Towards Precision Medicine for Diabetes in Pregnancy

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In the present study, we propose to investigate the efficacy of pharmacological treatment of GDM (using metformin) by the pathophysiological cause of hyperglycemia, namely reduced insulin sensitivity or reduced insulin secretion. Primary Objective:...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON51350

Source
ToetsingOnline

Brief title
ToPMedDiP

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Maternal complications of pregnancy

Synonym
Diabetes in Pregnancy, Gestational Diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Zuyderland Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Continuous Glucose Monitoring, Gestational Diabetes, Insulin Sensitivity, Metformin

Outcome measures

Primary outcome

Study parameters will be collected at mid-gestation (24-27 weeks), end gestation (35-37 weeks), and 6 weeks after delivery, as indicated in Table 1.

Primary outcomes of this study will be time in range during 7 days continuous glucose monitoring. Requirement for additional insulin-treatment will be abstracted from medical records and reported in %.

Secondary outcome

Insulin sensitivity and sensitivity will be calculated as Matsuda-Index and Stumvoll-indices, using the available samples of the routine OGTT, namely 0, 60 and 120 min: Matsuda = 10,000/ SQRT(Gluc0 * INS0 * Glucmean * INSmean); Stumvoll(1st) = 1194 + 4.724 × Ins0 * 117.0 × Gluc60 + 1.414 × Ins60. Women will be classified as having low insulin secretion and/or low insulin sensitivity as <25th percentile of a reference cohort of 256 women at 24-28 weeks, characterized in 2019 at the Transmural Womens Daycare Center at Maastricht University Medical Center, in accordance with Powe et al.

Secondary outcomes will be HbA1c, the proportion of GDM-patients with no defined pathophysiology or patients with GDM not requiring medication, pre-pregnancy BMI, gestational weight gain, maternal and infant outcomes,

physical activity, eating behavior, body composition and time in (glucose) range and hyper and hypo-glycemic events as assessed by medical records abstraction, accelerometry, validated questionnaires, bioimpedance analysis, and continuous glucose monitoring, respectively. Furthermore, we will assess lipidemia and metabolic hormones, including glucagon, and prolactin.

Study description

Background summary

Gestational diabetes mellitus (GDM) affects up to one in six pregnancies in Europe,(1) and close to one in two pregnancies in women with obesity.(2) GDM increases the risk for pregnancy complications including preeclampsia, C-section and birth injuries. Moreover, impairments in glucose metabolism during pregnancy pertain after pregnancy(3-5) and increase the risk for obesity and type 2 diabetes mellitus in both the mother(6, 7) and the baby.(8-11)
In 2016, Powe and Hivert(12) demonstrated that GDM is heterogeneous in its pathophysiology and outcomes. In their cohort study, among the GDM-patients, 30% had impaired glucose-stimulated insulin secretion (pancreatic β-cell function), but were insulin sensitive (herein referred to as *GDM-Secretion*), whereas 50% were insulin resistant, ie low insulin sensitivity, but had normal insulin secretion (*GDM-Sensitivity*). In 2019, we have confirmed heterogeneity of GDM in a Dutch cohort (at MUMC), with comparable distributions (20% GDM-Secretion, 50% GDM-Sensitivity).
To date, the treatment of GDM is universal for all GDM patients. First hyperglycemia is targeted by lifestyle modification including dietary modification. For patients with persistent hyperglycemia, pharmacological intervention is initiated using metformin, an insulin-sensitizer. In case of insufficient repression of hyperglycemia by metformin, insulin is supplemented. Insulin is the last step of treatment because it can cause hyperinsulinemia and hypoglycemia in the mother and the infant. Metformin on the other hand passes the placenta and can have long-lasting effect on the infants metabolism. Importantly, the choice and efficacy of treatments is questioned because maternal, infant and long-term offspring outcomes for GDM are significantly worse as compared to women without GDM-diagnosis(13). Specifically, for patients requiring additional insulin-therapy, which is 15-46% based on current literature, delayed regression of hyperglycemia may adversely affect neonatal outcome. We have recently demonstrated that the total hyperglycemic exposure during pregnancy (as AUC) is most relevant towards infant outcomes that spot-assessments of hyperglycemia,(14) supporting the notion that a delay in

appropriate treatment will likely contributes to deleterious metabolic imprinting of the fetus.
Unequivocally, authors of clinical studies,(15-19) meta-analysis(20-22) and practical guidelines(23, 24) call for interventions more personalized to the patient, but surprisingly little guidance is offered as to how personalization should be attempted. In most reports, personalization of lifestyle modification refers to modulation of the intervention to facilitate adherence and thereby to increase the effect sizes on gestational weight gain or diet quality. The effect sizes of such intervention are small and poorly effective in reducing GDM. To our knowledge, only two studies (in the US) are currently performed to consider the heterogeneity of GDM in its treatment; both are currently ongoing, one using dietary intervention (PI: Powe, NCT04187521) and one pharmacological intervention (PI: Feghali NCT03029702), yet, as far as published records show, with different study designs, in different health acre contexts (more frequent insulin resistance and insulin-treatment, poorer health care), and in different study populations, ie US vs NL, likely with very different lifestyles.

Study objective

In the present study, we propose to investigate the efficacy of pharmacological treatment of GDM (using metformin) by the pathophysiological cause of hyperglycemia, namely reduced insulin sensitivity or reduced insulin secretion.

Primary Objective: to assess differences in efficacy of metformin-treatment in GDM patients with insulin resistance vs low insulin secretion on glucose control
Secondary Objective(s): to assess differences in efficacy of metformin-treatment in GDM patients with insulin resistance vs low insulin secretion on maternal and infant pregnancy outcomes, including but not limited to gestational weight gain, complications during delivery, and lfiestyle factors.

Study design

We will use an intuitive prospective, observational study design to compare efficacy of metformin-treatment in GDM-patients with low insulin sensitivity to GDM-patients with low insulin secretion. Participants will be recruited at 24-28 weeks gestation, when GDM is assessed in clinical practice,(2, 25) followed-up at a second visit late in pregnancy (35-37 weeks gestation) until their 6-week postpartum control visit. Recruitment will be performed at the Gynecology clinic of Zuyderland Medical Center. Outcomes will be assessed at both pregnancy visits, and selected outcomes again at the postpartum visit.

Study burden and risks

The associated risks are minimal, because treatment follows clinical practice. The addition catheters being placed carry the risk of inducing slight bruises.

Given the observational nature of this study on patients treated per routine practice, study-participation invokes no group-related risk.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

having a confirmed single, viable pregnancy past 20 weeks gestation
Diagnosed GDM and treated with Metformin (as prescribed by Ob/Gyn)

Exclusion criteria

pre-existing diabetes

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-10-2023
Enrollment:	45
Type:	Actual

Ethics review

Approved WMO Date:	11-08-2022
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	09-07-2024
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL80773.096.22