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Hydroxychloroquine as an adjunct therapy in the management of type 2 diabetes in pregnancy: study protocol for a randomised controlled trial

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ABSTRACT

Introduction The increasing incidence of type 2 diabetes mellitus (T2DM) among women of reproductive age poses significant health risks for both mothers and their fetuses. Optimising blood glucose levels during pregnancy is particularly challenging, even with a combination of oral antidiabetic agents and insulin therapy. Hydroxychloroquine (HCQ) has been shown to lower glucose levels in non-pregnant populations and has demonstrated safety in pregnant women with systemic lupus erythematosus and rheumatoid diseases. In addition to its glucose-lowering effects, HCQ also exhibits immunomodulatory, antioxidant and anti-inflammatory properties. Given that both T2DM and pregnancy are pro-inflammatory states, inadequate glycaemic control may exacerbate adverse pregnancy outcomes. We hypothesise that adjunctive treatment with HCQ in this cohort could improve glycaemic control, reduce systemic inflammation and subsequently lower the risk of adverse pregnancy outcomes.

Methods and analysis This is a prospective, open-label, randomised controlled trial involving 56 pregnant women diagnosed with T2DM. Participants will be randomly allocated, using computerised randomisation software, into either a control group receiving standard care or an intervention group receiving standard care with HCQ 200 mg daily. The primary outcomes will be the difference in glycaemic parameters and inflammatory markers. Secondary outcomes include the assessment of pregnancy outcomes between the groups, such as gestational age at delivery, postpartum haemorrhage, fetal macrosomia and shoulder dystocia.

Ethics and dissemination This protocol has been approved by the National University of Malaysia Ethics Committee (JEP-2023–866). Study findings will be disseminated via presentations at academic conferences, publications in peer-reviewed journals and professional training and meetings to healthcare professionals.

Trial registration number This study was registered in ClinicalTrials.gov (NCT06319560) on 23 January 2024.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study focuses on pregnant women with type 2 diabetes mellitus (T2DM), a high-risk group with significant maternal and fetal complications.
⇒ The adjunctive use of hydroxychloroquine that targets both glycaemic control and inflammatory pathways, addressing two critical factors in diabetes and pregnancy.
⇒ As this is a single-centre study, the findings may not be widely generalisable to other populations or healthcare settings.
⇒ There is a risk of bias which may impact how the participants perceive and report their experiences as this is an open-label trial.
⇒ Participants are more likely to drop out in this trial if they feel dissatisfied with the assigned treatment due to the open-label trial.

INTRODUCTION

Diabetes mellitus is a chronic debilitating metabolic disease that affects quality of life and imposes a significant burden on healthcare. Insulin resistance, followed by hypersecretion of insulin from the pancreatic beta cells, along with excess adipose tissue and genetic markers, has resulted in the development of type 2 diabetes mellitus (T2DM). Apart from genetic studies, research has been done to improve the understanding of the role of adipose tissue in insulin resistance. Lipid metabolism has been hypothesised to cause inflammation and insulin resistance in the development of T2DM.[1] Inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) that are secreted by the white adipose tissue result in increased hepatic production of C reactive protein and promote further insulin resistance.[2–4] Laboratory studies showed that IL-6 induces apoptosis of the cells in the islet of Langerhans in the pancreas, while TNF-α reacts between excessive adipose tissue causing islet cell inflammation and subsequently the death of pancreatic beta-cells, thus resulting in insulin resistance.[3] Diabetes is characterised by a state of chronic low-grade

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inflammation, and this inflammation is often exacerbated during pregnancy. This heightened inflammation is linked to the physiological changes in pregnancy, such as insulin resistance and the development of gestational diabetes mellitus. Poor glycaemic control during pregnancy is a major contributing factor, increasing the risk of stillbirth, fetal hypoxia and cardiac dysfunction in the offspring.[5 6]

Pregnancy involves a physiological shift towards a low-grade inflammatory state, characterised by a balance between pro-inflammatory and anti-inflammatory markers. This shift is crucial for successful implantation, fetal development and parturition. During pregnancy, several cell types, including skeletal muscle cells, adipocytes, lymphocytes and natural killer cells, produce inflammatory markers or cytokines. These cytokines play a crucial role in modulating the immune response, influencing the maternal and fetal environment and potentially impacting pregnancy outcomes. Apart from the secretion of adipocytes and cytokines from the white adipose tissue, the placenta also acts as a predominant endocrine organ in the secretion of cytokines including IL-1β, IL-6 and TNF-α.[7 8] Reduction in insulin sensitivity is more pronounced from 20 weeks gestation onwards.[7 8] Kirwan *et al* in 2002 demonstrated an increase in TNF-α levels during late pregnancy among diabetic pregnant women as compared with normoglycaemic pregnant women.[7] These may explain the need for higher insulin doses towards the second half of pregnancy. Poorly controlled diabetes is strongly linked to poor maternal and neonatal outcomes including higher likelihood of caesarean section, preterm birth, stillbirth, fetal macrosomia, polyhydramnios, neonatal hypoglycaemia and fetal congenital anomalies.[5 6 9]

Hydroxychloroquine (HCQ) is an antimalarial drug that has hypoglycaemic effects.[10 11] It is safe to be used in pregnancy including in the first trimester. HCQ has been safely used for autoimmune and rheumatic diseases in pregnancy. It is known to cross the fetal placenta barrier and has proven to improve fetal outcomes in anti-Ro/La-positive mothers.[12] Chambers *et al* in 2022 performed a prospective study including 500 pregnant women who demonstrated no increased risk of structural birth defects[13] and low birth weight.[12 14–17] Follow-up of infants exposed to HCQ appeared to have no effect on neurodevelopment and visual function.[18 19] There was no increased risk of childhood infection when these children were followed up to 3.5 years.[19]

In patients with systemic lupus erythematosus (SLE), its usage during pregnancy reduces the risk of the disease relapse and is suggested to reduce the risk of diabetes.[20 21] Apart from its hypoglycaemic effect, it also has anti-inflammatory, antioxidant and immunomodulatory properties.[22 23] Metformin and insulin, a commonly used treatment in pregnancy, possess anti-inflammatory properties in addition to their hypoglycaemic effect. Pregnant women suffering from T2DM encounter enhanced insulin resistance due to the secretion of placental hormones, resulting in erratic suboptimal glycaemic control. Thus, they may require a very high dose of insulin on top of the maximum dose of metformin to maintain normoglycaemia. Evaluation of HCQ use in T2DM patients showed significant improvement of inflammatory markers which correlates with improvement in beta-cell function and insulin resistance.[21 24] Systematic reviews showed that glycaemic parameters such as fasting blood glucose, post-prandial glucose and haemoglobin A1c (HbA1c) showed a significant decrease when added to the standard treatment as compared with placebo.[25–28] Our working hypothesis is that HCQ if given to T2DM women can improve the blood sugar profile (HbA1c and serum fructosamine), reduce inflammation and lead to better pregnancy outcomes.

METHODS AND ANALYSIS

Design and setting

Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines were used as a reference.[28 29] We will conduct an open-labelled randomised controlled trial. The study will be conducted within 46 months (1 March 2024–1 January 2027) in Hospital Canselor Tuanku Muhriz, Cheras Kuala Lumpur. All T2DM pregnant women who attend our antenatal clinic in the obstetrics and gynaecology department will be invited to participate. The gestational age at recruitment is within 14 to 20 weeks' gestation. Participants will be randomised into two groups, either standard treatment with or without HCQ 200 mg daily. The block randomisation method was employed to ensure balanced allocation of participants between the control and intervention group. We used a block size of 4, which is a multiple of the number of study groups to generate all possible balanced group assignments within each block. For instance, with two treatment groups and a block size of 4, possible combinations are AABB, BBAA, ABAB, BABA, ABBA and BAAB. These sequences were then randomly placed to construct the allocation list. This randomisation sequence was generated using a computer-based random number generator. The allocation assignment was concealed in a sealed envelope which will only be opened once the participants' eligibility is confirmed and consent is taken. Both the investigators and participants will be aware of the treatment assigned. The intervention group will receive HCQ 200 mg once daily in addition to the standard treatment. The open-label design was chosen due to its practical constraint and the unavailability of a placebo for the control group. Furthermore, it will provide more insights into how these interventions perform in typical clinical settings. It may also increase participants' willingness to enrol and remain in the study if the intervention is perceived as beneficial.

Eligibility criteria

Inclusion criteria

- Singleton pregnancy.

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- Pregnant women with a confirmed diagnosis of T2DM.
- Willing to participate and sign the informed consent.

Exclusion criteria

- Autoimmune disease such as SLE or rheumatic disease.
- Chronic kidney disease.
- Fetal anomaly.
- Women on steroid therapy.
- Diabetic retinopathy.
- Known thalassaemia or thalassaemia carrier.
- Known allergy or have contraindications to HCQ.

Women were diagnosed with T2DM if at least two of the following criteria were met, with the diagnosis established prior to pregnancy.[29] Eligible participants will be recruited if they fulfilled the specified inclusion and exclusion criteria:

1. Fasting plasma glucose of ≥7.0 mmol/L.
2. 2-hour plasma glucose ≥11.1 mmol/L.
3. Random plasma glucose of ≥11.1 mmol/L.
4. HbA1c≥6.3%.

Procedures and data collection

Data including age, gestation at recruitment, parity, weight and height at pregnancy booking and medical background will be taken. Total blood volume of 15 mL will be withdrawn for HbA1c, full blood count and serum fructosamine, IL-6, IL-10 and TNF-α at recruitment. Blood for HbA1c, full blood count and serum fructosamine will be processed immediately in our local laboratory. For inflammatory markers, blood will be collected in a plain tube and left at room temperature for an hour before being centrifuged at 5000 rpm for 10 min. The serum will be stored at −80 degrees for analysis later via ELISA technique. The intervention group will receive HCQ 200 mg once daily in addition to the standard treatment. HCQ will be given between 16–20 weeks of gestation until delivery of the fetus. The HCQ tablet can be taken at any time of the day, and it is advisable to take with food to avoid the gastrointestinal side effects like nausea.

These investigations will be repeated prior to delivery. Both groups will receive the standard treatment throughout the antenatal period which consists of a review by the dietitian and routine antenatal and combined endocrinology clinic follow-ups for monitoring and adjustment of treatment. These data will be obtained during recruitment (baseline) and prior to delivery; dose of metformin and insulin; self-blood glucose monitoring; maternal complications such as preterm labour and postpartum haemorrhage; and perinatal outcomes such as fetal macrosomia, shoulder dystocia, neonatal hypoglycaemia and neonatal intensive care unit admission. Home blood glucose monitoring (HBGM) will be standardised to a staggered 7-point system consisting of pre-meals and 1 hour post-meals. All of the patients will be followed up every 2 to 4 weeks in our combined endocrine and antenatal clinic. After delivery, participants will be followed up twice (once at 6 months and subsequently at 12 months) postpartum for assessment of their infants. The height and weight of the infants will be measured. Any need for hospital admission for serious infections, antibiotics administration and hospitalisation frequency will be noted. Developmental milestones will be assessed according to the developmental milestones chart of Paediatric Protocols for Malaysian Hospitals 4th Edition 2019. The procedural flow chart is shown on (figure 1).

Intervention and drop-out criteria

Participants will be considered as drop-outs when they are lost to follow-up, withdraw consent, are non-compliant with medication (HCQ) or develop adverse drug effects. All participants will be followed up at a minimum of 4 weekly intervals. Compliance with HCQ will be assessed at each follow-up, whereby an indirect method of assessing adherence of participants in the HCQ group will be made. Each participant will be asked whether they are still taking the study medication and are required to bring the remaining medication for tablet count. Participants with a remaining of more than 20% of the scheduled medications will be considered as non-compliant and treated as drop-outs.[30]

Protocol safety

HCQ is generally well tolerated, and there is no known drug interaction between HCQ and insulin or metformin. However, given the glucose-lowering effects of HCQ, its use may potentiate the effects of concomitant use of insulin and metformin.[23 31 32] Participants will therefore undergo regular glycaemic monitoring through home blood glucose monitoring, and doses of insulin or metformin will be adjusted as clinically indicated to minimise the risk of hypoglycaemia.

Other common adverse events include gastrointestinal disturbances (nausea and vomiting), headache and skin reactions. Rare adverse events that have been reported at higher dosage or long-term use are retinopathy and prolonged QT interval. All participants will be screened a minimum of twice by an ophthalmologist; prior to recruitment and at 28–32 weeks for retinopathy, any women detected to have abnormal pulse rates will be subjected to an ECG.

Study outcomes

The primary outcomes will be the difference in glycaemic parameters (serum HbA1c, serum fructosamine, fasting and postprandial glucose) and serum inflammatory markers (IL-6, IL-10 and TNF-α) during recruitment and prior to delivery. Secondary outcomes will be the incidence of hypoglycaemia, the assessment of pregnancy outcomes, gestational age at delivery (preterm or term), type of labour (induced or spontaneous), mode of delivery (vaginal or caesarean section), presence or absence of postpartum haemorrhage and obstetric anal sphincter injuries, neonatal birth weight (presence of fetal macrosomia or large for gestational age), presence or absence of shoulder dystocia, the appearance, pulse,

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grimace, activity and respiration (APGAR) score at 5 min, number of neonates needing admission into neonatal intensive care unit up to 7 days of life, the height and weight of the infant at 6 and 12 months of age and any hospital admission of the infant from day 7 of life until 12 months of age.

Sample size

The sample size for the study is calculated using the following formula based on a study conducted among patients with T2DM in an Asian population receiving standard antidiabetic therapy (insulin, metformin and glimepiride).[33 34] In this study, the addition of HCQ to the intervention group resulted in a 1.3% reduction in HbA1c, compared with a 0.9% reduction in the control group.[34] This study was selected as the most appropriate reference due to the absence of comparable studies evaluating HCQ use among pregnant women with T2DM. The difference in the mean was 0.4, and the combined SD was 0.5. The statistical power was 80%, and the level of significance was 5%.

$$n = \frac{(u+v)^2(\sigma_1^2+\sigma_0^2)}{(\mu 1-\mu 0)^2}$$

μ=power 80% (0.84)
U=level of significance 95% CI (1.96)
μ1−μ0=mean difference in outcome of both groups
σ=SD of outcome in both groups

$$n = \frac{(0.84+1.96)^2(0.5^2+0.5^2)}{(1.3-0.9)^2}$$

n=25

Considering a 10% loss rate, 28 participants will be required in each arm, making a total sample size of 56.

Statistical analysis

Data analysis will be done using the Statistical Package for Social Sciences V. 26.0 (SPSS, Chicago, USA). Quantitative variables, such as women's age, BMI, parity, fasting and post-prandial glucose, will be presented as mean±SE of the mean. Categorical variables will be analysed using Pearson χ^2 and Fisher's exact test, while numerical variables will be analysed using t-tests and Pearson correlation. A repeated measures analysis of variance will be used to evaluate the effectiveness of the intervention. Additionally, an analysis of covariance will be conducted to control for potential confounding variables such as body

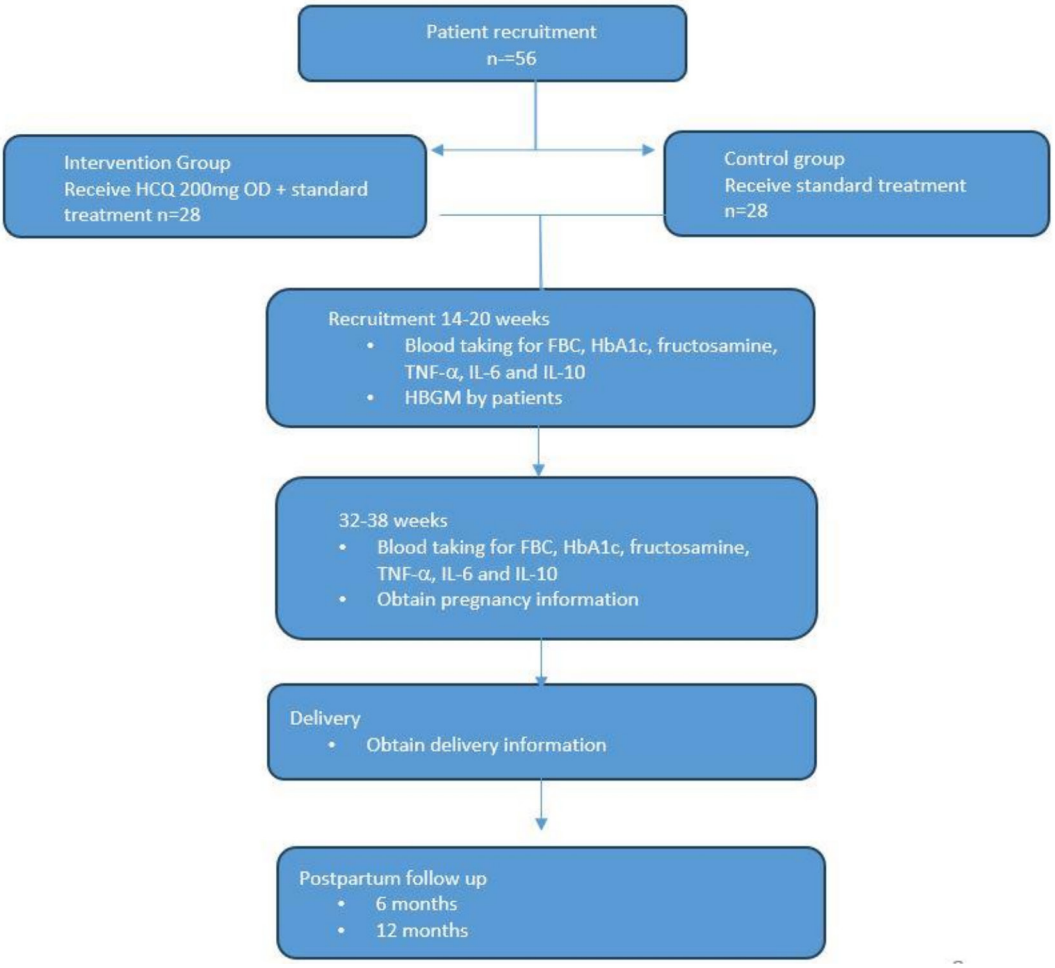

Figure 1 Study procedural flow chart. Overview of participant enrolment and study procedures. FBC, full blood count; HbA1c, haemoglobin A1c; HBGM, home blood glucose monitoring; HCQ, hydroxychloroquine; IL-6, interleukin-6; IL-10, interleukin-10; OD, once daily; TNF-α, tumour necrosis factor-alpha.

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mass index (BMI), maternal age and duration of T2DM. Otherwise, all the statistical tests will be two-tailed with a significance level set at p<0.05.

Patient and public involvement

Patients or the public were not involved in the design, conduct, or reporting or dissemination plans of our research.

Ethics and dissemination

The study will be conducted in compliance with the ethical principles outlined in the Declaration of Helsinki. The protocol has been approved by the National University of Malaysia Ethics Committee (JEP-2023-866) (online supplemental material 1). Written informed consent will be taken prior to study enrolment (online supplemental material 2). The Participant Information Sheet is provided in both English and Malay (online supplemental material 3). All participants will receive the standard medical care for their T2DM and pregnancy regardless of their group. Participation is voluntary. They have the right to withdraw at any stage of the research without giving any reason. Should there be any further amendments to the protocol, other than administrative ones, further approval will be obtained from the ethics committee. Any revisions of documents and amendments to the protocol originally submitted for review, unexpected events during the study period and new information that may adversely affect the safety of participants and publication will duly be communicated to the ethics committee.

Publication policy

Participants' personal information will not be disclosed nor identified when the findings of this research are published and presented.

Dissemination plan

Study findings will be presented in national and international scientific conferences, publication in peer-reviewed journals and sharing with healthcare professionals during professional training and meetings. Key findings will also be shared with community health professionals to inform future adjunctive management.

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Contributors NIB and RAR led the development of the study protocol. AMN, SI and PM contributed to the study design and methodological planning. NAW provided critical input on feasibility and implementation. NIB drafted the initial version of the protocol manuscript. RAR, NAW, AMN, SI and PM critically reviewed and revised the protocol for important intellectual content. All authors read and approved the final version of the protocol and agreed to be accountable for all aspects of the work. RAR is the guarantor for this protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the National University of Malaysia Ethics Committee (JEP-2023-866). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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