trials' results. Using multiple food diaries is generally considered to be the golden standard tool for assessing dietary intake in dietary interventional trials.³¹ However using this tool in a pregnant population can be quite cumbersome particularly for participants who care for large families and are in full-



time employment. While using an FFQ might offer a better and more efficient substitute, it still requires relatively high literacy, a characteristic not always available in our population of interest. It can also be less sensitive to detect subtle changes in the dietary intake compared to food diaries and 24 hour recalls.³² FFQs must also be validated within the study population.³¹ This might be a challenging task in ESTEEM due to the large variation in ethnic groups, food cultures and dietary habits in our population.

The use of a short screening tool such as the ESTEEM Q will offer an easy and sensitive tool to assess the intake of the nutrients of interest in the Mediterranean diet such as extra virgin olive oil and nuts. Introducing this short tool is far less complicated and can even be conducted over the phone which will help to improve returns. The limitation of using such tool is the limited information collected on the whole diet and the narrow focus on the Mediterranean nutrients' intake. Women will be recruited from multiple maternity units in the UK, which will allow us to recruit a multiethnic population with diverse food cultures. This will render ESTEEM findings more generalisable and transferable to clinical practice.

Some of the limitations in the design of the trial could affect the interpretation of its findings. The nature of the intervention makes it difficult to blind the participants and the clinicians, which could introduce bias. Furthermore, the control group will vary in the level of care available to mothers at various maternity units. For example, in some units, dietician support is provided for women with a BMI ≥ 30 kg/m² compared to >35 kg/m² or none in other units. It is also possible that knowledge of potential benefits of the study may motivate some women in the control group to follow the Mediterranean lifestyle, which could bias the results.

Poor adherence to the intervention is clearly an important factor that could bias the results of the trial. Using self-reporting dietary tools such as the FFQ and the ESTEEM Q will help us to estimate the adherence to the dietary intervention. We will conduct a sensitivity analysis of the treatment effect which takes account of the compliance rate defined by the attendance rate to the intervention sessions throughout the study.

A better assessment of the dietary intake could be achieved by using specific biomarkers such as hydroxytyrosol for olive oil intake and α -linolenic acids for nuts intake. Biomarkers offer an accurate and objective assessment of the nutritional intake. Their use, however, still has a number of limitations; it only offers a snapshot view of the intake over a limited time period and can be a relatively expensive and invasive tool.³³ Recording the return of empty packages can also provide a snapshot view of the consumption of provided nutrients, however, it is less specific and representative of the participant's individual intake.

There is increasing evidence on the possible benefit of Mediterranean diet on long-term childhood and maternal

outcomes. Observational data have shown a potential reduction in childhood asthma and eczema following in utero exposure to the diet.³⁴ Furthermore, the effects of nut exposure to pregnant mothers on subsequent nut allergy in children needs evaluation. The effect of Mediterranean diet on future risk of type 2 diabetes in these women at high risk of metabolic factors is not known.

CONCLUSIONS

The ESTEEM trial will evaluate the benefit of a Mediterranean-based diet to reduce the risk of complications in pregnant women with high metabolic risk factors.

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Contributors BHA wrote the first manuscript draft and is helping with in the study conduct; JD and AP are co-ordinating the study conduct and drafted the protocol; EP is delivering the intervention; RH and LB designed the statistical analysis plan, TJR, MB-R, GH and KSK helped in developing the protocol and ST revised the manuscript and is supervising the overall study conduct. All authors provided critical input to the manuscript.

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