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The efficacy of intermittent metformin plus lifestyle intervention for diabetes prevention in women with prediabetes and prior gestational diabetes: a randomized clinical, non-inferiority trial

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Abstract

Background In women with prediabetes after prior gestational diabetes mellitus (GDM), whether intermittent metformin treatment as needed is as effective as continuous use in preventing type 2 diabetes mellitus (T2DM) is unknown. We aimed to test whether an intermittent metformin treatment is non-inferior to continuous metformin strategy for prevention of T2DM in women with prediabetes after GDM.

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Methods A randomized, open-label, non-inferiority trial was conducted at three centers in China. Women aged 18–45 years with prior GDM and prediabetes at 4–12 weeks postpartum were randomly assigned to receive lifestyle intervention plus intermittent or continuous metformin treatment. In the continuous group, participants were initially treated with lifestyle intervention and metformin was initiated when lifestyle intervention alone failed to maintain euglycemia and continued without interruption throughout the trial. In the intermittent group, participants were initially treated with lifestyle intervention and metformin was added when they failed to maintain euglycemia and was discontinued if the glycemic status returned to normal. The primary outcome was the difference in incidences of newly diagnosed diabetes between the two groups during the 3-year follow-up, compared against a non-inferiority margin of 10-percentage-point by following the intention-to-treat principle. Secondary outcomes included the percentage of prediabetes remission, changes from baseline in body weight, body mass index, waist circumference, fasting plasma glucose, 2-h plasma glucose, and hemoglobin A1c.

Results Among the 376 women randomized, 11.5% of women in the intermittent group and 11.1% in the continuous group developed newly diagnosed T2DM after three years (absolute risk difference 0.4 percentage points [95% CI −6.5 to 7.4], meeting criteria for non-inferiority). None of the secondary outcomes were significantly different between the two groups. Women in the continuous group experienced higher rate of metformin-related vitamin B_{12} deficiency (13.5% vs 3.7% , $P = 0.001$).

Conclusions In postpartum women with prediabetes after GDM, a strategy of intermittent metformin as needed plus lifestyle intervention met the pre-specified 10-percentage-point non-inferiority margin for 3-year T2DM incidence compared with continuous metformin plus lifestyle intervention. The equivalence of the two metformin strategies needs to be confirmed in further trials with a narrower margin and a larger event count.

Trial registration The study was registered in the Chinese Clinical Trial Registry (ChiCTR-IOR-17012770).

Keywords Gestational diabetes, Prediabetes, Metformin, Lifestyle intervention, Prevention

Background

Gestational diabetes mellitus (GDM) affects 14% of all pregnancies worldwide [1]. Women with a history of GDM are at an almost 10-fold higher risk of developing type 2 diabetes mellitus (T2DM) postpartum than those without a history of GDM [2]. As 22%–35% of women with prior

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GDM develop T2DM after 5-20 years postpartum [3, 4], and 32.8% of women with GDM had prediabetes in the early postpartum period [5], guidelines recommend screening for prediabetes or diabetes at 4–12 weeks postpartum and a lifelong prevention for T2DM in women with a history of GDM [6-9]. For those with prior GDM and prediabetes, the American Diabetes Association (ADA) recommends intensive lifestyle intervention and/or metformin treatment [6] based on findings from the subgroup analysis of Diabetes Prevention Program (DPP), which showed that lifestyle intervention or metformin halved the incidence of T2DM in 350 postpartum women with prediabetes and prior GDM over 2-years of follow-up [10].

Despite the role of metformin in diabetes prevention among individuals with prediabetes [11], long term adherence is a challenge in a preventive context among those without symptoms [12]. In addition, long term metformin treatment is associated with common gastrointestinal adverse events [13] and increased risk of vitamin B_{12} deficiency [14]. Therefore, an approach using intermittent metformin treatment depending on glycemic status may offer benefit compared to continuous therapy if efficacy is similar.

We report an open-label, randomized clinical trial testing if intermittent metformin treatment as needed is non-inferior to continuous treatment on the incidence of T2DM over a three-year period in women with prediabetes after a recent pregnancy complicated by GDM.

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Methods

Study design

This was an open-label, parallel design, non-inferior, randomized controlled trial conducted in the First Affiliated Hospital of Sun Yat-sen University, Guangzhou Women and Children's Medical Center, and the Fifth Affiliated Hospital of Zunyi Medical University from September 2017 to December 2024. The trial adhered to the principles outlined in the Declaration of Helsinki (2013 revision) and the International Council for Harmonisation Good Clinical Practice guidelines. The trial was overseen by a steering committee and an independent monitoring committee appointed by the sponsor. The protocol and statistical analysis plan is available in Additional file 1. The trial is reported in accordance with the CONSORT 2010 Statement and the non-inferiority and equivalence extension.

Participants

Women were eligible if they were 18 to 45 years of age, had a history of GDM diagnosed during 24 and 28 weeks of gestation in a recent pregnancy according to "International Association of

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Diabetes and Pregnancy Study Groups" criteria [15], and were diagnosed with prediabetes according to the 1999 World Health Organization's criteria[16] based on 75-g oral glucose tolerance testing (OGTT) performed at 4–12 weeks postpartum. Exclusion criteria included: 1) pre-existing diabetes before pregnancy; 2) diabetes diagnosed at 4–12 weeks postpartum; 3) active or untreated malignant tumors at the the screening visit, or malignancy within 5 years prior to the screening visit; 4) a history of organ transplantation or autoimmune disease requiring long-term use of glucocorticoids or immunosuppressant agents; 5) a history of mental illness and inability to complete follow-up; 6) serious diseases or physically weak, and inability to complete this study per researcher evaluation; 7) severe cardiovascular, hepatic, or renal diseases.

Randomization and masking

Eligible participants were randomized 1:1 into two treatment arms, stratified by the participating centers. A statistician not involved in the study encoded and prepared random envelopes, which were sequentially numbered, opaque, and sealed. Both the investigators and participants were unaware of the allocation before randomization but were informed afterwards. Participants, site staff, and treating physicians were not masked to therapy allocation, but the endpoint adjudication committee was masked to treatment group.

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Procedures

All participants received counseling on lifestyle intervention alone for the first 6 months after randomization and were asked to adhere to the lifestyle intervention throughout the trial. Lifestyle intervention counseling was provided by qualified research staff every three months. Guidance on lifestyle modification included 150 minutes of moderate-intensity exercise per week along with healthy diet choices consistent with the 2017 ADA guideline [17]. Lifestyle intervention fixed the 2017 ADA guideline version for protocol stability throughout the trial.

For women assigned to the continuous metformin group, metformin was initiated once lifestyle intervention alone failed to maintain euglycemia according to self-monitoring of blood glucose (SMBG) or OGTT and continued without interruption until the end of the trial regardless of changes in glycemic status. For those allocated to the intermittent metformin group, metformin was supplied when lifestyle intervention alone failed to maintain euglycemia according to SMBG or OGTT and was subsequently discontinued if the glycemic status returned to normal at a later visit (Additional file 2: Fig.S1). In both groups, metformin was initiated at 500 mg twice daily and titrated to a maximum dose of 1000 mg twice daily for the rest of the trial period. Participants were

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required to stop lactation if they initiated metformin. Metformin intervention was stopped uniformly in both groups if participants were pregnant during follow-up. All outcome assessments were performed without interrupting the assigned intervention, except that metformin was not taken on the morning of the OGTT. If participants were diagnosed with diabetes at interim, they were referred to routine diabetes care instead of the interventions of this study alone and did not receive further OGTT at later visits.

Study visits were conducted every three months from month-6 to collect SMBG, anthropometric measures, and adverse events, and to provide guidance on lifestyle interventions and metformin use. Participants were asked to record their lifestyle practice and metformin use. Participants were also advised to conduct SMBG by measuring fingerstick capillary blood glucose at least twice every month via personal glucometer models (Additional file 2: Table S1). All participants received standardized training on the use of glucometer models after randomization, delivered by a certified diabetes educator. Quality-control procedures were performed for each glucometer model according to manufacturer specifications and ISO 15197:2013 requirements. If the fasting capillary blood glucose ≥ 7.0 mmol/L or/and 2-h postprandial capillary blood glucose ≥ 11.1 mmol/L, participants were asked to return to the research center for further testing by OGTT to confirm diabetes. If SMBG indicated fasting capillary blood glucose ≥ 6.1 mmol/L and < 7.0 mmol/L, and 2-h postprandial capillary blood glucose < 7.8 mmol/L, or fasting capillary blood glucose < 7.0 mmol/L, and 2-h postprandial capillary blood glucose ≥ 7.8 mmol/L and < 11.1mmol/L, participants were asked to conduct additional SMBG on another day to confirm prediabetes. Euglycemia was defined if fasting capillary blood glucose < 5.6 mmol/L and 2-h postprandial capillary blood glucose < 7.8 mmol/L for three consecutive months, or fasting plasma glucose < 5.6 mmol/L and 2-h plasma glucose < 7.8 mmol/L on OGTT. All Participants underwent OGTT at the final study visit, and blood samples were collected to measure hemoglobin A1c (HbA1c) and vitamin B_{12} levels. For OGTT assessments, participants followed three days of adequate carbohydrate intake prior to testing. On the morning of testing, participants consumed 75-g of glucose solution after an overnight fast of 8-10 hours, with blood samples collection at fasting and 2-h after ingestion. The plasma glucose levels were measured using the hexokinase method at all three centers. The total number of OGTT performed per participant and proportion of participants who underwent SMBG-triggered confirmatory OGTT in each arm is summarized in Additional file 2 (Table S2). HbA1c levels were measured by ion-exchange high-performance

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liquid chromatography (Bio-Rad, CA, USA). Vitamin B_{12} levels were measured using a DxI 800 Access Immunoassay System (Beckman Coulter, CA, USA; reference range: 148 to 664 pmol/L) in the First Affiliated Hospital of Sun Yat-sen University and Architect i2000sr Autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA; reference range: 148 to 652 pmol/L) in the Guangzhou Women and Children's Medical Center and the Fifth Affiliated Hospital of Zunyi Medical University. Adherence to lifestyle intervention was evaluated with a questionnaire (Additional file 2: Table.S3) and adherence to metformin was assessed by a self-reported the number of days of medication as prescribed at each visit.

Outcomes

The primary outcome was newly diagnosed diabetes on OGTT, defined according to World Health Organization criteria[16] as fasting plasma glucose ≥ 7.0 mmol/L or 2-h plasma glucose ≥ 11.1 mmol/L. The diagnosis of diabetes was confirmed by at least one additional plasma glucose test or OGTT on another day unless there was unequivocal hyperglycemia with acute metabolic decompensation or obvious symptoms. Interim diagnoses of diabetes during follow-up were counted as the primary outcome. Prespecified secondary outcomes included the percentage of prediabetes remission based on fasting plasma glucose < 5.6 mmol/L, and OGTT 2-h plasma glucose < 7.8 mmol/L [18], change from baseline in body weight, body mass index (BMI), waist circumference, fasting plasma glucose, 2-h plasma glucose, and HbA1c. Safety endpoints were the incidence of all adverse events, including gastrointestinal symptoms, hypoglycemia, and vitamin B_{12} deficiency (defined as serum vitamin B_{12} < 148 pmol/L), etc.

Statistical analysis

The sample size for the trial was calculated to show the non-inferiority of the intermittent metformin intervention to the continuous metformin intervention in women with prediabetes after GDM with regard to the primary endpoint. The 3-year cumulative incidence of diabetes was previously reported as approximately 18% for metformin intervention in women with a history of GDM [10, 19]. With one-sided testing ($\alpha = 0.05$, $1-\beta = 0.8$), a non-inferiority margin of 10%, randomization ratio of 1:1, and accounting for 5% dropout rate, we calculated that a sample size of 376 would be necessary to reject the null hypothesis of inferiority.

The primary analysis followed the intention-to-treat principle, which included all randomized women. We used multiple imputation for missing outcomes in the primary analysis, assuming the data were missing at random. A total of 5 imputed data sets with 50 iterations were generated, and

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estimates were combined across data sets with the use of Rubin's rule. Specifically, logistic regression models were fit using groups formed by random assignment and baseline characteristics including maternal age, highest level of education, ethnicity, BMI, fasting plasma glucose, 2-h plasma glucose, HbA1c, insulin use during pregnancy. The multiple imputation was conducted using R software version 4.5.1 (R Foundation for Statistical Computing) with the analysis packages mice, version 3.17.0. A secondary per protocol analysis including only participants who completed the trial was performed to assess the robustness of the results. For the primary outcome, we calculated the point estimate and 95% confidence interval (CI) of the difference in cumulative incidence of diabetes diagnosis between both groups and compared the upper limit of the 95% CI with the non-inferiority margin. The 95% CI for the difference in incidence of diabetes was calculated by the Miettinen-Nurminen method. Risk ratio and 95% CI were estimated from log-binomial regression model with the robust estimator. Kaplan-Meier curves were used to estimate the cumulative incidence of diabetes over time, and the log-rank test was used to assess differences. Prespecified subgroup analyses were completed for the primary outcome according to maternal age (< 35 or ≥ 35 years), the baseline BMI (< 24 or ≥ 24 kg/m^2), and family history of diabetes (yes or no). To explore whether any interactive effects were mediated by maternal age, baseline BMI, or family history of diabetes, logistic regression models with the interaction terms of metformin intervention-by-subgroup were conducted. Secondary outcomes, including the remission rate of prediabetes and changes in body weight, BMI, waist circumference, fasting plasma glucose, 2-h plasma glucose, and HbA1c, were analyzed using χ^2 test or Wilcoxon rank-sum test.

The categorical variables of baseline characteristics and adverse events were described as the number of cases (percentage) and compared by Fisher's Exact test or χ^2 test as appropriate. The baseline characteristics with continuous data were presented as mean (standard deviation [SD]) and changes from baseline were presented as median (interquartile range [IQR]). Depending on the distribution of the data, continuous variables were compared using *t*-tests or Wilcoxon rank-sum test between two groups. A two-sided *P* value ≤ 0.05 was considered statistically significant. SPSS version 25 was used for statistical procedures.

Results

Participants characteristics

A total of 462 postpartum women were screened between September 2017 and December 2021,

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of whom 376 were randomly assigned and received the allocated intervention. Of those who underwent randomization, 334 women (167 [88.8%] in the continuous metformin group and 167 [88.8%] in the intermittent metformin group) completed the 3-year follow-up (per protocol set). Among participants who dropped out during follow-up, 10 were lost to follow-up, 3 withdrew consent, and 8 became pregnant again in the continuous metformin group, while 6 were lost to follow-up, 1 withdrew consent, and 14 became pregnant again in the intermittent metformin group (Additional file 2: Fig.S2). The mean (SD) age of all participants was 33.6 (4.4) years, the mean weight (SD) was 56.5 (7.8) kg, and the mean BMI was 22.3 (2.9) kg/m^2. The characteristics of the participants at baseline were similar between the two groups (intention-to-treat set [Table 1] and per protocol set [Additional file 2: Table S4]). The actual metformin exposures in the two groups are shown in Additional file 2 (Table S5-6). There were no significant between-group differences in the adherence to the twice-monthly SMBG schedule, lifestyle intervention and metformin at each visit (Additional file 2: Table.S7-8).

Primary outcome

Among 376 women, 42 women dropped out during follow-up. In the intention-to-treat analysis after multiple imputation (Additional file 2: Table S9), the incidence of diabetes was 11.1% (95% CI 6.5% to 15.7%) in the continuous metformin group and 11.5% (95% CI 6.6% to16.4%) in the intermittent metformin group (Table 2). The upper limit of the 95% CI around the difference was lower than the pre-specified non-inferiority margin of 10-percentage-point (absolute risk difference 0.4 percentage points [95% CI −6.5 to 7.4]), indicating that the intermittent metformin plus lifestyle intervention was non-inferior to continuous metformin plus lifestyle intervention. In the per protocol analysis, the incidence of diabetes was 10.2% (95% CI 6.5% to 15.7%) in the continuous metformin group and 10.8% (95% CI 6.9% to16.4%) in the intermittent metformin group, with absolute risk difference 0.6 percentage points (95% CI −6.2 to 7.4) in incidence (Table 2), consistent with the intention-to-treat analysis meeting criteria for non-inferiority. The cumulative incidence of diabetes development over time was similar in both groups according to Kaplan-Meier estimates (log-rank P = 0.800 in the intention-to-treat analysis and log-rank P = 0.700 in the per protocol analysis) (Additional file2: Fig.S3).

The subgroup analyses were performed for the primary outcome according to maternal age (< 35 or ≥ 35 years), the baseline BMI (< 24 or ≥ 24 kg/m2), and family history of diabetes (yes or no). The baseline characteristics of participants in each subgroup were similar between the two

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metformin intervention groups (Additional file 2: Table S10-15). The first imputed data set was used to presented the number of events within each subgroup in the intention-to-treat analysis. There were no significant differences between the imputed data sets. The number of events within each subgroup in other four imputed data sets is shown in Additional file 2 (Table S16). The results of the analyses with the imputed data sets were virtually identical to those in the cohort with complete cases and were thus consistent with a per protocol analysis across all subgroups (Fig.1). There were no significant treatment-by-subgroup interactions (all interaction *P* values > 0.05).

Secondary outcomes

The secondary outcomes are summarized in Additional file 2 (Table S17). Overall, 101 (60.5%) of 167 women in the continuous metformin group and 93 (55.7%) of 167 women in the intermittent metformin group achieved remission of prediabetes (between-group difference −4.8 [95% CI −16.0 to 6.4], *P* = 0.438). Among participants who achieved remission of prediabetes, 61.4% of women in the continuous metformin group and 58.1% in the intermittent metformin group maintained euglycemia for sustained 3 consecutive months or more (*P* = 0.637, Additional file 2: Table S18). Reduced body weight (-3.3 [4.0] vs -3.1 [4.2] kg, between-group difference 0.1 [95% CI −0.8 to 1.0], *P* = 0.860), BMI (-1.2 [1.7] vs -1.3 [1.7] kg/m^2, between-group difference −0.1 [95% CI −0.4 to 0.3], *P* = 0.677), and waist circumference (-4.2 [4.8] vs -4.1 [5.2] cm, between-group difference 0 [95% CI −1.0 to 1.1], *P* = 0.979) were observed in both treatment groups, with no substantial between-group differences (Additional file 2: Table S16). The changes from baseline to final visit in fasting plasma glucose (0.1 [0.6] vs 0.1 [0.6] mmol/L, between-group difference 0 [95% CI −0.1 to 0.2], *P* = 0.692), 2-h plasma glucose (-1.2 [2.3] vs -1.0 [2.0] mmol/L, between-group difference 0.1 [95% CI −0.3 to 0.6], *P* = 0.779), and HbA1c (0.0 [0.5] vs 0.1 [0.5] %, between-group difference 0 [95% CI −0.1 to 0.1], *P* = 0.533) were similar between the two groups (Additional file 2: Table S17).

Safety

The adverse events that occurred during the study period are summarized in Table 3. A total of 63 (34.1%) adverse events were reported in the continuous metformin group and 39 (20.9%) in the intermittent metformin group (*P* = 0.004). The most common adverse events were gastrointestinal disorders (14.6% for the continuous metformin group and 12.3% for the intermittent metformin group, *P* = 0.516). For metformin-related adverse events, a significantly higher proportion of vitamin B_{12} deficiency was noted in the continuous metformin group than in the intermittent

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metformin group (13.5% vs 3.7%, $P = 0.001$). No deaths or serious adverse events were reported during the trial. No participant withdrew due to adverse events. Occurrences of mild adverse events, such as gastrointestinal disorders, hypoglycemia, rash, and vertigo, were similar between the two groups.

Discussion

To our knowledge, this is the first randomized trial to compare intermittent and continuous metformin regimens for diabetes prevention in women with prediabetes after a recent pregnancy complicated by GDM. We found that in individuals with prediabetes after GDM, intermittent metformin therapy as needed was non-inferior to continuous treatment in preventing diabetes. This finding was consistent across subgroups according to age, BMI, and family history of diabetes. This result is relevant for diabetes prevention for at least 7.3 million women who develop prediabetes [5] after GDM[1] globally every year.

Multiple randomized controlled trials have demonstrated the efficacy of metformin for diabetes prevention in adults with prediabetes [20-23]. The DPP study, which included 3195 participants with prediabetes and followed-up for more than 20 years, provided strong evidence for the effectiveness of metformin in diabetes prevention in adult populations [24]. Women with prediabetes and prior GDM were one of the subgroups shown to benefit from metformin [25]. However, continuous preventive use in individuals without symptoms is often limited due to challenges with adherence [12]. A previous study in adults with prediabetes reported that treatment with short-term metformin resulted in an improvement in glucose tolerance that lasted for up to 6 months after withdrawal of metformin [26], suggesting that metformin used intermittently depending upon glycemic status may be effective. To date, all published trials investigating metformin to prevent T2DM have used continuous medication throughout the entire study period [20-23]. Therefore, we explored whether metformin treatment can be discontinued when glycemic status returns to normal in women with prediabetes and prior GDM.

In this study, the 3-year cumulative incidence of diabetes was 11.5% in the intermittent metformin group and 11.1% in continuous metformin group, meeting the criteria for non-inferiority. Furthermore, the incidence of diabetes in our study was lower than those in the GDM subgroup of DPP (the 3-year cumulative incidence of diabetes was 14% in lifestyle intervention alone and 18% in metformin alone [19]), as well as in a previous trial among Chinese women after GDM which reported a rate of 15% in those received lifestyle intervention alone at the end of 3-

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year follow-up [27]. The lower incidence of diabetes progression in the present study suggested that the combination of lifestyle intervention with metformin may enhance the effectiveness of diabetes prevention, consistent with the recent data reporting a further 17% decreased risk of developing T2DM when metformin was added to lifestyle intervention in adults with prediabetes [22]. The younger participants (mean age 34 years compared to 43 years [19] and 39 years[27] in previous studies) may be also an explanation for the lower incidence in this study. In addition, the different postpartum timing at enrollment (median interval, 2.2 months vs 12 years) and the baseline glycemic status (mean HbA1c, 5.2% vs 5.9%) were potential drivers of the difference in the incidence of diabetes between our study and DPP.

The reversal of prediabetes to normal glucose regulation is associated with reduced incidence of future diabetes and microvascular complications [28, 29]. In the present study, the overall remission rate of prediabetes was approximately 60% in both groups over 3 years of follow-up, which was substantially higher than that (approximately 24%) among general prediabetic population in DPP study [18]. This may be in part explained by the different times to initiate the intervention between the two studies. We started the intervention soon after the diagnosis of prediabetes was made, around two months after delivery, while the intervention in DPP commenced on average 12 years after GDM [10]. Screening and intervention during the early postpartum period after GDM may provide an opportunity to reduce the progression of insulin resistance and β-cell dysfunction by hyperglycemia, and increase the likelihood of achieving remission of prediabetes.

The association between long-term metformin therapy and vitamin B_{12} deficiency has been previously reported [14]. Evidence shows that the cumulative metformin dose correlated strongly with vitamin B_{12} deficiency [30] and metformin impaired vitamin B_{12} absorption in a dose- and duration-dependent manner [31]. We found that more women in the continuous metformin group had vitamin B_{12} deficiency than in the intermittent group during follow-up. However, this difference in vitamin B_{12} deficiency was observed in an exploratory analysis without baseline measurement and its functional markers (methylmalonic acid and homocysteine) assessment. Therefore, longitudinal measurement of vitamin B_{12} and its functional markers before and after medication is necessary to demonstrate the effect of intermittent metformin strategy in reducing vitamin B_{12} deficiency.

This study has several limitations. (1) Due to the open-label design, participants and

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investigators were aware of intervention allocation. However, the fact that the primary and secondary endpoints were generated from biochemical and anthropometric measurements by blinded technical staff reduces potential bias. (2) The pre-specified 10-percentage-point non-inferiority margin was wide relative to the established absolute effect of metformin and the observed incidence of diabetes was lower than that assumed for the power calculation. The non-inferiority of intermittent metformin strategy compared to continuous metformin strategy should be confirmed in further trials with a narrower margin and a larger event count. (3) The absence of central randomization may weaken the allocation concealment integrity and methodological flexibility. However, the random envelopes were sequentially numbered, opaque, and sealed to minimize the risk of selection bias. (4) The evaluation of adherence to lifestyle intervention and metformin was based on participants' concise self-reports, instead of instruments or scales that have been validated for assessment of adherence to lifestyle intervention and returned pill count or medication possession ratio for assessment of medication adherence. (5) Due to the absence of baseline vitamin B_{12} levels in this study, it was difficult to distinguish the inference about incident deficiency versus pre-existing low status. (6) The attrition rate was higher than expected, largely owing to the unplanned re-pregnancy and the COVID-19 pandemic during the study. (7) The absence of long-term follow-up beyond 3 years restricted inference about durability of the intermittent metformin strategy. (8) Since single-country, single-ethnicity (predominantly Han Chinese) cohort and only women with prediabetes after GDM were included in this study, the findings need to be validated in general and diverse populations with prediabetes for a long-term follow-up.

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Conclusions

In postpartum women with prediabetes after GDM, a strategy of intermittent metformin as needed plus lifestyle intervention met the pre-specified 10-percentage-point non-inferiority margin for 3-year T2DM incidence compared with continuous metformin plus lifestyle intervention. The width of this margin relative to the established absolute effect of metformin, together with the observed event rate below that assumed for the power calculation, indicated that equivalence of the two strategies should be confirmed in further trials with a narrower margin and a larger event count.

Abbreviations

ADA American Diabetes Association

BMI Body mass index

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CI Confidence interval

DPP Diabetes Prevention Program

GDM Gestational diabetes mellitus

HbA1c Hemoglobin A1c

IQR Interquartile range

OGTT Oral glucose tolerance testing

SD Standard deviation

SMBG Self-monitoring of blood glucose

T2DM Type 2 diabetes mellitus

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Authors' contributions

Conceptualization: XPC. Data curation: XPC, FHL. Formal analysis: FHL, LP, CLX, HMX, ZTL, NC. Funding acquisition: XPC. Investigation: FHL, LP, CLX, HMX, ZTL, NC, YHZ, SHL, YJZ, YMW, SFY, YC, XYH, YPL, WZC, CXW, WPD, HTC, LHL, SBH, HL. Methodology: XPC, LL. Project administration: XPC, YBL. Resources: XPC, YBL. Supervision: XPC, YBL. Statistical analysis: LL, WXX. Validation: HMX, ZTL, NC. Visualization: FHL, LP, CLX. Writing-original draft: FHL, LP, CLX, HMX, ZTL, NC. Writing-review & editing: XPC, MSP, YBL, LL. All authors read and approved the final manuscript.

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Data availability

De-identified individual participant data, including outcome data (primary and secondary endpoints), baseline covariates (demographics, clinical characteristics, and laboratory values), and adverse events (MedDRA-coded), will be shared upon reasonable request. Requests will be reviewed by the study's Data Sharing Committee for scientific merit and alignment with informed consent. Approved requestors will sign a Data Use Agreement and receive data via secure encrypted transfer. The dataset is being deposited in Vivli platform (https://vivli.org) and will be accessible upon publication.

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Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (Approval No. [2017]124) and registered in the Chinese Clinical Trial Registry (ChiCTR-IOR-17012770). Written informed consent was obtained from all participants.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including images, videos, or case details) that would require consent for publication.

Competing interests

The authors declare no competing interests.

Declaration of generative artificial intelligence use

No generative artificial intelligence tools were used in the preparation of any part of this manuscript. All work was conducted solely by the authors.

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Figure Legend

Fig.1 Forest plots of incidence of diabetes in subgroup analyses. (A) Intention-to-treat analysis. Result was obtained from the first imputed data set. There were no significant differences between the imputed data sets. (B) Per protocol analysis.

Supplementary Information

Additional file 1: Study protocol and statistical analysis plan.

Additional file 2: Supplementary Figure and Tables. Fig.S1. Intervention profile. Fig.S2. Flowchart of trial participants. Fig.S3. Cumulative incidence of diabetes. Table S1. The manufacturers and analytical accuracy of glucometer models. Table S2. The total number of OGTT performed per participant and proportion of participants who underwent SMBG-triggered confirmatory OGTT in the two groups. Table S3. Lifestyle intervention assessment questionnaire. Table S4. Characteristics of the participants at baseline (per protocol set). Table S5. Metformin exposures in the two groups. Table S6. Number of participants who received metformin and the dose achieved at each study visit. Table S7. Adherence to the twice-monthly SMBG schedule in two groups at each visit. Table S8. Adherence to lifestyle intervention and metformin in two groups. Table S9. Multiple imputation results of newly diagnosed diabetes in the full analysis set during

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3-year follow-up. Table S10. Characteristics of the participants at baseline (aged < 35 years). Table S11. Characteristics of the participants at baseline (aged ≥ 35 years). Table S12. Characteristics of the participants at baseline (BMI < 24 kg/m2). Table S13. Characteristics of the participants at baseline (BMI ≥ 24 kg/m2). Table S14. Characteristics of the participants at baseline (without family history of diabetes). Table S15. Characteristics of the participants at baseline (with family history of diabetes). Table S16. Subgroup analyses in the imputed data set 2-5. Table S17. Secondary outcomes. Table S18. Remission time point of prediabetes

Table 1 Characteristics of the participants at baseline

Characteristic	**Continuous metformin (n = 188)**	**I**
Maternal age		
Age, mean (SD), years	33.6 (4.4)	
< 35 years, n (%)	116 (61.7)	
Median enrollment time after delivery (IQR), months	2.3 (1.9 – 3.0)	
Highest level of education, n (%)		
High school or below	6 (3.2)	
Associate/trade degree	29 (15.4)	
College or above	153 (81.4)	
Ethnicity, n (%)		
Han	170 (90.4)	
Other	18 (9.6)	
GDM in a prior pregnancy (before the index pregnancy), n (%)	23 (12.2)	
Family history of diabetes, n (%)	65 (34.6)	
Body weight, mean (SD), kg	56.3 (8.4)	
BMI, mean (SD), kg/m^2	22.3 (2.9)	
< 24 kg/m^2, n (%)	135 (71.8)	
Waist circumference, mean (SD), cm	79.9 (7.3)	
Fasting plasma glucose, mean (SD), mmol/L	4.8 (0.5)	
2-h plasma glucose, mean (SD), mmol/L	9.1 (0.8)	
HbA1c, mean (SD), %	5.2 (0.4)	
Insulin use during pregnancy, n (%)	6 (3.2)	
Breastfeeding after delivery*, n (%)	180 (95.7)	
Duration of lactation, median (IQR), months	12.0 (8.5 – 16.0)	

* Breastfeeding status was recorded at randomization.

Table 2 Primary outcome

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	Participants	Incidence of diabetes, % (95% CI)	Absolute risk difference in incide
Intention-to-treat analysis*			
Continuous metformin	188	11.1 (6.5 to 15.7)	–
Intermittent metformin	188	11.5 (6.6 to 16.4)	0.4 (−6.5 to 7.4)
Per protocol analysis			
Continuous metformin	167	10.2 (6.5 to 15.7)	–
Intermittent metformin	167	10.8 (6.9 to 16.4)	0.6 (−6.2 to 7.4)

*In the intention-to-treat analysis, the estimates and 95% CI were the pooled data after multiple imputations. Five complete datasets were imputed within each group for missing endpoint and combined the estimates from each imputed dataset into one overall estimate. The 95% CI for the difference in incidence was calculated by the Miettinen-Nurminen method.

†Risk ratio and 95% CI were estimated from log-binomial regression model with the robust estimator.

Table 3 Safety endpoints

System organ class Preferred term	Total adverse events, n (%)			Metf
	Continuous metformin (n = 185)*	Intermittent metformin (n = 187)*	*P* value	Continuous me (n = 185)
All	63 (34.1)	39 (20.9)	0.004	59 (31.9
Gastrointestinal disorders	27 (14.6)	23 (12.3)	0.516	27 (14.6
Nausea	16 (8.6)	11 (5.9)	0.304	16 (8.6)
Diarrhea	10 (5.4)	8 (4.3)	0.612	10 (5.4)
Vomiting	1 (0.5)	4 (2.1)	0.372	1 (0.5)
Metabolism and nutrition disorders	34 (18.4)	14 (7.5)	0.002	30 (16.2
Vitamin B12 deficiency	28 (15.1)	10 (5.3)	0.002	25 (13.5
Hypoglycemia	6 (3.2)	4 (2.1)	0.542	5 (2.7)
Nervous system disorders	0	2 (1.1)	0.449	0
Vertigo	0	2 (1.1)	0.449	0
Skin disorders	2 (1.1)	0	0.247	2 (1.1)

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Rash	2 (1.1)	0	0.247	2 (1.1)

* The participants who did not receive any study intervention were excluded from the safety analysis.

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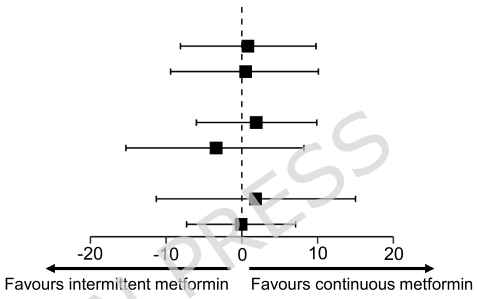
Subgroups	Intermittent metformin (events/total)	Continuous metformin (events/total)	Difference in incidence % (95% CI)	Interaction *P* value
Maternal age				
<35 years	14/109	14/116	0.8 (−8.1 to 9.8)	0.996
≥35 years	7/79	6/72	0.5 (−9.4 to 10.1)	
Baseline BMI				
<24 kg/m^2	18/138	15/135	1.9 (−6.0 to 9.9)	0.426
≥24 kg/m^2	3/50	5/53	−3.4 (−15.3 to 8.2)	
Family history of diabetes				
Yes	11/64	10/65	1.8 (−11.3 to 15.0)	0.833
No	10/124	10/123	−0.1 (−7.3 to 7.1)	



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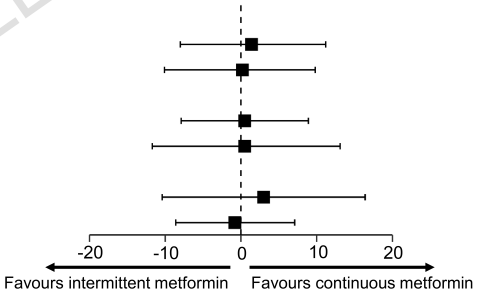
Subgroups	Intermittent metformin (events/total)	Continuous metformin (events/total)	Difference in incidence % (95% CI)	Interaction *P* value
Maternal age				
<35 years	12/92	12/103	1.4 (−8.0 to 11.2)	0.893
≥35 years	6/75	5/64	0.2 (−10.1 to 9.8)	
Baseline BMI				
<24 kg/m^2	15/124	14/121	0.5 (−7.9 to 8.9)	0.981
≥24 kg/m^2	3/43	3/46	0.5 (−11.7 to 13.1)	
Family history of diabetes				
Yes	9/58	7/56	3.0 (−10.4 to 16.4)	0.633
No	9/109	10/111	−0.8 (−8.6 to 7.1)	



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