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Effectiveness and acceptability of metformin in preventing the onset of type 2 diabetes after gestational diabetes in postnatal women: a protocol for a randomised, placebo-controlled, double-blind feasibility trial — Optimising health outcomes with Metformin to prevent diAbetes After pregnancy (OMAhA)

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ABSTRACT

Introduction Up to half of all women diagnosed with gestational diabetes mellitus develop type 2 diabetes within 5 years after delivery. Metformin is effective in preventing type 2 diabetes in high-risk non-pregnant individuals, but its effect when commenced in the postnatal period is not known. We plan to assess the feasibility of evaluating metformin versus placebo in minimising the risk of dysglycaemia including type 2 diabetes after delivery in postnatal women with a history of gestational diabetes through a randomised trial.

Methods and analysis Optimising health outcomes with Metformin to prevent diAbetes After pregnancy (OMAhA) is a multicentre placebo-controlled double-blind randomised feasibility trial, where we will randomly allocate 160 postnatal women with gestational diabetes treated with medication to either metformin (intervention) or placebo (control) tablets to be taken until 1 year after delivery. The primary outcomes are rates of recruitment, randomisation, adherence and attrition. The secondary outcomes are maternal dysglycaemia, cost and quality of life outcomes in both arms, and acceptability of the study and intervention, which will be evaluated through a nested qualitative study. Feasibility outcomes will be summarised using descriptive statistics, point estimates and 95% CIs.

Ethics and dissemination The OMAhA study received ethics approval from the London-Brent Research Ethics Committee (18/LO/0505). Trial findings will be published in a peer-reviewed journal, disseminated at conferences, through our Patient and Public Involvement advisory group (Katie's Team) and through social media platforms.

Trial registration number ISRCTN20930880

Strengths and limitations of this study

- Double-blind randomised feasibility study on trial processes, glycaemic effects, cost and quality of life outcomes.
- Qualitative evaluation of the acceptability of the trial and intervention to participants and healthcare professionals.
- Pragmatically designed with patient and public advisory input on trial design, management and dissemination of findings.
- Exclusion of participants with non-proficiency in English language as this group may include minority ethnic groups who are most at risk for type 2 diabetes and can potentially benefit from the trial.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition with glucose intolerance first diagnosed in pregnancy. Up to 50% of women diagnosed with gestational diabetes progress to type 2 diabetes within the first 5 years after delivery.[1] Women with gestational

diabetes who require pharmacological treatment are at an increased risk of progression to type 2 diabetes.[2] However, only a fifth of women with gestational diabetes undergo postnatal screening for type 2 diabetes in the first year, with many lost to follow-up further on.[3] Undiagnosed type 2 diabetes increases the risks of stillbirth, miscarriage and congenital abnormalities in subsequent pregnancies.[4]

Metformin has been shown to be effective in reducing the incidence of type 2 diabetes in general populations at risk of the disease.[5] In systematic reviews of randomised trials, metformin reduced the risk of developing type 2 diabetes by up to 50% in women with a history of gestational diabetes.[6 7] One of the large primary studies, the Diabetes Prevention Programme, demonstrated that the reduction in type 2 diabetes risk persisted 10 years after commencing metformin in women with gestational diabetes.[5] However, none of the studies commenced the intervention in the postnatal period, and these involved mostly older women than young mothers.[8]

The immediate postnatal period offers a unique window of opportunity to intervene and prevent progression to type 2 diabetes especially in women who are at an increased risk of this condition and also lowering the risks of entering subsequent pregnancies with undiagnosed type 2 diabetes. Metformin intake in the postnatal period has the potential to achieve these benefits. Although metformin is currently offered in pregnancy to treat gestational diabetes, the acceptability of continuing or starting the medication in the immediate postnatal period and taking it for a prolonged period after delivery is not known. Prior to a large-scale randomised placebo-controlled trial on the effectiveness of metformin to prevent type 2 diabetes after gestational diabetes, a feasibility study is needed. The use of a placebo in the trial is needed to recognise the psychobiological effects attributable to the overall therapeutic context in the clinical setting.

Aims and objectives

We aim to conduct a feasibility study on the effectiveness of metformin in preventing dysglycaemia and progression to type 2 diabetes after delivery in women with gestational diabetes using metformin compared with placebo, and to assess the acceptability of the intervention and study procedures to women and healthcare professionals.

Primary objectives

Our primary objective is to obtain real-time data relevant to the trial design and trial processes such as recruitment, randomisation, follow-up and outcome assessment. We will determine the proportion of screened women who are eligible, the proportion recruited and randomised, and women's adherence to the study protocol and intervention. We will collect data on the rates of follow-up at 6–13 weeks, 6 months and 1 year post delivery.

Secondary objectives

Our secondary objectives include assessment of acceptability of the trial to women, their perceptions of risk and benefits of metformin, barriers to adherence, and the dose of metformin that is acceptable to women. We will explore the acceptability of the trial to healthcare professionals, barriers to recruitment and adherence to study protocol and intervention delivery. The potential role of the intervention and the trial in routine clinical practice will also be explored. We will obtain preliminary estimates on the effects of metformin on dysglycaemia (pre-diabetes (impaired fasting glucose, impaired glucose tolerance) and type 2 diabetes), and weight change at 1 year after delivery, identify any side effects from the intake of metformin to mothers and their babies, and obtain relevant cost data to inform future economic evaluation. See table 1 for the definitions of maternal dysglycaemia. We will determine the robustness of the randomisation and data collection process, healthcare professionals' adherence with the study protocol in secondary and in

Table 1 Definitions of maternal dysglycaemia using various diagnostic criteria

Variable	Definition	Recommending organisation
Impaired fasting glucose	A fasting plasma glucose between 6.1 and 6.9 mmol/L	NICE Guidance[26]
Impaired glucose tolerance	A fasting plasma glucose of <7.0 mmol/L or a 2-hour venous plasma glucose (after ingestion of 75 g oral glucose load) of 7.8–11.0 mmol/L.	WHO diagnostic criteria recommended by NICE[26]
High risk of type 2 diabetes	A blood glucose measurement of HbA1c ((42–47 mmol/mol) 6.0%–6.4%) or a fasting blood glucose of 5.5–6.9 mmol/L	NICE Guidance[26]
Gestational diabetes	A fasting plasma glucose level of 5.6 mmol/L or above or a 2-hour plasma glucose level of 7.8 mmol/L or above, after ingestion of 75 g oral glucose load	NICE Guidance[9]
Type 2 diabetes	A fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or 2-hour plasma glucose ≥11.1 mmol/L in OGTT or HbA1c>48 mmol/mol (6.4%)	WHO diagnostic criteria recommended by NICE Guidance[26]

NB: WHO- World Health Organisation, NICE- National Institute for Health and Care Excellence, HbA1c- Haemoglobin A1c.
NICE, National Institute for Health and Care Excellence; OGTT, oral glucose tolerance test.

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Women diagnosed with gestational diabetes as per the National Institute for Health and Care Excellence criteria, at time of consent and who are treated with metformin and/or insulin in pregnancy.	1. Women diagnosed with pre-existing type 1 or type 2 diabetes 2. Women with a body mass index of ≥50 kg/m^2 3. Known contraindications to metformin ► Hypersensitivity to metformin hydrochloride or to any of the excipients. ► Liver failure or liver dysfunction at the time of trial entry. ► Renal failure or renal dysfunction at the time of trial entry. ► Intravascular administration of iodinated contrast agents planned or received within 48 hours from commencing study medication, (metformin can be taken only after renal function has been re-evaluated and found to be normal.)
2. Aged 16 years or over at the time of consent.	4. Known very severe lactose intolerance
3. Able to provide written informed consent in English language.	5. Women being treated with metformin postnatally, for polycystic ovary syndrome
	6. Any acute conditions at the time of trial entry with the potential to alter renal function

primary care and identify the level of support required for successful recruitment.

METHODS

Ethical approval and study setting

The Optimising health outcomes with Metformin to prevent diAbetes After pregnancy (OMAhA) trial is a multicentre, randomised, placebo-controlled, double-blind, feasibility trial with a nested qualitative evaluation. Ethical approval was granted by the London-Brent Research Ethics Committee (18/LO/0505), in May 2018. The OMAhA trial will be conducted at Royal London Hospital (RLH), Whipps Cross University Hospital (WXH) and Newham University Hospital (NUH) over a period of 20 months (November 2018–July 2020).

Recruitment, randomisation and blinding

Setting

Women will be recruited from the joint obstetric diabetes antenatal clinic of the participating hospitals.

Eligibility

Pregnant women diagnosed with gestational diabetes and on treatment with either metformin or insulin or both and fulfil the criteria in table 2 are eligible for recruitment.

Screening and consent

Potentially eligible participants will be screened to confirm eligibility prior to being approached by a member of the research team during their antenatal visit to the joint obstetric diabetes clinic. A record of women who are screened, but not eligible, and eligible women who do not provide consent will be kept in the screening log. Anonymised information on these participants will include age, ethnicity and reasons for being ineligible or declining consent.

Eligible participants will receive the patient information sheet (PIS) prior to their hospital booking visit. A researcher will approach the eligible woman and review the PIS and answer any questions. We will obtain written informed consent to participate in the quantitative part of the study. A small proportion of participants will also be asked to provide written informed consent for the qualitative part of the study. In cases where women have been approached during their antenatal visits, but had not given consent yet, they may be consented post delivery but before discharge. We will collect baseline information on demographics and clinical characteristics after obtaining consent. The validated European Quality of life 5-Dimensions 5-Level scale (EQ-5D-5L) questionnaire will be administered to capture quality-adjusted life years (QALYs) in all participants.

Randomisation

Prior to postnatal discharge, recruited participants will be asked to confirm their willingness to continue with the trial. Once consent is obtained, participants will be randomised using an online randomisation system (epiGenesys, University of Sheffield), and allocated to either the active (metformin) or placebo treatment. We will adopt a randomisation scheme (allocation ratio 1:1) based on permuted blocks of random block size (sizes 4, 6 and 8), stratified by participating site (RLH, WXH or NUH) with no minimisation or adaptive strategies.

Blinding

The treatment allocation lists will be created by an independent statistician, allowing all members of the research team, research midwives, site staff, investigators, pharmacists, as well as women to remain blinded. Sharp Clinical Services MIA (investigational medicinal product) 10284 will undertake the final packaging and labelling of the medicinal products, to further ensure complete blinding

to all, apart from the independent statistician. The online randomisation system will also provide the unblinding service if required. The study code will only be broken for valid medical or safety reasons such as severe adverse events (SAEs), or in the event of a patient being diagnosed with type 2 diabetes during the course of the study and if they or their general practitioner (GP) request this information in order to determine further management.

Intervention and control arms

Participants will be provided with either placebo or metformin sustained-release 500 mg tablets after childbirth, prior to postnatal discharge. Participants will be advised to commence the trial medication from discharge until 12 months post delivery, to achieve a target dose regimen of 2 g/day. The placebo is identical in appearance, smell and taste to the metformin tablets. For metformin-naïve participants, the study tablets will be titrated in increments of 500 mg to reduce gastrointestinal side effects. The titrating dosing schedule will be: 1 g daily in week 1, 1.5 g daily in week 2 and 2 g daily in week 3 until the end of the study. For women continuing metformin, they will be titrated to the target dose in a similar way. All trial participants will be contacted by the research midwives to increase the dose of their trial medication accordingly. The target dose can be taken as four 500 mg tablets with a meal one time a day or two tablets two times per day with meals. Dosage will be adjusted based on participant tolerance to side effects, adverse events (AEs) and if women request to have at least 1 g/day.

As part of routine clinical practice and independent of the trial, women may receive advice, guidance and interventions in line with the NICE guideline on preventing type 2 diabetes.[9]

Outcomes

Primary outcomes

Primary outcomes include process evaluation outcomes such as the proportion of screened women who are eligible; the proportion of eligible women who are recruited; the proportion of recruited women who are randomised; attrition rates and adherence rates with the intervention.

Secondary outcomes

- Acceptability outcomes such as women's views of the recruitment process; risk of type 2 diabetes and benefits of metformin;factors that influence their decision to participate and adhere to the intervention and the optimum dose of metformin acceptable to mothers postnatally. Additionally, healthcare professionals' experience on approaches to prevent type 2 diabetes after gestational diabetes including their views on the barriers to recruitment, adherence and retention.
- Clinical outcomes such as maternal dysglycaemia (prediabetes (impaired fasting glucose, impaired glucose tolerance) and type 2 diabetes, see table 1 for definitions) at 6–13 weeks and 1 year after delivery; fasting and 2-hour glucose post 75 g glucose load, insulin levels, HbA1c levels and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) at 6–13 weeks, and 1 year; HbA1c levels and proportion of women with type 2 diabetes at 6 months after delivery; maternal weight gain at 6 months, and 1 year after delivery; breast feeding at 3 months, 6 months and 1 year; and side effects of metformin in mothers and their babies.
- Economic outcomes such as EQ-5D-5L, health and social care resource use and costs.
- Study conduct related outcomes such as the frequency and nature of protocol deviations, randomisation issues, data queries and monitoring findings for dispensing medication; and specific requests from health professionals for support to ensure successful recruitment.

Participant follow-up

Follow-up visits and outcome assessment

Randomised participants will be followed up at three study visits: 6–13 weeks, 6 months and 1 year post delivery. Participant follow-up will be conducted primarily in person or by phone based on availability. Within a week post discharge, participants will be contacted by the research midwives to ensure or encourage the immediate commencement of the trial medication. Between visits, participants will be contacted monthly by phone to review progress, document any side effects, encourage adherence and remind participants to discontinue their study medication for 1 week prior to their next follow-up visit. To encourage adherence, participants will be offered an optional mobile Application (Dosecast)[10] with daily automated reminders to take the intervention. Participants will also receive short motivational updates every 2–3 months by text or email, about study progress, with the aim of promoting ongoing engagement with the study. At each follow-up visit, maternal and baby outcomes will be collected, along with whole blood samples. An oral glucose tolerance test will be performed at the 6–13-week and 1-year visits in accordance with standard NHS laboratory practice and logged onto a secure NHS database. HbA1c will be tested at all three follow-up visits to diagnose type 2 diabetes. Non-routine tests, fasting insulin and c-peptide will be carried out by Affinity Biomarker Labs (Imperial College London, W12 0BZ). HOMA-IR will be calculated from the fasting glucose and fasting insulin levels.[11] Maternal and baby outcomes will also be collected as outlined in figure 1.

Participants will self-report adherence by using a paper-based diary or mobile app[10] depending on their preference. Participants will also be asked to bring in their unused medication bottles for tablet counting. Participants who successfully complete their research visits will be reimbursed with a £10 shopping voucher for their efforts, at each of the three follow-up visits.

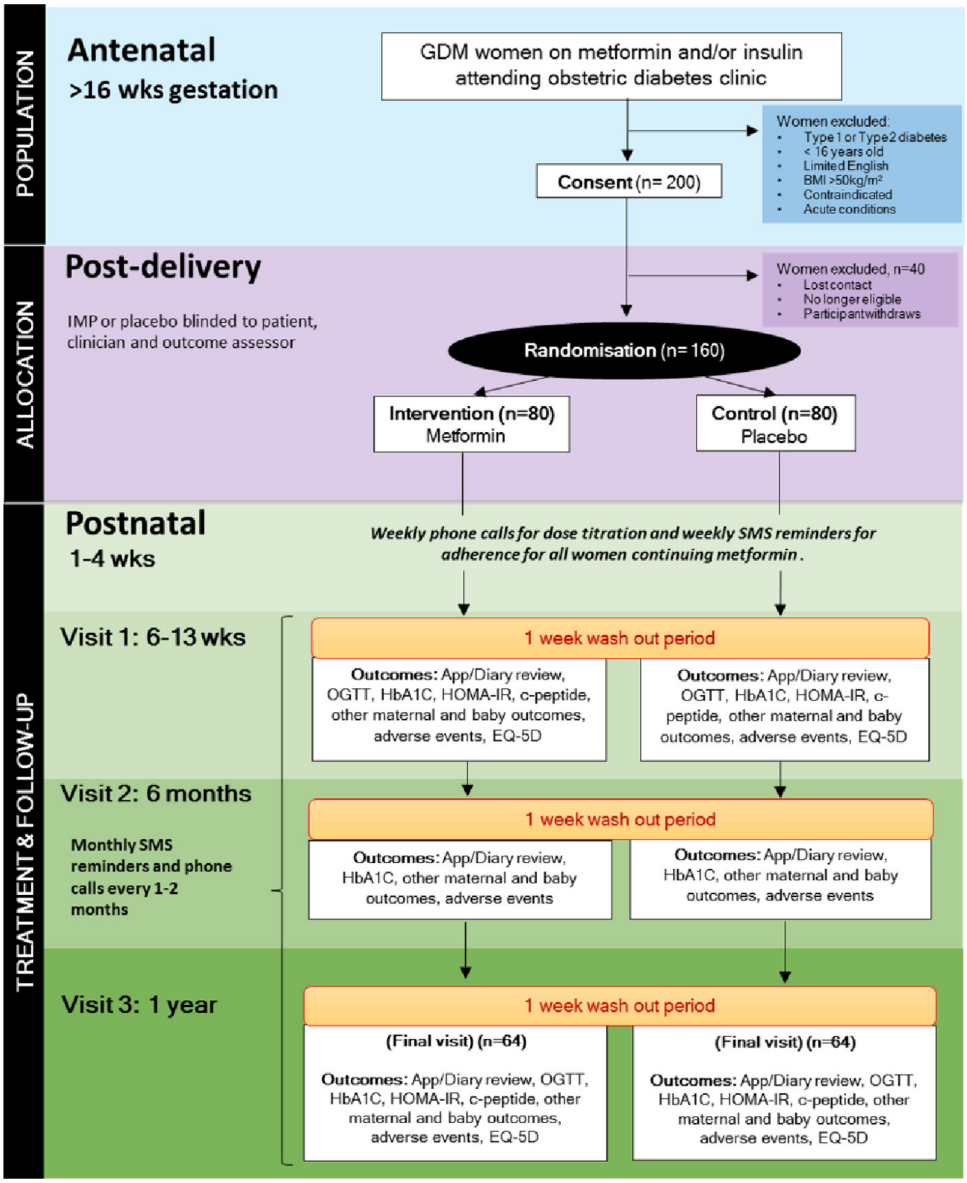

Figure 1 Flow chart of the Optimising health outcomes with Metformin to prevent diAbetes After pregnancy feasibility trial. BMI, body mass index; GDM, gestational diabetes mellitus; HOMO-IR, Homeostasis Model Assessment of Insulin Resistance; OGTT, oral glucose tolerance test.

Withdrawal criteria

Withdrawal of consent will be respected and recorded on the final study form, and the participant will continue with NHS standard practice for follow-up care. A participant can also be withdrawn by her clinical team or the trial investigators if it is considered to be medically necessary. Where possible, the withdrawn participant will be followed up for all safety and efficacy outcomes. Following testing for type 2 diabetes, women found to have pre-diabetes will stay on the trial. Women diagnosed with type 2 diabetes will be withdrawn from the trial and transferred to primary care for further treatment. In this event, if women provide consent, their GP will be notified of their diagnosis. On request, the GP will be notified of their treatment allocation to inform further treatment decision.

Sample size

We expect that at least 1000 women diagnosed with gestational diabetes annually are eligible for participation. We anticipate one-third of these women to consent and be randomised to the study, resulting in 160 women randomised over 6 months. With an attrition rate of 20%, we expect 128 of the 160 women to remain in the trial and 80% (102/128) to be followed up. These numbers will allow for the estimation of 95% CIs for trial feasibility outcomes with amplitudes of around 10% in the worst case of p=q=0.5.

Qualitative evaluation

Recruitment observation

After obtaining verbal consent from eligible women being approached, a qualitative researcher will observe

the recruitment process in a sample of participants at each site to gain detailed knowledge of women's needs and concerns during recruitment, as well as factors within the recruitment setting that may influence participation.

Semistructured interviews

Following consent, a purposive sample of 10–15 women will be interviewed around the 6–13-week visit, and 5–8 women near their 12 months visit. The main goal of purposive sampling is to ensure variation in particular characteristics of the population under study that may influence their response towards the intervention (eg, previous diagnosis of GDM, parity, ethnicity). The first set of interviews at 6–13 weeks post discharge will explore participants' views of the recruitment process, understanding of type 2 diabetes, their perception of risk of developing type 2 diabetes, reasons for participation, perceived acceptability of metformin, the adherence tools and possible reasons for non-adherence. The second set of interviews will focus on participants who found adherence particularly easy or difficult, and explore perceptions of follow-up procedures and adherence to the intervention. Concepts identified from the first set of interviews will inform discussions in the second interviews. Alongside this, we will endeavour to interview a sample of women who drop out of the trial. Interviewees will receive a £10 voucher for their time.

Approximately, 10 healthcare professionals who are involved in the intervention delivery or care of women with postnatal type 2 diabetes will be interviewed. This may include research midwives, diabetes specialist midwives, trial coordinators, GPs and diabetologists. We will explore experiences of intervention delivery, potential role of the intervention in routine practice and perceived barriers and support required for its implementation in practice.

Qualitative interview data will be analysed thematically using constant comparison techniques, to identify and interpret patterns (themes) within the data, which represent beliefs and experiences that participants share (or differ on) in relation to the research questions. Transcripts will be coded for themes and subthemes in relation to the trial experiences of women and healthcare professionals. We will develop an analytical framework to capture inter-relationships between themes.

Statistical analysis

Data will be analysed using descriptive statistics to inform trial feasibility and process. We cannot reliably assess the effect of the intervention on outcomes, given the size of this feasibility study and hence hypothesis testing is not proposed. We will summarise feasibility outcomes using standard methods for proportions and other descriptive statistics, and where appropriate, we will present point estimates of proportions, and effect sizes (eg, mean differences and relative risks) with associated 95% CIs.

Economic evaluation

The cost–utility analysis of metformin versus placebo will involve using a short-term time horizon (the 'within trial' period), which will inform the definitive trial. The cost–utility measures will be the incremental cost per unit of change per QALY gained. The costs to women in the intervention and control group will be assessed from the perspectives of the NHS, personal and social services. Cost components include the cost of metformin and placebo including their administration, cost of routine tests, laboratory tests and further investigations, costs of clinic visits, hospital admissions (length of stay), antenatal costs, postnatal costs, neonatal costs and costs to treat AEs. Resource use data will be prospectively collected at patient level using clinical records and diaries. Unit costs will be taken from standard sources. Quality of life outcomes will be assessed from data collected using a validated questionnaire. Data on health-related quality of life collected using the EQ-5D-5L questionnaire will inform the QALYs calculation. The QALYs experienced from baseline to end of trial will be calculated as the area underneath this profile. Cost–utility will be calculated as the mean cost difference between the intervention and control group divided by the mean difference in outcomes to give the incremental cost-effectiveness ratio.

Pharmacovigilance and safety

Any untoward medical occurrence in a participating woman which may or may not be related to or caused by the medicinal product is an AE. Any untoward medical occurrence in a participating woman that is life threatening results in death, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity is a SAE. All serious SAEs and suspected unexpected serious adverse reaction will be reported to the sponsor and medicinal product provider (as per supply agreement) within 24 hours of the chief investigator or local investigators becoming aware of the event.

Trial oversight, monitoring and data management

The trial will be overseen monthly by a trial management group (TMG) at the Barts Research Centre for Women's Health at Queen Mary University of London. The trial will also be overseen by two independent groups, the trial steering committee (TSC) and the data monitoring committee (DMC) ensuring that the trial is conducted according to the principles of Good Clinical Practice in Clinical Trials.

The OMAhA study will be monitored via on-site monitoring using a trial monitoring plan. Any serious breach that significantly affects the safety, physical or mental integrity of the participants or the scientific value of the trial will be made known to the sponsor within 24 hours. The research team at Barts Health NHS Trust will have access to participants' personal data for consent, data entry into case report forms and follow-up. However, all participant data will be pseudoanonymised using a

unique identifier before use. All participant data will be held securely and treated as strictly confidential.

Progression criteria

To randomise 160 women over 8.5 months, we will need to recruit 200 women at Barts Health NHS Trust. An average monthly recruitment rate of 15 women or more, adherence rates of ≥75% or more to the study intervention (high adherence) and a follow-up of 80% or more will be clear indicators of progression to a full-scale trial. An average recruitment rate of five women or less monthly, adherence <50% and follow-up <50% will require a full re-evaluation of trial processes taking into account the qualitative findings prior to progression to a full-scale trial. Any estimates between the two criteria aforementioned will trigger a re-evaluation of trial procedures with minimal to moderate changes to improve outcomes.

Participant and public involvement and dissemination

Participant and public involvement

Katie's Team, a women's health specific patient and public involvement advisory group[12 13] has codeveloped the OMAhA study protocol by providing input into the design (reviewing and refining the protocol, participant-facing documents and input into the qualitative interview schedule). As members of the TSC, they will assess study conduct.

Dissemination

Findings from the OMAhA study will be published in a peer-reviewed journal and disseminated through conference presentations with input from Katie's Team, and the findings will be circulated to participants as fact sheets. We will also disseminate the findings to our local community groups and other relevant stakeholders through the Maternity Service Liaison Committees and social media platforms.

DISCUSSION

The OMAhA trial is a crucial step towards global efforts to reduce the burden of type 2 diabetes by targeting high-risk women with gestational diabetes. Until now, it is not known if metformin, a drug that prevents type 2 diabetes in the general population at risk, is also effective in postnatal period to prevent the disease after a history of gestational diabetes.[8] Our feasibility study is conducted in inner city multiethnic populations of young women within an NHS setting, who are at highest risk of developing both gestational diabetes and type 2 diabetes. The effectiveness and acceptability of metformin in new mothers are not known necessitating the need for a trial in this area.

Metformin is an oral hypoglycaemic agent which has been used for over 60 years as an effective oral glucose lowering agent for type 2 diabetes. The use of metformin in gestational diabetes is recommended by NICE for treatment of gestational and type 2 diabetes.[9] Metformin is excreted into human breast milk and to date no adverse effects have been observed in breastfed infants,[14] and is the recommended drug for treatment of type 2 diabetes in postnatal mothers.[9] It is available as either immediate release tablets or sustained-release tablets taken orally, both of which are approved for the treatment of non-diabetic patients at high risk of developing type 2 diabetes.[15] Maximum plasma metformin concentrations are reached more slowly with the sustained-release formulation compared with immediate-release metformin.[16] In the OMAhA trial, we will be using the sustained-release formulation which allows us to implement a simpler dosing regimen, with increased tolerability thus improving patient adherence and greater glycaemic control.

The OMAhA study's research question was prioritised by our Patient and Public Involvement (PPI) Group, the Katie's Team, comprising women and families with lived experiences of gestational diabetes. In our work leading to the proposal, we surveyed mothers with gestational diabetes, and healthcare professionals on intervention strategies for preventing progression to type 2 diabetes in women developing gestational diabetes. Our survey of 106 healthcare professionals showed that 80% (17/21) of midwives and about 50% (11/21) of the obstetricians were unsure of the future risk of type 2 diabetes after gestational diabetes.[17] This further hinders provision of interventions to prevent type 2 diabetes in the postnatal period. Three-quarters of mothers (50/67) were interested in continuing metformin after delivery to prevent type 2 diabetes. Two-thirds (52/77) of healthcare professionals said that they would offer metformin as part of a trial if available.[18] Our meta-analyses of women with gestational diabetes identified women with high glucose levels, and those who needed insulin in pregnancy to be at high risk of progression to type 2 diabetes,[2] and hence our target population includes women with gestational diabetes on medication.

A full-scale definitive trial on the effectiveness of metformin in preventing type 2 diabetes in postnatal women will require a large sample size and resources.[19] Randomisation, follow-up and adherence assessment can be challenging especially in the immediate postnatal period with new mothers. The physical and emotional tiredness of caring for a newborn, as well as the personal and family adjustment required can hamper adherence and visit attendance.[20] Adverse delivery outcomes that may extend postnatally such as postcaesarean complications may hamper commencement of the trial medication in the early postnatal period.[21] Concerns with metformin use while breast feeding, acceptability of the drug regimen and duration are possible barriers to study and intervention adherence. A feasibility study is vital to assess these study process related outcomes to inform the definitive trial avoiding unnecessary attrition and poor adherence, allowing for savings in costs, time and other resources. The qualitative component of the OMAhA study aims to explore the impact of these barriers, ascertain the actual rates of follow-up, adherence and attrition,

identify support strategies and alternative solutions prior to a large-scale trial.

By recruiting participants from the joint obstetric diabetes clinic, we will be able to engage with the women who are already on metformin. Providing information on their subsequent risk of type 2 diabetes is expected to increase their motivation to join the study and adhere to the protocol.[22] Our qualitative evaluation will assess the recruitment process on women's concerns, motivations as well as contextual factors which may optimise or undermine research participation. By exploring the randomisation rates which are assessed after delivery, our study will determine if the experience of childbirth impacted on women's willingness to continue with the trial.

The feasibility of collecting the required clinical outcome data also needs to be assessed, given the low uptake of postnatal screening for type 2 diabetes especially at 6–13 weeks after birth.[23] The OMAhA study includes features to encourage visit attendance and retention in the study such as regular communication with women through phone calls and texts, and reminders of upcoming appointments. We also provide dedicated research staff to collect blood samples for outcomes to minimise the waiting times, and encourage visit attendance, and also reimburse women for their time through vouchers. To encourage adherence, participants are offered an optional mobile application with daily automated reminders to take the intervention. By regular contact with participants, we aim to foster engagement with the study, and in doing so, reinforce the potential benefits of the intervention and study, advising on ways to overcome potential challenges or side effects of the intervention, encouraging adherence.

Our qualitative evaluation will explore the influence of these support strategies on adherence, visit attendance and retention, as well as eliciting suggestions from mothers and healthcare professionals on ways to best help with associated challenges. All of these learnings will inform the design and conduct of the full-scale definitive trial. As well as a nested qualitative evaluation, we have PPI input on the methodology and design to enhance acceptability and integration into routine practice.[24] The iterative process of trial monitoring and progress review by the TMG and an independent team of clinical specialists and patient representatives (TSC and DMC) will aid in resolving any challenges in study conduct, in addition to ensuring the safety of the trial.[25]

Our findings on feasibility and process outcomes will guide our decision to progress to a full-scale trial. Our progression criteria are arbitrary, and we will combine these with qualitative insights on solutions to factors which may have undermined recruitment, follow-up and adherence, in addition to recommendations from the TSC.[25]

CONCLUSION

The OMAhA study findings will inform the conduct of a full-scale definitive trial on the effects of metformin in reducing the risk of dysglycaemia including type 2 diabetes after delivery in women with a history of gestational diabetes.

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