Pregnancy Outcomes: Effects of Metformin Study (POEM Study), a long term randomized controlled study in gestational diabetes mellitus

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This study has been transitioned to CTIS with ID 2024-519386-21-00 check the CTIS register for the current data. The central aim of the POEM Study: to investigate whether the early start of metformin on top of standard care may improve the treatment...

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

Summary

ID

NL-OMON54531

Source
ToetsingOnline

Brief title
POEM Study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)
- Pregnancy, labour, delivery and postpartum conditions

Synonym
Gestational Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Bethesda Diabetes Research Center
Source(s) of monetary or material Support: Ministerie van OC&W,aanvraag bij diabetesfonds;provincie;gemeentes ,Novo Nordisk,Sanofi-aventis

Intervention

Keyword: Diabetes, Gestational Diabetes Mellitus, Metformin, RCT

Outcome measures

Primary outcome

Main endpoint:

The GDM Outcome Score (GOS) has been defined as the composite endpoint at delivery for the power analysis and sample size calculation of the POEM Study, based on the existing international literature (Ainuddin 2015; Balsells 2015; Balani 2009; Goh 2011) and the Dutch pregnancy outcomes in general practice. GOS consists of eight components (with estimated prevalence in GDM): large for gestational age baby (20%), premature delivery (5%), admission for neonatal care (5%), instrumental delivery (10%), birth trauma (5%), neonatal hypoglycaemia (10%), caesarean delivery (15%), and pregnancy related hypertension (15%), with an estimated cumulative prevalence of 85%.
The individual GOS is the crucial primary endpoint in Phase A of the POEM Study, being defined as a continuous, individual variable for each pregnancy, ranging from 0 to 8. Additionally, as a semi-quantitative variable the dichotomous endpoint GOS positive (1-8) versus GOS negative (0) will be evaluated as a variant of the primary endpoint. The occurrence of T2D and weight development in the mother and weight development in the child are the

three co-primary endpoints in Phase B & C of the POEM Study.

Secondary outcome

Mother:

Different subtypes of maternal hypertension: pre-eclampsia, eclampsia and gestational hypertension

Proteïnuria (% of pts with A/C > 3,5 mg/mmol; mean ± SD)

Maternal glycemic control

Postpartum glucose tolerance

Maternal weight gain (kg) and change in body composition (fat impedance) from inclusion until delivery

Insulin rescue after failure of study medication (% of pts)

Maternal urinary tract infection (% of patients)

Caesarean delivery (% of pts)

FPG (mean ± SD)

Acceptability of treatment according survey: % of patients preferring the treatment received during the trial (M vs I)

Maternal mortality

Thrombosis (in pregnancy and/or childbed)

Maternal metabolic variables from blood samples, including blood cell counts, kidney and liver functions, lipids, vitamin spectrum, calcium, albumen, phosphate, magnesium, TSH, uric acid, FPG, insulin and C-peptide.

Diabetes development

Weight development

Hypertension development

Thrombotic and CV incidents

Child:

Fetal macrosomia (birth weight > 4,000 grams) and customized

large-for-gestational-age infants

Birth trauma

Miscarriages and stillbirth

Neonatal anthropometric measurements

Intra-uterine development measured by ultra-sonography (skull, abdominal

circumference (AC), length and other variables) with intervals of 4 weeks;

neonatal body composition

Preterm birth before 37 weeks

Dystocia of the shoulder during delivery

Neonatal plasma glucose (mean ± SD)

Neonatal hypoglycaemia < 3.8 mMol

Neonatal jaundice (prematurity of the liver)

Need for phototherapy (%)

Neonatal admission of any cause

Urgency for intensive neonatal care (NICU)

Apgar scores (mean ± SD)

Prematurity

Neonatal mortality

CongeniGrowth and weight development

Gonadal and gender development

Educational and intellectual development (level of education achieved during

phase C)

Development of any chronic disease

tal anomaly

Neonatal metabolic variables from blood samples through the umbilical cord,

including blood cell counts, kidney and liver functions, lipids, vitamin

spectrum, calcium, albumen, phosphate, magnesium, TSH, uric acid, FPG, insulin

and C-peptide. Also gene expression will be studied (methylation of RNA, DNA).

Neonatal urine samples for storage at -80 oC.

Study description

Background summary

The POEM Study is an original and new RCT, designed to investigate the (long-term) effects of metformin on top of standard of care (diet + lifestyle + insulin rescue if needed) in gestational diabetes mellitus (GDM). The following outcomes in mother and child are studied:
• pregnancy outcomes at delivery, the GDM Outcome Score (GOS), a composite primary endpoint consisting of eight components: (1) large for gestational age baby (LGA), (2) premature delivery, (3) admission for neonatal care, (4) instrumental delivery, (5) birth trauma, (6) neonatal hypoglycaemia, (7) caesarean delivery, and (8) pregnancy related hypertension;
• metabolic, growth, cognitive and gender outcomes (like the development of obesity, diabetes, chronic morbidity and other variables) up to 20 years after delivery.

Background of GDM.
GDM is an expression of insulin resistance during pregnancy with an increasing prevalence of 5-10% in registered pregnancies (2007-2010). However, the occurrence of GDM may be underestimated worldwide, since the screening and detection of GDM is suboptimal. Moreover, the prevalence of GDM is still increasing as the pregnant population becomes older and more obese. The presence of diabetes before pregnancy excludes the diagnosis GDM, since, by definition, GDM is prediabetes being converted into type 2 diabetes (T2D) during pregnancy.

Effects of GDM on fetal and maternal outcomes.
GDM may occur from week 16 in pregnancy. Though GDM itself does not affect the organogenesis in the first 12 weeks of pregnancy, GDM harms mother and child through unfavorable effects on outcomes of pregnancy with increased risks of macrosomia (birth weight >4,000 grams) and/or large-for-gestational-age infants (LGA), being related with fetal steatosis, enlarged placenta and polyhydramnion; preterm births; dystocia of the shoulder during delivery; instrumental delivery; Caesarean delivery; fetal neonatal hypoglycemia; fetal prematurity of organs (neonatal jaundice due to prematurity of the liver); neonatal admission; maternal pre-eclampsia and eclampsia; maternal urinary tract infections. Moreover, GDM is associated with increased risks of maternal T2D (50% within 5 years after GDM) and obesity, as well as T2D in the offspring. In addition, insulin resistance preceding GDM may also unfavorably affect the earlier course of pregnancy.

Treatment of GDM and need for insulin sensitizing strategies.
Insulin therapy added to a low carbohydrate diet is still the standard of care for GDM. Insulin therapy, however, increases appetite, weight gain and the risk of hypoglycaemia. Even if tight insulin therapy is successful, women with GDM still have an increased incidence of obstetric and neonatal complications as compared to non-diabetic controls. All these findings lead to the urgency for better strategies for the treatment of women with GDM. Not only glucotoxicity, but also (exaggerated growth inducing) mechanisms related to increased insulin resistance in pregnancy may contribute to unfavorable outcomes of GDM in mother and child. Therefore, the insulin sensitizing, orally administered biguanide metformin may have specific benefits in the treatment of GDM - as have been shown in T2D, the ultimate state of insulin resistance. However, RCT*s with metformin in GDM and long term follow up are still lacking. Still no scientific data are available about the long term effects of metformin during GDM, in mother and child many years after delivery.

Metformin: new perspectives in the treatment of GDM.
Increasing observational studies on metformin in GDM indicate that treatment with metformin seems at least as safe and effective compared to insulin with clinically relevant outcomes. These observations support that pregnant women treated with metformin may gain less weight, may develop less often pregnancy-induced hypertension, may have fewer preterm births and may have improved neonatal outcomes compared with those treated with insulin. Very recently, prevention of maternal weight gain during and after GDM has appeared to be an important predictor for the conversion of GDM into T2M. Although these observational studies are promising, the small numbers and the open label designs limit definite conclusions. RCT*s offering convincing evidence for the use of metformin in GDM are needed. Therefore, we designed the POEM trial with an intensive follow-up during pregnancy and a long term extension period of 20 years thereafter to evaluate the durable safety and efficacy of metformin in GDM for mother and child.

Metformin: safety in GDM.
Although it is known that metformin crosses the placenta, cohort studies and meta-analysis did not show a drug safety issue about metformin use in patients with GDM (exposure to metformin during gestational age of 20-40 weeks), and in patients with polycystic ovary syndrome - being an indication for metformin treatment to restore fertility - after becoming pregnant (exposure to metformin during gestational age of 0-40 weeks), if contraindications are excluded. Very recently, a systematic review and meta-analysis on glibenclamide, metformin and insulin for the treatment of GDM shows favorable outcomes for metformin concerning birth weight, risk of macrosomia, risk of neonatal hypoglycaemia and maternal weight gain. Metformin is generally considered a safe and non-teratogenic drug. However, most studies were underpowered for the evaluation of safety. RCTs are needed to provide conclusive safety data of metformin in GDM. Trials like the POEM trial are required to determine an evidence based position of metformin in the new guidelines for the treatment of GDM.

Study objective

This study has been transitioned to CTIS with ID 2024-519386-21-00 check the CTIS register for the current data.

The central aim of the POEM Study: to investigate whether the early start of metformin on top of standard care may improve the treatment of GDM for mother and child. Metformin is used as a tool to reduce insulin resistance, the underlying cause of GDM. In the POEM Study, the effects of metformin on top of standard care in GDM are compared during pregnancy until 6 weeks after delivery (Phase A), from 6 weeks until 1 year after delivery (Phase B) and from 1 until 20 years after delivery (Phase C) with more specified objectives reflected by well-defined clinically relevant endpoints (Table 1 of protocol).

The main hypothesis of the POEM Study: This is the first RCT to test the hypothesis that metformin (particularly early given from the start of the diagnosis GDM) versus controls with insulin rescue in both study arms improves clinically relevant outcomes in mother and child during pregnancy, at delivery and over the long term of 20 years after delivery - on top of standard of care. We hypothesize that metformin given to women with GDM will reduce the GOS, a continuous variable (range: 0-8) expressing the presence of 0-8 outcomes per pregnancy: large for gestational age baby (LGA), premature delivery, admission for neonatal care, instrumental delivery, birth trauma, neonatal hypoglycaemia, caesarean delivery, and pregnancy related hypertension), as well as the future life risks of obesity, metabolic syndrome and diabetes in mother and child, puberty and adolescence included.

The approach to test this hypothesis: The standard of care for the treatment of GDM can be defined as a triad: intensive counseling for diet and lifestyle + intensified follow-up + rapid insulin rescue if needed, according to validated

international guidelines (ADA and EASD).
The additional reduction of the (growth promoting) hyperinsulinaemia by metformin is expected to favor the outcomes of GDM in mother and child, considering the results of observational studies described above. The design of this RCT will permit a reliable comparison between the two study arms, metformin users or controls, to test the main hypothesis of the POEM Study. The early start of the study medication, the design and the long period of follow up, together, may strengthen this RCT to detect a realistic effect of metformin (early targeting the causal insulin resistance of GDM) on clinically relevant outcomes.

Study design

This study is a multicenter randomized controlled trial comparing metformin versus controls in 500 patients with GDM (n1 = n2 = 250, randomized 1:1) on top of counseling for diet and lifestyle, the standard of care. In cases of failure to reach treatment goals, insulin rescue will follow in both arms - expected to be less needed in the metformin group. All patients will be treated to target accordingly to the guidelines and GCP (intensive follow-up during pregnancy), reflected in the study protocol. After delivery, mother and child are followed for a period of 20 years. Study medication is continued until 1 year after delivery. If during the long-term follow-up another pregnancy occurs, the original treamtent will be repeated according protocol. These secondary pregnancies will be evaluated within the POEM Study.

Design with three phases. The POEM Study is divided into three phases:
• Phase A - from inclusion until 6 weeks after delivery; interventional study with exposure of M vs C in mother and (unborn) child;
• Phase B - from 6 weeks until 1 year after delivery; interventional study with exposure of M vs C in mother;
• Phase C - from 1 until 20 years after delivery; observational extension study in mother and child.

Setting of the study. The POEM Study will be performed in the setting of the multidisciplinary outpatients clinics (Endocrinology, Diabetology, Obstetrics) in The Netherlands.

Intervention

This study is an RCT comparing metformin versus controls in 500 patients with GDM (n1 = n2 = 250) on top of counseling for diet and lifestyle. Metformin tablets of 850 mg will be titrated within the first three weeks after inclusion from once up to three times daily, if tolerated. The maximally tolerated dose will be continued until 1 year after delivery. If the aim of target values of glycaemic control is not met during GDM, insulin rescue will be started according to best medical care. If the aim of target values of glycaemic

control is not met during Phase B and/or C, anti-hyperglycemic treatment will be extended (or started) according actual guidelines for the treatment of type 2 diabetes.
Metformin: safety in GDM. Cohort studies and meta-analysis did not show a drug safety issue about metformin in patients with GDM (gestational age 20-40 weeks), and in patients with polycystic ovary syndrome (PCOS) after becoming pregnant (gestational age 0-40 weeks), if contraindications are excluded. Metformin is generally considered a safe and non-teratogenic drug.

Study burden and risks

The POEM Study and its intervention (metformin on top of standard care) is considered rather safe and even potentially beneficial, based on observational data.

Discomfort as mentioned in Section:
- side effects of Metformine (e.g. gastro-intestinal complaints)
- discomfort by blood drawing
- nausea by OGTT.

The POEM Study has a negligible risk according to the METC risk classification of the VU Medical Center Amsterdam.
Use of metformin has a risk of lactic acidosis in the presence of contra-indications, like diarrhea, dehydration and sepsis. Therefore, use of metformin will be stopped if contra-indicated.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

- Pregnant women with gestational diabetes mellitus (GDM) defined as a FPG >/= 5,3 mMol and/or an OGTT with a PG >/= 7,8 mMol, two hours after the oral intake of 75 gram glucose
- Written informed consent
- Age 18-45 years
- Gestational age at inclusion 16-34 weeks
- HbA1c at inclusion <= 48 mmol/mol (6.5% Hb)

Exclusion criteria

- Diabetes Mellitus before pregnancy, except previous GDM
- Proteïnuria (ACR > 35 mg/mmol) at screening
- Malignancy during the last 5 years before inclusion, except non-melanoma skin cancer
- Psychiatric and/or mood disorder potentially affecting compliance of treatment
- Chronic liver failure and/or ASAT and/or ALAT > 3x ULN
- Chronic renal failure with a GFR < 45 ml/min/1.73m2
- Chronic pulmonary failure with hypoxia
- Significantly uncontrolled hypertension - SBP > 160 mm Hg despite medical treatment
- Chronic treatment with oral corticosteroids
- Intolerance for metformin and/or earlier use of metformin in this pregnancy
- Membership of the POEM study group

- Severe fetal anomaly at inclusion - like major neural tube defect or malformation of heart and/or large vessels
- Ruptured membranes
- Gemelli (twin pregnancy)
- Bariatric surgery in medical history
- Current hyperemesis gravidarum

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-11-2019
Enrollment:	1000
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Metformin HCL TEVA 850 mg
Generic name:	Metformin HCL TEVA 850 mg
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-01-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-06-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
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Application type:	Amendment
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Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-05-2022
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Approved WMO Date:	19-08-2022
Application type:	Amendment
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-01-2023

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-08-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-10-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EU-CTR	CTIS2024-519386-21-00
EudraCT	EUCTR2015-002148-15-NL
ClinicalTrials.gov	NCT02947503
CCMO	NL56411.000.17