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Metformin in the prevention of type 2 diabetes after gestational diabetes in postnatal women (OMAhA): a UK multicentre randomised, placebo-controlled, double-blind feasibility trial with nested qualitative study

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ABSTRACT

Objective To determine the feasibility of a definitive trial of metformin to prevent type 2 diabetes in the postnatal period in women with gestational diabetes.

Design A multicentre, placebo-controlled, double-blind randomised feasibility trial with qualitative evaluation.

Setting Three inner-city UK National Health Service hospitals in London.

Participants Pregnant women with gestational diabetes treated with medication.

Interventions 2 g of metformin (intervention) or placebo (control) from delivery until 1 year postnatally.

Primary outcome measures Rates of recruitment, randomisation, follow-up, attrition and adherence to the intervention.

Secondary outcome measures Preliminary estimates of glycaemic effects, qualitative exploration, acceptability of the intervention and costs.

Results Out of 302 eligible women, 57.9% (175/302) were recruited. We randomised 82.3% (144/175) of those recruited, with 71 women in the metformin group and 73 women in the placebo group. Of the participants remaining in the study and providing any adherence information, 54.1% (59/109) took at least 75% of the target intervention dose; the overall mean adherence was 64% (SD 33.6). Study procedures were found to be acceptable to women and healthcare professionals. An increased perceived risk of developing type 2 diabetes, or a positive experience of taking metformin during pregnancy, encouraged participation and adherence to the intervention. Barriers to adherence included disruption to the medication schedule caused by the washout periods ahead of each study visit or having insufficient daily reminders.

Conclusions It is feasible to run a full-scale definitive trial on the effectiveness of metformin to prevent type 2 diabetes in women with gestational diabetes, during the early postnatal period. Adherence and engagement with the study could be improved with more regular reminders and potentially the addition of ongoing educational or peer support to reinforce messages around type 2 diabetes prevention.

Trial registration number ISRCTN20930880.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A combined qualitative and quantitative study design, informed by a women's health patient and public advisory group, resulted in the demonstration of feasibility of using metformin in the postnatal period to prevent progression to type 2 diabetes in women with pre-existing gestational diabetes.
⇒ The prespecified set of progression criteria allowed us to demonstrate the feasibility of the study.
⇒ Recruitment of participants from three inner-city National Health Service hospitals ensured the generalisability of the study.
⇒ The follow-up of participants was adversely impacted by the COVID-19 pandemic.
⇒ There was limited ongoing interaction with the participants in the study, which may have affected the outcome assessment.

INTRODUCTION

Gestational diabetes mellitus is glucose intolerance first recognised antenatally, affecting 14%–20% of all pregnancies worldwide.[1 2] Following delivery diabetes usually resolves, although 50% of women will progress to type 2 diabetes within the following 5 years.[3] Pharmacological and lifestyle interventions implemented in the postnatal period may postpone

diabetes development and increase uptake of postnatal diabetes testing.[4]

Metformin is widely used as a first-line antidiabetic drug to control blood glucose levels.[5] It has also been used in studies for diabetes prevention in people at risk of developing diabetes, in women with polycystic ovarian syndrome and to promote weight reduction.[5 6] In the Diabetes Prevention Programme (DPP) metformin was found to be effective in decreasing the incidence of diabetes.[7] The results of the DPP Study have shown that women with a history of gestational diabetes have a sevenfold increased risk to develop diabetes and at a younger age compared with women without a history of gestational diabetes.[8] However, the DPP Study was conducted 12 years post gestational diabetes diagnosis. There are a few recent studies done in the postnatal period, but they are not large enough to prove the effectiveness of metformin in diabetes prevention and are focused on weight loss or on recruitment of overweight women with a history of gestational diabetes.[9–11]

The aim of the OMAhA (Optimising health outcomes with Metformin to prevent diAbetes After pregnancy) Study was to assess the feasibility of running a full-scale definitive trial on the effectiveness of metformin in preventing type 2 diabetes in the immediate postnatal period, in women who had gestational diabetes. We undertook a randomised controlled feasibility trial comparing metformin to placebo, with a nested qualitative study. We estimated rates of recruitment, randomisation, follow-up, attrition and adherence to the intervention. We examined preliminary glycaemic effects and costs.

METHODS

The OMAhA Trial was a multicentre, randomised, placebo-controlled, double blind feasibility trial with a nested qualitative study and economic evaluation. The full study protocol is published elsewhere,[12] with some salient descriptions and any modifications mentioned below.

Participants and setting

Pregnant women diagnosed with gestational diabetes and on treatment with either metformin or insulin or both were identified and recruited from the joint obstetric antenatal diabetes clinics in three inner-city hospitals in East London, Barts Health National Health Service (NHS) Trust, UK (table 1) (extensive list of eligibility criteria and screening and consent processes are published elsewhere).[12]

Intervention and control group

The intervention consisted of 2 g/day metformin (500 mg sustained-release tablets) taken either as a single or twice daily dose with food. The control consisted of a placebo taken to the same schedule. Metformin-naïve patients followed a 3-week titration schedule (starting at 1 g/day). Dose reductions for side effects were permitted down to a minimum of 1 g/day. Treatment was given from delivery until 1 year postnatally. The placebo was similar in colour, size and taste. Prior to a study visit, participants were advised to observe a 1 week washout period to generate patient baseline data of glycaemic control. Patients were asked to self-report adherence via paper diary or study mobile App. A protocol amendment introduced a £10 voucher incentive for participants to supply adherence data at their study visits.

Table 1 OMAhA Inclusion and exclusion criteria[12]

Inclusion criteria	► Women who are treated with either metformin or insulin in pregnancy and are diagnosed with gestational diabetes, per the National Institute for Health and Care Excellence (NICE) criteria, at the time of consent ► Aged 16 years or above at the time of consent
Exclusion criteria	► Women unable to provide written informed consent in English ► Women diagnosed with pre-existing diabetes ► Women with a body mass index of ≥50 kg/m^2 ► Women with known contraindication to metformin ► Women with very severe lactose intolerance ► Women being treated with metformin postnatally, for polycystic ovarian syndrome ► Any acute conditions that might alter renal function

OMAhA, Optimising health outcomes with Metformin to prevent diAbetes After pregnancy.

Outcomes

Primary outcomes included the proportion of screened women who were eligible; the proportion of eligible women who were recruited; the proportion of recruited women who were randomised; as well as study attrition, and adherence rates (online supplemental appendix 1 for feasibility outcomes). Secondary outcomes included acceptability (capturing women's and healthcare professionals' views on the study based on qualitative data); laboratory outcomes such as maternal dysglycaemia including type 2 diabetes, impaired fasting glucose and impaired glucose tolerance as defined by National Institute for Health and Care Excellence (NICE) guidelines (online supplemental appendix 2 for definitions), fasting and 2-hour glucose levels following an oral glucose tolerance test, insulin levels, Haemoglobin A1C, homoeostasis model assessment of insulin resistance, weight gain, breastfeeding status and adverse effects; economic outcomes (health and social care resource use and costs); and study conduct outcomes (protocol deviations and data queries).

Sample size, randomisation and blinding

The target recruitment rate was 200 participants to achieve a target randomisation sample size of 160 participants, considering attrition between recruitment and

randomisation. In this NHS Trust approximately 1000 women are diagnosed with gestational diabetes per year and are eligible for participation; we anticipated a third to consent and be randomised to the study, resulting in 160 women randomised over 6 months. An attrition rate of 20% would result in 128 women who remain in the trial and 80% (102/128) to be followed up. These numbers allow the estimation of 95% CIs for laboratory outcomes with amplitudes of around 10% in the worst case of p=q=0.5.[12] Recruited women, who have provided informed consent, were randomised after delivery and before hospital discharge to either intervention (metformin) or placebo, at 1:1 allocation ratio, using an online system hosted by epiGenesys (University of Sheffield). The allocation was concealed, and allocation lists were produced by an independent statistician using permuted blocks of random block size (sizes 4, 6 and 8), stratified by participating site with no minimisation or adaptive strategies. All members of the central and local research teams, clinical staff and participants remained blinded to study allocation.

Participant follow-up

After randomisation, study visits were scheduled at 6–13 weeks, 6 months and 1 year postnatally. The first and last of these visits coincided with routinely scheduled visits for this population. The 1-year study visit also marked the end of follow-up. In between study visits, participants received monthly text reminders and a phone call from the local research team every 1–2 months (depending on adherence and tolerability) to document adverse events (AEs) and promote adherence. Participants using the study app received automated reminders when their doses were due. Women who developed type 2 diabetes or who became pregnant again during the study were discontinued; they were categorised as having reached their end of study timepoint.

Analysis

A prespecified statistical analysis plan was used for all analyses. Data were analysed using descriptive statistics, using proportions with 95% CI for feasibility outcomes. Adherence was recorded with the use of case report forms, participants were asked to bring back the tablets they did not use in every visit, the app and the paper diary were two other methods used by participants to report adherence. For continuous laboratory outcomes, we calculated the effect sizes (eg, mean differences) with 95% CI. For continues variables a one-way analysis of variance was used to evaluate differences between groups, adjusted by centre. Maternal dysglycaemia analysis was based on all randomised participants. We report the rates of dichotomous clinical outcomes and costs in the two groups of the study. Main statistical analyses were performed using R, V.3.6.1.

Qualitative study

Qualitative data were generated through semistructured interviews (interview schedule available online supplemental file 1) with a purposive sample of participants, 13 women (online supplemental appendix 3A) and 5 healthcare professionals (3 research midwives and 2 diabetes specialist midwives). Interviews lasted from 30 min to 60 min. Women received a £10 voucher as compensation for travel expenses. Interviews with participants were focused on participants' views of the recruitment process, their diabetes risks, reasons for participation, acceptability of metformin, the adherence tools and possible reasons for non-adherence. Interviews with healthcare professionals included staff involved in the intervention delivery or care of women with postnatal type 2 diabetes and explored their experiences of intervention delivery. Interviews followed a schedule (online supplemental file 1) and were recorded following separate written informed consent. A mixed-methods researcher (CEA) with experience in qualitative research in this population undertook the interviews and completed the analysis. Qualitative analysis was supervised and validated by an experienced academic qualitative researcher (AH). This increases the credibility of the qualitative findings. Qualitative interview data were analysed thematically (online supplemental appendix 3B).

Economic evaluation

We undertook a preliminary economic evaluation to compare the costs and outcomes associated with intervention metformin versus treatment as usual (placebo). The outcome measure was quality-adjusted life years (QALYs), which combine length of life and quality of life, and is consistent with NICE recommendations.[13] The base case analysis took a UK NHS and personal social services perspective.[13] Resource use data were included from all three participating centres and UK unit costs were applied. Costs were calculated in 2019 UK £. The time horizon was 1 year, reflecting the main outcomes follow-up in the trial, and was the longest time period over which data were collected for all participants; 1 year was long enough to reflect all important differences in costs or outcomes between the two treatments. Given the time horizon, discounting was not applied to costs or outcomes.

Generic health status was measured at baseline (randomisation) and after delivery using the EuroQol-5 Dimensions Levels (EQ-5D-5L) Questionnaires.[14] Each EQ-5D-5L health state was converted into a single summary index (utility value) applying a formula that attaches weights to each of the levels in each dimension based on valuations by general population samples. Utility values of 1 represent full health, values of 0 are equivalent to death, negative values represent states worse than death. A utility profile was constructed for every participant assuming a straight-line relation between their utility values at each measurement point.

Patient and public involvement

Members of Katie's Team, a dedicated women's health patient and public advisory group,[15] advised on study

design, contributed to the development of patient-facing materials and interview schedules, were represented on the trial steering committee, and contributed to interpretation and dissemination of results.

RESULTS

Recruitment to the study began in November 2018 and ended in July 2019. The largest proportion of recruited women were Asian (70.9%, 124/175) (table 2). At the time of recruitment, most women were being treated with metformin alone or in combination with insulin (90.3%, 158/175). Out of those who had previously been pregnant (n=149), a third had experienced gestational diabetes (29.5%, 44/149). Additionally, almost two-thirds of recruited women had a first-degree relative with type 2 diabetes (65.1%, 114/175).

Primary outcomes

Of the 973 assessed for eligibility, 31% (302/973) met the eligibility criteria. Of these, 57.9% (175/302) consented to the study, and a subsequent 82.3% (144/175) were randomised to the intervention group or control group (figure 1 and table 3). The rates of recruitment and randomisation across all participating sites are presented in figure 2 (2A, 2B, 2C, 2D). The most common reason for women declining to participate in the OMAhA Study was unwillingness to take the intervention (13.2%, 40/302).

At the first follow-up at the 6–13 weeks postnatal period, 77.1% (108/140) of randomised women attended (excluding those women who had become pregnant again, developed type 2 diabetes or withdrew from the study). This fell to 54.6% (71/130) at 6 months and remained stable until the end of the study with 55.7%

Table 2 Baseline characteristics of OMAhA participants

Variable	Metformin (n=71)	Placebo (n=73)	Non-randomised (n=31)	Total (n=175)
Maternal age in years, mean(SD)	33.7 (5.2)	33 (5.6)	32.3 (4.3)	33.2 (5.2)
Gestational age in weeks, mean(SD)	32.3 (5.9)	33.7 (4.5)	31.4 (4.6)	32.8 (5.2)
Body mass index in kg/m^2, mean(SD)	29.5 (5.5)	29.7 (5.7)	30.5 (5.6)	29.7 (5.6)
Higher education, n(%)	35 (49.3%)	36 (49.3%)	18 (58.1%)	89 (50.9%)
Ethnic groups, n(%)				
Asian	51 (71.8%)	53 (72.6%)	20 (64.5%)	124 (70.9%)
Black	7 (9.9%)	4 (5.5%)	3 (9.7%)	14 (8.0%)
White	9 (12.7%)	11 (15.1%)	7 (22.6%)	27 (15.4%)
Mixed-other	3 (4.2%)	5 (6.8%)	1 (3.2%)	9 (5.1%)
Declined to give information	1 (1.4%)	0 (0.0)	0 (0.0%)	1 (0.6%)
Obstetric and medical history, n(%)				
Primigravida	9 (12.7%)	12 (16.4%)	5 (16.1%)	26 (14.9%)
Previous gestational diabetes*	17 (27.4%)	21 (34.4%)	6 (23.1%)	44 (29.5%)
Family history of type 1 diabetes†	3 (4.2%)	6 (8.2%)	2 (6.5%)	11 (6.3%)
Family history of type 2 diabetes†	44 (62.0%)	47 (64.4%)	23 (74.2%)	114 (65.1%)
Polycystic ovary syndrome	0 (0.0%)	2 (2.7%)	3 (9.7%)	5 (2.9%)
Gestational diabetes diagnosis, mean (SD)				
Gestational age at diagnosis in weeks	23.3 (6.5)	23.5 (6.5)	22.3 (5.6)	23.2 (6.3)
Fasting glucose in mmol/L	5.5 (1)	5.2 (0.7)	5.5 (0.6)	5.4 (0.8)
2-hour postprandial glucose in mmol/L	9.3 (1.9)	9 (1.7)	8.9 (1.6)	9.1 (1.8)
Gestational diabetes treatment, n(%)				
Metformin only	40 (56.3%)	49 (67.1%)	19 (61.3%)	108 (61.7%)
Insulin only	10 (14.1%)	5 (6.8%)	2 (6.5%)	17 (9.7%)
Metformin and insulin	21 (29.6%)	19 (26.0%)	10 (32.3%)	50 (28.6%)
Delivery				(n=144)‡
Gestational age at delivery in weeks, mean (SD)	37.7 (1.1)	38 (0.9)	N/A	37.9 (1)
Live birth, n(%)	71 (100.0%)	73 (100.0%)	N/A	144 (100%)
Caesarean section, n(%)	27 (38.0%)	28 (38.4%)	N/A	55 (76.4%)

*Applies only to multiparous women, therefore n=62 in the metformin group; n=61 in the placebo group.
†Family history in first-degree relatives only.
‡Delivery data were not collected for non-randomised participants.
OMAhA, Optimising health outcomes with Metformin to prevent diAbetes After pregnancy.

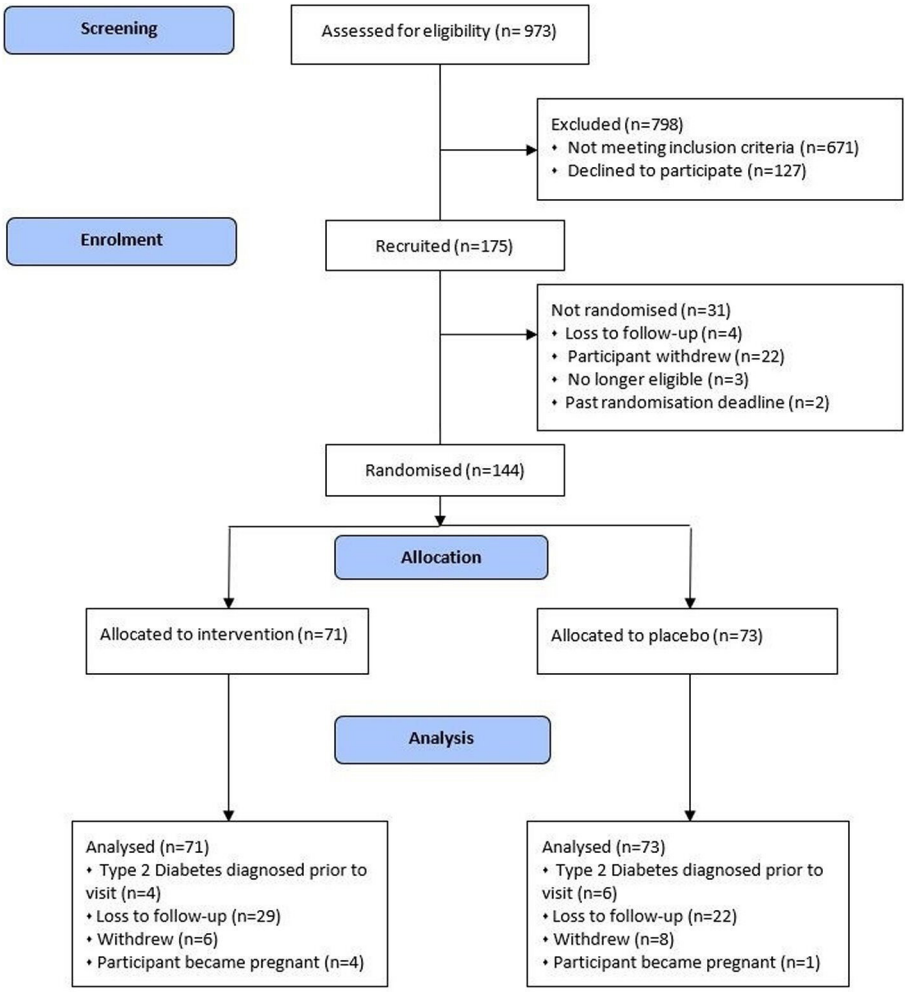

Figure 1 Flow chart of OMAhA study participants. OMAhA, Optimising health outcomes with Metformin to prevent diAbetes After pregnancy.

(64/115) at 12 months postnatally. Outcome data collection was affected by the COVID-19 pandemic restrictions in the UK, meaning that many of the 12-month visits were completed remotely over the phone. The attrition rate over the entire course of the study was 46.8% (65/139, ie, excluding from the denominator the five participants who had become pregnant again) (table 3).

Of the 109 women who reported adherence on at least one visit, 54.1% (59/109) reported taking at least 75% of their target dose (table 3), with a mean adherence of 64% across all three study visits. Details on adherence across individual study visits are presented in online supplemental appendix 4. This also shows that a higher proportion of app users (85.7%; 12/14) versus diary users (69.2%; 27/39) took at least 75% of

Table 3 Primary outcome measures

Process outcomes	Metformin	Placebo	Overall
Recruitment (of n=302 eligible population)			175/302 (57.9%)
Randomisation (of n=175 recruited)			144/175 (82.3%)
Attrition, n (%)*	35/67 (52.2%)	30/72 (46.8%)	65/139 (46.8%)
Women with adherence information, n (%)	56/71 (78.9%)	53/73 (72.6%)	109/144 (75.7%)
Adherence† 75%, n (%)‡	29/56 (51.8%)	30/53 (56.6%)	59/109 (54.1%)

Attrition is defined as loss to follow up or withdrawal from study; Adherence mean is calculated by averaging the adherence over the three visits using completed values. Women with adherence information on at least one visit are included in the calculations; Adherence rate.
*Women who became pregnant after randomisation are excluded from the denominator.
†Denominator included only women with adherence information.
‡75%=calculated the proportion of patients for whom we have adherence information on at least one visit and average adherence ≥75%.

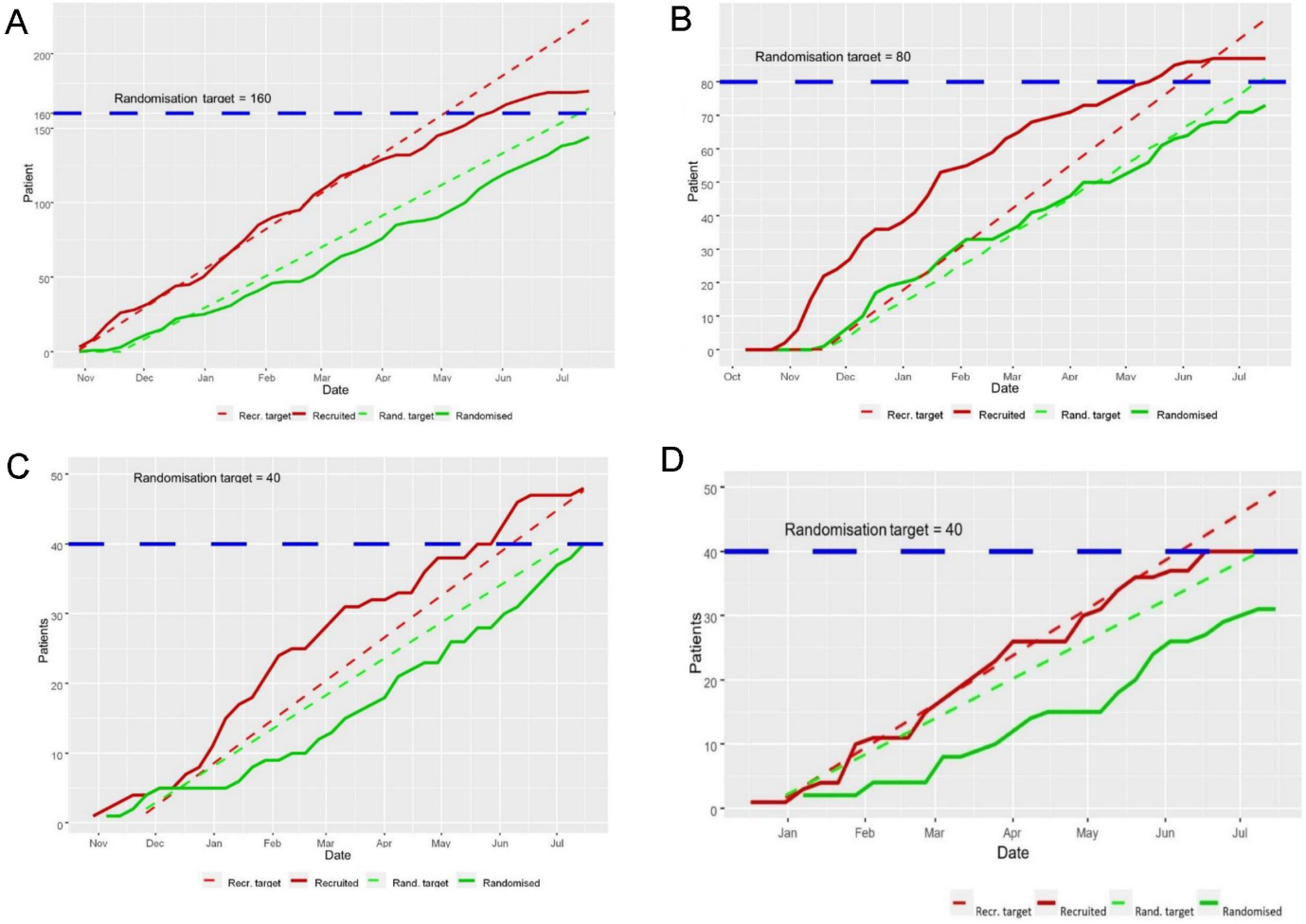

Figure 2 (A) Overall recruitment and randomisation rates across sites. (B) Recruitment and randomisation rates at Royal London Hospital. (C) Recruitment and randomisation rates at Whipps Cross Hospital. (D) Recruitment and randomisation rates at Newham University Hospital.

their study tablets. A sensitivity analysis showed that women who had a first-degree relative with type 2 diabetes took almost three quarters of their study tablets throughout the 12-month study period (mean 71.5%, SD 33.5 at 6–13 weeks; mean 70.8%, SD 36.4 at 12 months) (online supplemental appendix 5).

Secondary outcomes

Glycaemic outcomes

At the first study visit (6–13 weeks postnatally), the overall levels of dysglycaemia were higher in the metformin group (47.9%, 34/71) compared with the placebo group (39.7%, 29/73). Both rates of dysglycaemia were reduced by 12 months, to 18.3% (13/71) in the metformin group and 24.7% (18/73) in the placebo group (table 4). Around 5% of women in both groups were diagnosed with type 2 diabetes early, at their 6–13 weeks postnatal visit (table 4). The total proportion of women diagnosed with type 2 diabetes by 12 months postnatally was 7% (5/71) in the metformin group, and 9.6% (7/73) in the placebo group. Online supplemental appendix 6A,B give details on other glycaemic and clinical outcomes, as well as breastfeeding status in both groups.

AEs and study conduct outcomes

There were 39 participants in each group (54.9%, 39/71 in the metformin group; 53.4%, 39/73 in the placebo group) who reported at least 1 AE, and a total of 77 AEs were reported in each group. There were eight related AEs (10.4%, 8/77) within the metformin group, and five related AEs (6.5%, 5/77) reported within the placebo group. Diarrhoea or gastric problems were reported as a related AE for 3.5% (5/144) of women in both groups.

In total, 12 serious AEs were reported for 11 women: 4.2% (5/12) in the metformin group and 5.8% (7/12) in the placebo group. Of these, two serious AEs were reported as related to the intervention, as admissions to emergency department for vomiting and sickness (1.7%, 2/12), and both were in the placebo group. A total of 17 protocol deviations were reported (8 in intervention; 9 in control). The most frequent deviations were changes to the visit schedule interval. There were no significant differences in the number of data queries between groups.

Cost outcomes

The total cost of the medication was £2402 in the intervention group and £2150 in the control group. The

Table 4 Dysglycaemia and type 2 diabetes rates

Outcomes (metformin; placebo)	Metformin n=71	Placebo n=73	Total n=144
6–13 weeks postnatally			
Any dysglycaemia n (%)	34/71 (47.9%)	29/73 (39.7%)	63 (43.7%)
Type 2 diabetes (T2D) since randomisation*	4	4	8
Impaired fasting glucose (54; 54)	4	5	9
Impaired glucose tolerance (54; 54)	12	12	24
High risk of T2D (57; 56)	19	14	33
6 months postnatally			
Any dysglycaemia† n (%)	8/71 (11.3%)	8/73 (11.0%)	16 (11.1%)
Type 2 diabetes since randomisation*	4	5	9
High risk of T2D (40; 36)	4	3	7
1 year postnatally			
Any dysglycaemia† n (%)	13/71 (18.3%)	18/73 (24.7%)	31 (21.5%)
Type 2 diabetes since randomisation*	5	7	12
Impaired fasting glucose (15; 17)	1	2	3
Impaired glucose tolerance (15; 17)	4	4	8
High risk of T2D (15; 18)	5	7	12

See online supplemental appendix 1 for definitions of terms.
*For the outcome of type 2 diabetes, data are presented cumulatively across all visits.
†T2D at any time point up to this visit, and other dysglycaemia at this time point.

assumption made was that even where participants did not attend or did not report adherence, they were still taking the intervention according to the last dosage reported. Patients in both groups had the same amount of general practicioner consultations, midwife visits, emergency department attendances, admissions and diagnostic procedures, (£10 967 vs £11 865 in the intervention and control groups), but in the control group the cost is spread on more patients (on average £354 vs £330 per patient in the intervention and control groups, respectively). The cost of AEs was assessed in both groups and was very similar.

The QALYs at 1 year were similar in both groups, but slightly higher in the intervention group (0.94 QALYs per patient over 1 year) compared with the control group (0.92 QALYs). We did not calculate an incremental cost-effectiveness ratio of the intervention compared with placebo as there is no improvement in outcomes and the results could be not significant. For the same reason we also did not run a sensitivity analysis.

Qualitative findings

Self-perceived risk of developing type 2 diabetes

Women and midwives cited a family history of type 2 diabetes as the primary motivation for participating in the study. Others described the challenging experience of previously self-managing gestational diabetes and wanted to avoid a repeat of that experience.

> I felt like that was a motivating factor for people as well, that if people and their family had already got this, they were quite likely…they'd seen first-hand what it's like to have type two diabetes. (Research midwife, Site 1)

Women with a history of gestational diabetes in previous pregnancies without developing type 2 diabetes postdelivery, and those recently diagnosed with gestational diabetes at the time of recruitment, doubted they would develop type 2 diabetes following their current pregnancy, so tended to decline consent. The self-perceived risk of type 2 diabetes also influenced women's commitment to taking the study medication throughout the study. Some felt it contributed to their weight loss postdelivery, which encouraged adherence. Others said they lost motivation over time.

> In the beginning I was really happy to take part because I've just had gestational diabetes and I know how much I suffered. Couldn't eat this, couldn't eat that, …I really don't want to be on that again in the future. With that thought I was so excited, I thought no, I'm going to take it every day. I want to prevent type two diabetes….And I just let go and now I just crave for sugary stuff. (Yasmin, Site 1)

Midwives felt a negative test result for type 2 diabetes by 6 months postdelivery was a disincentive to continue the intervention. Some women reported resuming part-time work shortly after birth and were unable to attend follow-up visits due to work and childcare commitments. Another disincentive was the washout period ahead of each appointment—many struggled to get back into a routine of taking tablets regularly and ended up stopping the medication.

Metformin: perceived safety and habit of daily intake

Limited side effects and an already established routine from metformin use in pregnancy gave women confidence to continue the tablets after birth, encouraging participation. A few women expressed concerns for potential harm to the baby through breast feeding but were happy to participate once reassured by the midwife. Women who experienced severe side effects from metformin during pregnancy declined consent. Women were comfortable continuing the same dose of tablets administered during their pregnancy.

> Because when I was pregnant I took two in the morning, two in the evening. So I just continued, yeah. (Halima, Site 1)

This daily habit of taking medications helped with adherence—partners were said to be supportive, reminding women to take the tablets. Some women forgot their tablets particularly if they didn't have the app reminders and the tablets were not in plain sight. Others who had missed a dose or forgotten to take the tablets for a long period of time felt that resuming the tablets would no longer be beneficial to the study or themselves and so refrained from doing so. Following a healthy diet coupled with normal glucose readings on their home blood glucose tests further minimised women's motivation to resume the tablets.

> Actually, first in the beginning I did used to take it… most days I took two…along with the vitamins… I was in that routine of taking tablets. Then I think after three months I kind of let go…. Taking it the other day, and not the other…And then after six months I just let go completely… This is not going to work… I'm not taking it consistently…I wasn't getting the full benefit…That's why I stopped taking it after six months completely. (Yasmin, Site 1)

General perspectives of the study and recommendations for improvement

Women interviewed gave positive remarks about the recruitment process. They felt they had received adequate information to decide on study participation and were informed they could withdraw at any point. Participants remarked positively on the study, as a simple and convenient intervention for the much-needed prevention of a health problem that affects both women and their families. They were appreciative of the opportunity to potentially prevent diabetes and indicated interest in participating in future studies. Most women were satisfied with the current design with no recommendations for improvement. Some suggested an additional social support group or group forum where women can be educated on the causes and prevention of diabetes and provide mutual support through shared experiences.

> … if they're educated…more of a reminder of what diabetes can do, what it can result to. Because people sometimes forget… you have to remind them…So sending…information or maybe a group chat, where people can…talk about what they've experienced… and then other mothers can get involved. And maybe a support group…. and then inform them of diabetes, inform them of research, how it can help you. (Kira, Site 1)

DISCUSSION

Summary of key findings

Our feasibility double-blinded randomised trial has shown that it is feasible to recruit, randomise and follow-up women in the first postnatal year, to evaluate the effects of metformin in preventing type 2 diabetes. The study intervention and procedures are acceptable to women and healthcare professionals, and the study was based on a prospective protocol.[12] Attendance and adherence may be improved with strengthened engagement measures, such as better use of app reminders, introduction of educational or peer support, or by reviewing the need for washout periods before study visits. Women's own diabetes risk perception is an important factor affecting participation and adherence.

Strengths and limitations

We showed that it is feasible to recruit, in an inner-city NHS trust, multiethnic high-risk women to the study intervention. Most women participating in the study were of Asian or black ethnic origin and thus at a higher risk to develop type 2 diabetes and at a younger age compared with white women.[16–18] We recruited and randomised women within a planned timeframe. We assessed the cost of laboratory tests, intervention and AEs in both groups and found them to be very similar. The rate of overall dysglycaemia (including type 2 diabetes) was slightly lower in the metformin group compared with the placebo group at 12 months, but this should be interpreted with caution due to the low number of blood samples collected during pandemic restrictions. We explored the acceptability of the intervention and the procedures and identify key factors that affect adherence and attrition, which will be addressed prior to a full-scale trial.

An unforeseeable limitation of the study was that face-to-face attendance to study visits would be affected by the COVID-19 pandemic. Despite this, half the women participating in the study attended 6-month and 12-month visits. However, the larger than anticipated loss to follow-up is likely to impact on the evaluation of clinical and laboratory outcomes at the end of the study. Data on adherence were collected retrospectively, which might have caused some recollection problems; however, there is no reason to believe this would differ between study groups. We made assumptions about the unit costs used to assess the NHS resource use and used average cost for each type of hospital contact; this may have affected the results if the reasons for contact varied between groups. Finally, most of the 1-year QALY data were missing and the analysis

might not reflect the outcomes of the intervention. One of the three sites contributed disproportionately to data collection and patient follow-up, due to ongoing staffing constraints during the study period.

Interpretation of findings and comparison with existing literature

Diabetes risk perception affects participation, adherence and attrition rates in similar studies focused on diabetes prevention. When women feel they have a high chance of developing type 2 diabetes they are more prone to take part in a study and adhere to the study intervention, but women who perceive their risk as low are more likely to withdraw or decline consent.[19] This was reflected in our study, where women who did not develop type 2 diabetes within 6 months postnatally considered their risk low.

We recognised that returning to work or receiving a normal glucose test result at 6–13 weeks or 6 months postnatally was, for some, a disincentive to continue in the study. The element of peer support should be further examined alongside improved discussion from clinicians about the risk of diabetes.[4 20 21] We found a 5% rate of diabetes, and we are confident that this is new-onset type 2 diabetes as all women in the participating hospitals have had Haemoglobin A1c screening at booking to rule out pre-existing diabetes.

There were no serious AEs related to the metformin group. The DPP Study did not provide safety data for women with reproductive potential as it excluded women who are breast feeding or planning a pregnancy.[22] A similar study assessing the effectiveness of metformin and dapagliflozin (alone and combined) in the postnatal period in overweight women after gestational diabetes in pregnancy, randomised 66 women but at study end (6 months postnatally) only 49 women completed the intervention.[9] They highlighted this population is likely to have another pregnancy within the postnatal period, which should be considered in the design of the study, as it will impact the attrition rates. In the DPP, 68.8% of participants had high adherence to metformin;[8] this result is comparable to our study as it would be clustered as amber based on our progression criteria (online supplemental appendix 1). DPP participants were diagnosed with impaired glucose tolerance which might have increased their motivation to adhere to the intervention.

Clinical and research implications

Our feasibility study achieved 'green' status in rates of recruitment and randomisation, and 'amber' in attrition and adherence, as markers of progression to a full-scale trial. The qualitative findings indicate that when women receive normoglycaemic results and if they perceive their risk of developing diabetes as low this can negatively affect engagement with the study. Loss of motivation and disruption to dose regimens affected adherence negatively. However, when women received app notifications or had a first-degree relative with diabetes, they were more likely to show steady adherence throughout the study.

In the DPP Study, there was a 50% risk reduction in type 2 diabetes following metformin use in women with previous gestational diabetes.[8 22] Unlike OMAhA, the DPP Study did not deliver the intervention in the postnatal period. In our study, the overall dysglycaemia rate was lower in the metformin group than in the placebo group at 12 months, although this needs to be interpreted with caution due to our sample size. There was a notable reduction in participant engagement with the study from 6 months, with half of the participants completing the last visit (53.2%). One suggested barrier was the washout period ahead of every study visit, which became burdensome particularly when participants needed to reschedule appointments. Including a washout period only at the final 12-month postnatal visit would avoid stop-starting the intervention multiple times. Future studies will need to incorporate implementation measures such as removal of the washout period between visits to reduce attrition and improve adherence. Other suggested measures are the inclusion of a group chat to promote peer support, to provide an education session about type 2 diabetes development and use the app reminder feature to improve adherence. Furthermore, an internal pilot within such a large-scale trial will allow us to ensure that the required follow-up has been achieved, prior to proceeding to full recruitment.

CONCLUSIONS

It is feasible to run a full-scale trial on the effectiveness of metformin for type 2 diabetes prevention in the early postnatal period in high-risk ethnically diverse women and prevent type 2 diabetes in women with gestational diabetes. The challenges in adherence assessment and follow-up need to be addressed.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Data availability statement Data are available upon reasonable request. Individual participant data linked to the results reported in this article (inclusive of text, tables, figures and appendices) will be available after de-identification. Other data available include the study protocol, informed consent form and the statistical analysis plan. Data will be available from 3 months to 5 years following the article's publication. Data can be made available to researchers who provide a methodological approach to achieve the aims of an approved proposal. Release of data will be subject to a data use agreement between the contractor and the third party requesting the data. The data use agreement must detail the agreed use and appropriate management of the research data to be shared and include a requirement for recognition of the contribution of the researchers who generated the data and the original funder. Proposals should be directed to a.bolou@gre.ac.uk. Prior to gaining access a data access agreement will need to be signed.

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