BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056282
Article Type:	Protocol
Date Submitted by the Author:	17-Aug-2021
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Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, OBSTETRICS, PAEDIATRICS

Pregnancy Outcomes: Effects of Metformin (POEM) study: a protocol for a long-term, multicentre, open-label, randomised controlled trial in gestational diabetes mellitus

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Word Count: 3465

ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is a common disorder of pregnancy with health risks for mother and child during pregnancy, delivery, and further lifetime, possibly leading to type 2 diabetes mellitus (T2DM). Current treatment is focused on reducing hyperglycaemia, by dietary and lifestyle intervention and, if glycaemic targets are not reached, insulin. Metformin is an oral blood glucose lowering drug and considered safe during pregnancy. It improves insulin sensitivity and has shown advantages, specifically regarding pregnancy-related outcomes and patient satisfaction, compared to insulin therapy. However, the role of metformin in addition to usual care is inconclusive and long-term outcome of metformin exposure in utero are lacking. The primary aim of this study is to investigate the early addition of metformin on pregnancy and long-term outcomes in GDM.

Methods and analysis: The POEM study is a multicentre, open-label, randomised, controlled trial. Participants include women with GDM, between 16 and 32 weeks of gestation, who are randomised to either usual care or metformin added to usual care, with insulin rescue in both groups. Metformin is given up to one year after delivery. The study consists of three phases (A-C): A – until 6 weeks after delivery; B – until 1 year after delivery; C – observational study until 20 years after delivery. During phase A, the primary outcome is a composite score consisting of: (1) pregnancy-related hypertension, (2) large for gestational age neonate, (3) preterm delivery, (4) instrumental delivery, (5) caesarean delivery, (6) birth trauma, (7) neonatal hypoglycaemia, (8) neonatal intensive care admission. During phase B and C the primary outcome is the incidence of T2DM and (weight) development in mother and child.

Ethics and dissemination: The study was approved by the Central Committee on Research Involving Human Subjects in the Netherlands. Results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT02947503.

STRENGHTS OF THIS STUDY

- The POEM study is the first RCT to test the hypothesis that early initiation of metformin at the start of the diagnosis GDM added to dietary and lifestyle intervention (versus dietary and lifestyle intervention alone) improves clinically relevant outcomes in mother and child.
- The POEM study is the first RCT that studies the effects of metformin in GDM on mother and child during pregnancy, at delivery and for 20 years thereafter.
- The POEM study is the first RCT that studies the effects of continuing metformin exposure in the direct post-partum period (during lactation).

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common disorders of pregnancy with a prevalence estimated up to 17% worldwide. There is a wide variation between countries, due to different populations, screening approaches and diagnostic criteria.[1–5]

GDM is an expression of chronic insulin resistance, worsened by the hormonal and metabolic physiology of pregnancy and inadequate pancreatic β-cell adaptation.[6–9] Women are often asymptomatic and therefore testing occurs in women with risk factors for GDM with a fasting plasma glucose and an oral glucose tolerance test. GDM is associated with suboptimal maternal and neonatal outcomes such as offspring large for gestational age (LGA), macrosomia, shoulder dystocia, pregnancy-related hypertension, caesarean section, neonatal hyperinsulinemia and hyperbilirubinemia.[10–13] After delivery both mother and child show an increased risk of cardiometabolic disease, specifically obesity and progression to type 2 diabetes mellitus (T2DM) in mothers, and early childhood obesity and development of (pre)diabetes in adolescence.[14–18]

Prior research has shown strong associations between maternal blood glucose levels – even in the near-normal range - and pregnancy-related outcomes as well as childhood adiposity and insulin resistance.[15,18,19] Therefore, current treatment primarily strives to normalize glycaemic levels and consists of dietary and lifestyle interventions with regular self-monitoring of blood glucose levels.[20] If blood glucose levels exceed the target ranges, antihyperglycemic medication is recommended. Most treatment guidelines recommend insulin therapy as the first choice.[20] However, insulin has several disadvantages as it is associated with increased maternal weight gain, maternal and neonatal hypoglycaemia and patients are burdened with storage, intensified self-monitoring and frequent subcutaneous injections.[21] In addition, insulin therapy is costly and burdens the health care system by medical education and frequent contacts. Finally, although insulin administration could compensate for the β-cell dysfunction, insulin sustains the hyperinsulinemia and does not treat the underlying insulin resistance. Perhaps this explains why women with GDM and with optimal glycaemic control still show unsatisfactory (pregnancy) outcomes.[13,22,23]

Mechanisms related to insulin resistance rather than low-grade glucotoxicity may contribute to the pathophysiology of the complications in GDM. This makes metformin a logical option for women with GDM. Metformin (dimethylbiguanide) is an oral blood glucose lowering drug (OBGLD) and has numerous mechanisms of action. It primarily inhibits the gluconeogenesis in the liver and acts as a insulin sensitizer – especially in the liver, and to a lesser extent in muscle and adipose tissue.[24,25] Additionally, it improves glucose sensing in the intestine and mechanisms through the incretin system are also involved.[25–27] Since insulin secretion is unaltered, the risk of hypoglycaemia is negligible.[28] Metformin is widely used in T2DM and to a lesser extent in GDM. In GDM, metformin compared to insulin and other OGBLD, reduces maternal and neonatal weight gain, the risk of pregnancy related hypertension, neonatal intensive care admission and hypoglycaemia.[24,29–32] Additionally, metformin shows anti-inflammatory and anti-thrombogenic effects [33–37] and higher patient satisfaction compared to insulin.[21] Several international treatment guidelines already recommend metformin treatment above insulin therapy if dietary and lifestyle interventions fail to adequately treat hyperglycaemia.[38–40] No studies on the use of metformin prior to considering insulin therapy exist.

Although hyperglycaemia usually resolves between 48 hours post-partum, most GDM patients have a degree of chronic insulin resistance,[41] which persists after delivery and is

not treated adequately with current therapy. It is hypothesized that the addition of metformin to GDM care reduces the risk of developing T2DM.[16,42,43] In mice, metformin exposure in utero and during lactation has shown to improve glucose tolerance and insulin secretion in the adult male offspring.[44,45] Additionally, metformin reduces the incidence of T2DM in pre-diabetic adults with and without a history of GDM.[42,43] Despite these findings, no studies investigated the effects of continued administration of metformin in the direct post-partum period.

Despite the confirmed and theoretical advantages of metformin, its role in treatment guidelines is still inconclusive. The POEM study aims to address this unmet need – as a long-term RCT. In this RCT we will study the effects of immediate metformin treatment added to dietary and lifestyle intervention from the start of GDM, on a broad spectrum of outcomes in mother and child, up to 20 years after delivery.

METHODS

Design and setting

The POEM study is a long-term, multicentre, randomised controlled, open-label, trial comparing usual care to metformin added to usual care. The trial consists of three distinct phases (A, B and C), and has a 20 year follow-up period after delivery.
Phase A (from inclusion until 6 weeks after delivery) and phase B (from 6 weeks until 1 year after delivery) are the interventional phases, while phase C (from 1 until 20 years after delivery) is the long-term observational phase.
The study will be conducted in the Netherlands and embedded in regular care with multidisciplinary GDM treatment teams usually consisting of a gynaecologist, internist, diabetes specialist nurse, midwife and dietician.

Ethical compliance

The methods employed in this trial were judged and approved by the Central Committee on Research Involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, CCMO, the National Medical Ethical Committee in the Netherlands). EudraCT number is 2015-002148-15. The trial was registered prospectively in the United States Clinical Trial registry (NCT02947503).

Public involvement

The Dutch Diabetes Association was involved in the preparation of this trial and approved the protocol.

Study population

GDM is diagnosed using a 75-gram oral glucose tolerance test (OGTT) according to the national Dutch guidelines.[20] Currently, screening for GDM in the Netherlands occurs based on predisposing risk factors, to be known; BMI > 30 kg/m², a history of a neonate with a birth weight > p95 or > 4500 grams, a first degree family member with diabetes mellitus, ethnic groups with a higher risk of diabetes mellitus (Hindus and women from South-Asia, Afro-Caribbean, Middle-East, Morocco or Egypt), a medical history of unexplained foetal death and women with polycystic ovary syndrome. Women with these risk factors are tested between 24-28 weeks of gestation. Women with a medical history of GDM are tested at 16 weeks of gestation.[20] The OGTT is also performed in case of clinical features of GDM such as suspected macrosomia or polyhydramnios.

Women are eligible for inclusion in this study if they have a fasting plasma glucose (FPG) ≥ 5.3 mmol/l and/or a 2-hour post-load glucose ≥ 7.8 mmol/l after a 75-gram OGTT. This inclusion strategy is based on national guidelines and the WHO criteria of 1999 and 2013, also including mild cases of GDM given this population also exhibits some degree of chronic insulin resistance and consequently sub-optimal outcome.[15,46]
The inclusion and exclusion criteria are listed in Table 1. The upper gestational age limit for inclusion is set at 32 weeks, to allow at least 6 weeks of metformin exposure during pregnancy. With the current screening policy, we expect that most participants will be treated ≥ 12 weeks during phase A.

Inclusion and randomisation
Eligible women will be informed about the study by either a research nurse, investigator or a healthcare provider (internist, diabetes specialist nurse, midwife or gynaecologist). Prior to participation written informed consent is obtained. Participants are randomised, stratified for age and duration of pregnancy and allocated 1:1 to either metformin and dietary and lifestyle intervention (MDL) or to dietary and lifestyle intervention alone (DL). Randomisation with stratification (for age and pregnancy duration) will be performed in the electronic case report form (eCRF) using Castor EDC.

The flowchart for eligibility, randomisation, intervention and control group and visit frequencies in the three phases of this study is presented in Figure 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Pregnant women with GDM defined as a FPG ≥ 5,3 mmol/l and/or an OGTT with a PG ≥ 7,8 mmol/l, two hours after the oral intake of 75 gram glucose
2. Age 18-45 years
3. Written informed consent
4. Singleton pregnancy
5. Gestational age at inclusion 16-32 weeks
6. HbA1c at inclusion ≤ 48 mmol/mol

Exclusion criteria
1. Diabetes Mellitus before pregnancy, except GDM
2. Proteinuria (UACR > 35 mmol/mol) at screening
3. Chronic liver disease and/or ASAT/ALAT >3x ULN
4. Chronic renal failure with GFR < 45 ml/min/1.73 m2
5. Malignancy during the last 5 years, except non-melanoma skin cancer
6. Psychiatric and/or mood disorders potentially affecting compliance of treatment
7. Chronic pulmonary failure with hypoxia
8. Significantly uncontrolled hypertension (SBP > 160 mmHg despite medical treatment)
9. Chronic treatment with corticosteroids
10. Intolerance for metformin and/or earlier use of metformin in this pregnancy.
11. Involvement in the POEM study
12. Severe foetal anomaly at inclusion
13. Ruptured of membranes (ROM)
14. Inability to understand or read Dutch language
15. Bariatric surgery in medical history

FPG = fasting plasma glucose , OGTT = oral glucose tolerance test, GDM = gestational diabetes mellitus, UACR = urine albumin creatinin ratio, ULN = upper limit of normal, SPB = systolic blood pressure.

Intervention: metformin
The intervention group will receive metformin tablets of 850 mg (TEVA), titrated within approximately 15 days up to three times daily, if tolerated. The maximally tolerated dose will be continued until 1 year after delivery. Metformin will be stopped according to clinical judgement during, for example, severe diarrhoea with dehydration, severe illness with fever and/or sepsis.

Obstetric care
Obstetric care will be performed according to usual practice of the participating centre. Regular ultrasonography with foetal biometry (abdominal circumference, femur length, head circumference, estimated foetal weight and amniotic fluid volume) is performed approximately every four weeks. Timing of delivery will be performed according to usual practice of GDM with dietary and lifestyle intervention without insulin, which is often an expectant approach. If insulin rescue is needed, or in case of expected LGA, it is generally recommended to consider induction of labour around 38-39 weeks.[20]

Diabetes care
All participants will be referred to a diabetes specialist nurse, dietician and internist according to routine GDM care. In both groups, glucose monitoring and dietary and lifestyle intervention will be performed according to usual care with guidance by a diabetic nurse and a dietician. The diabetes specialist or research nurse instructs the participants about measuring procedures according to national guidelines.[47] CareSens^{TM} glucose meters will be used as the standard system for blood glucose measurements in all participants. Dietary and lifestyle interventions are embedded in regular care, and are performed according to the Dutch and WHO guidelines (physical activity and a well-balanced diet with carbohydrate redistribution and (mild) carbohydrate restriction).[48]

The participants will be asked to collect two 7-point blood glucose profiles in the week prior to the research visits. For the other weeks participants will collect 4-point blood glucose profiles according to usual care. The blood glucose levels will be reviewed by a diabetes nurse specialist or medical doctor at least every 1-2 weeks. At inclusion, laboratory safety tests will be performed to exclude e.g., renal- or liver diseases. Glycated haemoglobin (Hba1c), renal and liver function will be checked every 8 weeks in phase A.

In both groups, insulin rescue will be started at the discretion of the internist if the allocated treatment is not sufficient to achieve the target values of glycaemic control at least more than two times (FPG $\leq$ 5.3 mmol/l and PG < 7.8 mmol/l). According to normal standard of care, the internist may choose to commence insulin rescue only temporarily if there is a reversible factor for dysregulation (medication/food/stress/fever).
If target values are not met more than two times in Phase B or C (FPG $\leq$ 7.0 mmol/l or PG $\leq$ 10.0 mmol/l), anti-hyperglycaemic treatment will be started (or extended) according to national guidelines for the treatment of T2DM.[49]

Neonatal care
Neonatal care will be performed according to usual care. Most sites will perform glucose monitoring if the neonate has a birth weight > p90 and/or if mother receives insulin therapy.

Follow-up and data collection
The follow-up and data collection per visit are presented in Table 2. All data will be recorded in the eCRF per site. In phase A, participants will have visits every four weeks until delivery,

and 6 weeks after delivery. In phase B, participants will have visits twice a year, at 6 and 12 months after delivery. In phase C, participants will have visits once a year for a duration of 20 years after delivery. Additional blood samples from the mother (research panel) and urine samples from the child will be collected and stored at -80 °C for later analyses and to study the effects of metformin regarding metabolic, development and safety outcomes.

Table 2. Measurements per visit

Phase A										**Phase B**			**Phase C**
		R							**D**				
Visit number	1	2	3	4	5	6	7	8	9	10[1]	11	12	13 to 31
Weeks	-1	0	4	8	12	16	20	24					
Time (mo) after delivery										1,5	6	12	2 to 20 years
Visit window (±days)	7	7	7	7	7	7	7	7	7	7	14	14	14
General													
Baseline characteristics	X												
Medical/obstetric history	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
Physical examination		X								X		X	Every four visits
Vital signs, body weight	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
7 points BGM review		X	X	X	X	X	X	X		X	X	X	
AE/SAE/endpoint report		X	X	X	X	X	X	X	X	X	X	X	Every visit
Check compliance			X	X	X	X	X	X		X	X	X	
Check GOS									X	X			
Check fetal sonography		X	X	X	X	X	X	X					
EQ-5D-5L and WHO-5		X		X		X				X		X	Every other visit
Lactation evaluation										X	X	X	
Development child										X	X	X	Every visit
Samples													
Safety panel mother[2]	X									X		X	
Regular panel mother[3]		X		X		X		X		X	X	X	Every visit
Research panel mother		X		X		X		X		X	X	X	Every visit
OGTT mother[4]	X									X			Every other visit
Morning urine mother		X		X		X		X		X		X	Every four visits
Urinalysis		X		X		X		X					
Morning urine child										X		X	Every four visits
Delivery													
Umbilical cord sampling									X				
Histological samples									X				
Neonatal glucose[5]									X				
First urine child									X				

R = randomisation
D = delivery
[1] Visit 10 is completing phase A and starting phase B
[2] Safety panel (fasting): UACR, blood cell count, haemoglobin, creatinin, urea, sodium, potassium, albumen, calcium, phosphate, γGT, AF, ASAT, ALAT, LDH, CRP, TSH, FT4, anti-TPO.
[3] Regular panel (fasting): Hba1c, haemoglobin, FPG, creatinin, ASAT, ALAT, B12, MMA (if B12 < 220 mmol/l)
[4] When the OGTT is performed prior to visit 1, this data will be used

[5] According standard of care a neonatal plasma glucose can be measured postpartum
BGM = blood glucose monitoring, AE = adverse event, SAE = serious adverse event, GOS = GDM outcome score, OGTT = oral glucose tolerance test

Additional pregnancies

If a new pregnancy occurs during phase B, this pregnancy will be entirely exposed to the allocated treatment strategy. There is no evidence for safety issues concerning metformin exposure in the first trimester.[50–55] If a pregnancy occurs during phase C this pregnancy will be treated according to regular clinical practice.

Primary outcome measures

The primary outcome measure during phase A consists of a composite endpoint at delivery and is termed the GDM Outcome Score (GOS). The GOS is an ordinal variable ranging from 0-8 and consists of eight components which are shown in Table 3. Additionally, the dichotomous endpoint GOS positive (1-8) versus GOS negative (0) will be evaluated as a variant of the primary outcome. The incidence of T2DM and weight development in mother and child are the co-primary outcome measures in Phase B and C.

Table 3. Primary outcome measures

Phase A	Phase B and C
GDM Outcome Score (GOS) score (range 0-8):	Incidence of maternal T2DM
1. Pregnancy related hypertension	Weight and BMI (category) development mother
2. Large for gestational age (LGA) at delivery (weight > 90th percentile)	Weight and BMI (percentile) development child
3. Premature delivery (< 37.0 weeks of gestation)	
4. Instrumental delivery	
5. Caesarean delivery	
6. Birth trauma	
7. Neonatal hypoglycaemia (< 2.6 mmol/l)	
8. Admission to the neonatal intensive care unit	

Secondary outcome measures

The secondary outcome measure during phase A consists of two composite endpoints at delivery and is termed the maternal outcome score (MOS) and neonatal outcome score (NOS). Both are ordinal variables consisting of the components shown in Table 4. Moreover, each separate component of the eight components of GOS is a secondary endpoint in Phase A.

The Dutch version of the EuroQol-5D-5L (EQ-5D-5L) and The World Health Organisation-Five Well-Being Index (WHO-5) will be administered to evaluate health-related quality of life. The EQ-5D-5L is a commonly used questionnaire to measure health-related quality of life.[56] This questionnaire can be used to obtain quality-adjusted life years (QALYs). Using the Dutch algorithm,[57] a utility score can be produced ranging from 0 to 1, with 0 indicating the worst imaginable health and 1 indicating the best imaginable health state.[57] The WHO-5 is a 5-item short and non-invasive generic rating scale measuring subjective psychological well-being.[58] The questionnaire consists of five items and the participant is asked to rate how well each of the 5 statements applies to her when considering the last 14 days. It has been used as a screening tool for depression but is also widely used as outcome measure in clinical trials to capture (improvement in) well-being caused by various pharmacological interventions.[58,59]

Finally, biometric, metabolic and hormonal variables collected during the study will be evaluated as a variant to the secondary outcome during phase A and B. During phase C, the secondary outcome concerns the developmental milestones of the child and development of

chronic disease for mother and child. A complete overview of secondary outcome measures is presented in appendix 1.

Table 4. Secondary outcome measures

Phase A	
Mother	**Child**
Maternal outcome score (MOS):	*Neonatal outcome score (NOS):*
Caesarean delivery	IRDS requiring oxygen therapy
Pre-eclampsia, eclampsia, HELPP and PIH	Stillbirth and neonatal death
Maternal mortality	Preterm birth
Postpartum haemorrhage	Shoulder dystocia
Thrombosis	Instrumental delivery
Each separate maternal component of GOS	Caesarean delivery
	Neonatal hypoglycaemia < 2.6 mml/l
	Neonatal jaundice needing phototherapy
	NICU admission
	Apgar score as a variable
	Apgar score < 7 at 5 minutes
	Congenital anomaly
	Each separate neonatal component of GOS
Phase B and C	
Mother	**Child**
Hypertension development	Gonadal and gender development
Thrombotic and CVD events	Puberty and maturation
Development of chronic disease	Educational and intellectual development
	Development of chronic disease

Drug safety

Observational studies and randomised trials did not show a drug safety issue in patients with GDM, polycystic ovarian syndrome (PCOS), T2DM and obesity.[21,51–53,55,60] Metformin is considered as a safe and non-teratogenic drug.[50,54,55] Limited concentrations of metformin are observed in breast milk (median concentrations ranging between 0,17-0,41 mg/L).[61–63] The mean relative infant dose ranges between 0.20-0.65% of the weight adjusted maternal dose.[61–63] Metformin use during lactation did no show adverse effects on the infants blood glucose levels or on growth, motor and social development.[61–64]

Safety monitoring

According to the risk classification of investigator-initiated research, this study has a small chance to induce minor damage leading to the qualification of a negligible risk study. Nevertheless, we installed a Data and Safety Monitoring Board (DSMB) to secure the safety of the participants. All serious adverse events (SAEs) will be reported. A study monitor will periodically visit all participating centres and ensure the rights and wellbeing of the participating subjects and to assess the quality of data collection and check if the rights, safety and wellbeing of the participants are reassured.

Sample size

The eight components of GOS and their estimated prevalence in GDM patients in the Netherlands are: LGA (16.5-19.9%), preterm delivery (4.4-6.4%), admission to neonatal intensive care (5%), instrumental delivery (7.5-8.2%), birth trauma (3.7%), neonatal hypoglycaemia (3.4-27.1%), caesarean delivery (12.1-23.8%) and pregnancy-related hypertension (8.8-12.5).[10,13] Metformin added to dietary and lifestyle intervention has never been compared to dietary and lifestyle intervention alone. Several meta-analyses

comparing metformin to insulin showed a lower incidence of LGA (pooled risk ratio (RR): 0.80 [0.64-0.99]) and macrosomia (pooled RR: 0.60 [0.45-0.79]), pregnancy induced hypertension (pooled RR: 0.56 [0.37-0.85]), neonatal hypoglycaemia (pooled RR: 0.63 [0.45-0.87]) and NICU admission (pooled RR: 0.72 [0.59-0.88]) [29,30,32,65]. Rates of caesarean section (pooled RR: 0.97 [0.80-1.19]), birth trauma (pooled RR: 0.86 [0.45-1.63]), preterm birth (pooled RR: 1.18 [0.67-2.07]) and assisted delivery (pooled RR: 1.34 [0.65-2.75]) did not differ between the groups.[29,30,32,65,66] By pooling the known effects of metformin versus insulin, so far, the effect size of metformin on GOS can be estimated as a relative risk reduction of 15%. We anticipated the early addition of metformin to dietary and lifestyle intervention results in a relative risk reduction of 25% on the GOS scale compared to the control group.

Based on the Groningen Pregnancy Outcome Database, the distribution of GOS was observed to be distributed according to a Poisson distribution of mean λ (and equal variance) close to 1. Assuming a Poisson parameter of λ=1, a ratio rate of 0.7 and a baseline final correlation in the range 0<R<0.2, we got the following results on several R and λ values in an acceptable pessimistic-optimistic range:

Table 5. Sample size calculation. Rows are values of events. Columns are values of rho.

^	R=0	R=0.2	R=0.4	R=0.6	R=0.8
0.5	442	425	372	283	160
1	221	213	186	142	80
1.5	148	142	124	95	54

The most likely value without considering the decrease of patients due to correlation corresponds to 221 patients per group (Table 5). We expect a drop out in the short-term Phase A of less than 10% after inclusion. Nevertheless, we will include an extra number of 29 patients per group, increasing the total sample size up to 500 patients (250 per group).

Data handling

All data will be recorded in the eCRF Castor EDC. This record will be filled in by the investigator or research nurses. Data will be handled confidentially and accordingly to the guidelines for privacy protection (AVG). The subjects will be identified only by a subject code in the eCRF and any electronic database. Data will be stored for a minimum of 15 years after study closure.

Data analysis

Data will be presented as means with standard deviation and/or 95% confidence interval or as median with interquartile range, depending on distribution. Categorical data will be assessed by comparing the event rates in the two groups using a chi-squared test. For continuous data, differences between groups will be assessed with the Student's t-test if the outcome is normally distributed and with the Mann-Whitney U test if not normally distributed.

The primary analysis will be by intention to treat. The effect of metformin on GOS will be studied using linear models. A list of covariates will be pre-specified prior to code breaking. During the follow-up before the end of the study, and in any event before the final blinded review, this model will be fitted to the on-going data by firstly applying existing predictors, and secondly adding possible variables, currently not investigated.

The aggregated secondary outcome measures MOS and NOS will be analysed similar to the primary outcome measure. A p-value of 0.05 will be considered significant in all analyses.

CONCLUSION

GDM is one of the most common medical disorders of pregnancy worldwide and is associated with suboptimal pregnancy-related and long-term outcomes for mothers and their offspring, even if euglycemia has been achieved. This suggests that other mechanisms than glycaemic control may be involved. Current treatment thrives to reduce hyperglycaemia but does not adequately treat the underlying insulin resistance and hyperinsulinemia. Only a few RCTs comparing metformin to insulin therapy have been performed. Long-term RCTs comparing metformin added to usual care versus usual care alone (diet and lifestyle intervention) from the start of GDM up to many years after delivery are lacking, especially concerning long term follow-up of growth, pubertal development and cardiometabolic health of the child. In addition, a long-term follow-up period with metformin exposure during GDM and lactation is needed to study the effects up to adolescence of the child. This multicentre randomised open-label controlled trial addresses this unmet need and will contribute to the primary treatment of GDM by providing insight into (1) immediate metformin treatment on top of dietary and lifestyle intervention versus dietary and lifestyle intervention, (2) continued metformin exposure in the direct post-partum period and (3) the long-term effects of metformin for both mother and child. As such, results of this study will provide a broad understanding of metformin in GDM and the pregnancy related outcomes as well as provide data on the long-term outcomes concerning safety and efficacy in mother and child.

ETHICS AND DISSEMINATION

The study protocol was approved by the Central Committee on Research Involving Human Subjects in the Netherlands and approval of the institutional review board of each participating centre will be obtained. The content authority of this trial was the Dutch Ministry of Public Health, Well-being and Sports (VWS). Changes in the study protocol will be submitted to the CCMO in amendments for approval.
Interim analyses are planned at the end of Phase A, B and C, with their own co-primary endpoints. Results of these interim analyses will be published in peer-reviewed journals. Additional analyses will be reported separately.

Authors' contributions

All authors contributed to the study design and protocol, drafting and revising the manuscript.

Funding statement

The POEM study is supported by grants from ZonMw (Dutch National Ministry of Health, project number 848017010), province of Drenthe (70617), Novo Nordisk BV (reference number 0072016) and Sanofi-Aventis BV (V170120, V160258, V150352). None of the funding partners has or will have any influence on the protocol, performance, data collection, data analysis, interpretation and/or publication of the POEM study.

Competing interests statement

KH received a lecture fee and travel grant from Novo Nordisk. All other authors declare they have no competing interests related to this study.

Legend Figure 1

FPG = fasting plasma glucose , OGTT = oral glucose tolerance test, GDM = gestational diabetes mellitus, MDL = metformin and diet and lifestyle intervention, DL = diet and lifestyle intervention.

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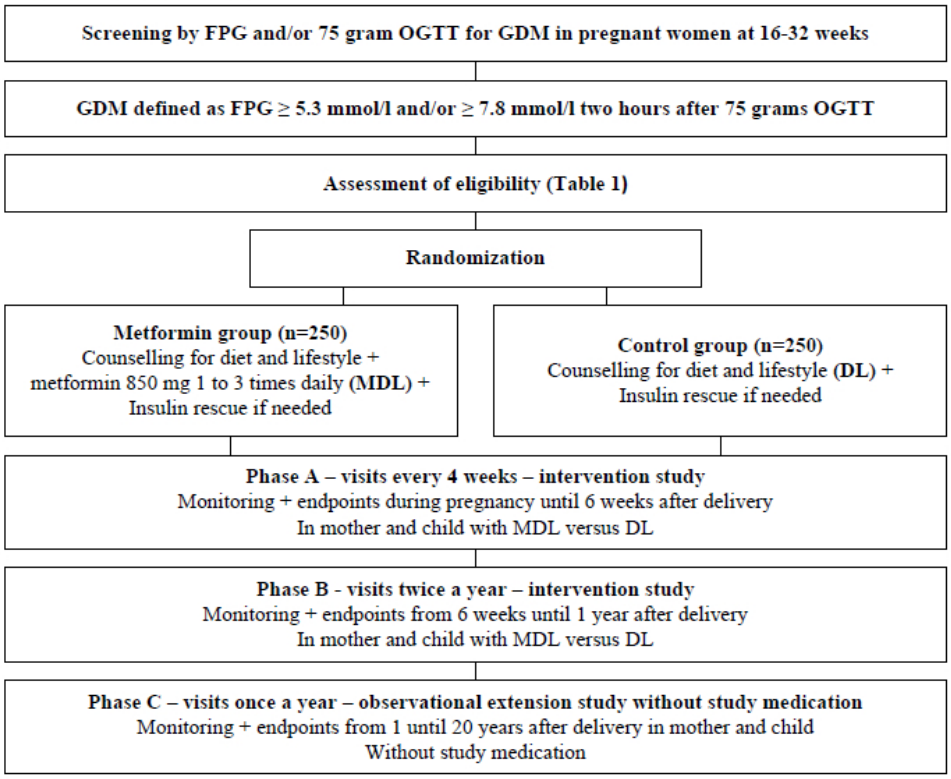
Figure 1. Flowchart



154x129mm (118 x 118 DPI)

Appendix 1: Secondary outcomes

Phase A	
Mother	**Child**
Maternal weight at inclusion, weight gain and change in body composition (impedance)	Intra-uterine growth measurements by ultrasonography
Maternal glycemic control: FPG and glucose tolerance at GDM diagnosis	Fetal weight at delivery
Proteinuria (UACR)	Fetal macrosomia
Insulin rescue and mean daily dose of insulin	LGA (neonatal weight > p90)
Acceptability of treatment	
Maternal urinary tract infection (no and %)	*Unfavourable neonatal outcome score (NOS)*
	IRDS needing CPAP, optiflow, mechanical ventilation and/or surfactant replacement
Unfavourable maternal outcome score (MOS)	Stillbirth and neonatal death
Caesarean delivery	Preterm birth (birth < 37.0 weeks)
Pre-eclampsia, eclampsia, HELPP and gestational hypertension	Shoulder dystocia
Maternal mortality	Instrumental delivery
Postpartum hemorrhage	Caesarean delivery
Thrombosis (in pregnancy and/or childbed)	Neonatal hypoglycaemia < 2.6 mml/l
Each separate neonatal component of GOS	Neonatal jaundice needing phototherapy
	NICU admission
	Apgar score as a variable
	Apgar score < 7 at 5 minutes
	Congenital anomaly
	Each separate neonatal component of GOS

Phase B and C	
Mother	**Child**
Incidence of T2DM and pre-diabetes	Growth and weight development
Weight and BMI (category) development	Gonadal and gender development
Incidence of hypertension	Puberty and maturation
Thrombotic and CVD (cardiovascular disease) events	Educational and intellectual development
Development of chronic disease	Development of chronic disease

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11,12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8-9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	In original protocol

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	In original protocol and IC
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n/a
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	8-9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Pregnancy Outcomes: Effects of Metformin (POEM) study: a protocol for a long-term, multicentre, open-label, randomised controlled trial in gestational diabetes mellitus

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056282.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Jan-2022
Complete List of Authors:	van Hoorn, Eline; University of Groningen, University Medical Center Groningen, Department of Endocrinology van Dijk, Peter; University of Groningen, University Medical Center Groningen, Department of Endocrinology Prins, Jelmer; University of Groningen, University Medical Center Groningen, Department of Obstetrics and Gynaecology Lutgers, Helen; Medical Centre Leeuwarden, Department of Internal Medicine Hoogenberg, Klaas; Martini Hospital, Department of Internal Medicine Erwich, Jan Jaap H.M.; University of Groningen, University Medical Center Groningen, Department of Obstetrics and Gynaecology Kooy, Adriaan; University of Groningen, University Medical Center Groningen, Department of Internal Medicine; Bethesda Diabetes Research Center
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Obstetrics and gynaecology
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, OBSTETRICS, PAEDIATRICS

Pregnancy Outcomes: Effects of Metformin (POEM) study: a protocol for a long-term, multicentre, open-label, randomised controlled trial in gestational diabetes mellitus

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Word Count: 3209

ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is a common disorder of pregnancy with health risks for mother and child during pregnancy, delivery, and further lifetime, possibly leading to type 2 diabetes mellitus (T2DM). Current treatment is focused on reducing hyperglycaemia, by dietary and lifestyle intervention and, if glycaemic targets are not reached, insulin. Metformin is an oral blood glucose lowering drug and considered safe during pregnancy. It improves insulin sensitivity and has shown advantages, specifically regarding pregnancy-related outcomes and patient satisfaction, compared to insulin therapy. However, the role of metformin in addition to usual care is inconclusive and long-term outcome of metformin exposure in utero are lacking. The primary aim of this study is to investigate the early addition of metformin on pregnancy and long-term outcomes in GDM.

Methods and analysis: The POEM study is a multicentre, open-label, randomised, controlled trial. Participants include women with GDM, between 16 and 32 weeks of gestation, who are randomised to either usual care or metformin added to usual care, with insulin rescue in both groups. Metformin is given up to one year after delivery. The study consists of three phases (A-C): A – until 6 weeks after delivery; B – until 1 year after delivery; C – observational study until 20 years after delivery. During phase A, the primary outcome is a composite score consisting of: (1) pregnancy-related hypertension, (2) large for gestational age neonate, (3) preterm delivery, (4) instrumental delivery, (5) caesarean delivery, (6) birth trauma, (7) neonatal hypoglycaemia, (8) neonatal intensive care admission. During phase B and C the primary outcome is the incidence of T2DM and (weight) development in mother and child.

Ethics and dissemination: The study was approved by the Central Committee on Research Involving Human Subjects in the Netherlands. Results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT02947503.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This is the first RCT to investigate immediate initiation of metformin at the start of GDM diagnosis added to dietary and lifestyle intervention versus dietary and lifestyle intervention alone.
- It is the first RCT to study the effects of metformin in GDM on mother and child during pregnancy, at delivery and for 20 years thereafter.
- The POEM study is the first RCT that studies the effects of continuing metformin exposure in the direct post-partum period (during lactation).
- Although the POEM study is a randomized multicentre RCT, the design is incorporated into usual practice. Confounding could be introduced due to variation in usual care.

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common disorders of pregnancy with a prevalence estimated up to 17% worldwide. There is a wide variation between countries, due to different populations, screening approaches and diagnostic criteria.[1–5]

GDM is an expression of chronic insulin resistance, worsened by the hormonal and metabolic physiology of pregnancy and inadequate pancreatic β-cell adaptation.[6–9] Women are often asymptomatic and therefore testing occurs in women with risk factors for GDM with a fasting plasma glucose and an oral glucose tolerance test. GDM is associated with suboptimal maternal and neonatal outcomes such as offspring large for gestational age (LGA), macrosomia, shoulder dystocia, pregnancy-related hypertension, caesarean section, neonatal hyperinsulinemia and hyperbilirubinemia.[10–13] After delivery both mother and child show an increased risk of cardiometabolic disease, specifically obesity and progression to type 2 diabetes mellitus (T2DM) in mothers, and early childhood obesity and development of (pre)diabetes in adolescence.[14–18]

Prior research has shown strong associations between maternal blood glucose levels – even in the near-normal range - and pregnancy-related outcomes as well as childhood adiposity and insulin resistance.[15,18,19] Therefore, current treatment primarily strives to normalize glycaemic levels and consists of dietary and lifestyle interventions with regular self-monitoring of blood glucose levels.[20] If blood glucose levels exceed the target ranges, antihyperglycemic medication is recommended. Most treatment guidelines recommend insulin therapy as the first choice.[20] However, insulin has several disadvantages as it is associated with increased maternal weight gain, maternal and neonatal hypoglycaemia and patients are burdened with storage, intensified self-monitoring and frequent subcutaneous injections.[21] In addition, insulin therapy is costly and burdens the health care system by medical education and frequent contacts. Finally, although insulin administration could compensate for the β-cell dysfunction, insulin sustains the hyperinsulinemia and does not treat the underlying insulin resistance. Perhaps this explains why women with GDM and with optimal glycaemic control still show unsatisfactory (pregnancy) outcomes.[13,22,23]

Mechanisms related to insulin resistance rather than low-grade glucotoxicity may contribute to the pathophysiology of the complications in GDM. This makes metformin a logical option for women with GDM. Metformin (dimethylbiguanide) is an oral blood glucose lowering drug (OBGLD) and has numerous mechanisms of action. It primarily inhibits the gluconeogenesis in the liver and acts as a insulin sensitizer – especially in the liver, and to a lesser extent in muscle and adipose tissue.[24,25] Additionally, it improves glucose sensing in the intestine and mechanisms through the incretin system are also involved.[25–27] Since insulin secretion is unaltered, the risk of hypoglycaemia is negligible.[28] Metformin is widely used in T2DM and to a lesser extent in GDM. In GDM, metformin compared to insulin and other OGBLD, reduces maternal and neonatal weight gain, the risk of pregnancy related hypertension, neonatal intensive care admission and hypoglycaemia.[24,29–32] Additionally, metformin shows anti-inflammatory and anti-thrombogenic effects [33–37] and higher patient satisfaction compared to insulin.[21] Several international treatment guidelines already recommend metformin treatment above insulin therapy if dietary and lifestyle interventions fail to adequately treat hyperglycaemia.[38–40] No studies on the use of metformin prior to considering insulin therapy exist.

Although hyperglycaemia usually resolves between 48 hours post-partum, most GDM patients have a degree of chronic insulin resistance,[41] which persists after delivery and is

not treated adequately with current therapy. It is hypothesized that the addition of metformin to GDM care reduces the risk of developing T2DM.[16,42,43] In mice, metformin exposure in utero and during lactation has shown to improve glucose tolerance and insulin secretion in the adult male offspring.[44,45] Additionally, metformin reduces the incidence of T2DM in pre-diabetic adults with and without a history of GDM.[42,43] Despite these findings, no studies investigated the effects of continued administration of metformin in the direct post-partum period.

Despite the confirmed and theoretical advantages of metformin, its role in treatment guidelines is still inconclusive. This multicentre randomised open-label controlled trial addresses this unmet need and will contribute to the primary treatment of GDM by providing insight into (1) immediate metformin treatment on top of dietary and lifestyle intervention versus dietary and lifestyle intervention, (2) continued metformin exposure in the direct post-partum period and (3) the long-term effects of metformin for both mother and child. As such, results of this study will provide a broad understanding of metformin in GDM and the pregnancy related outcomes as well as provide data on the long-term outcomes concerning safety and efficacy in mother and child.

METHODS AND ANALYSIS

Design and setting

The POEM study is a long-term, multicentre, randomised controlled, open-label, trial comparing usual care to metformin added to usual care. The trial consists of three distinct phases (A, B and C), and has a 20 year follow-up period after delivery. The first patient was included in December 2019 and the planned end date including phase C is in 2043.
Phase A (from inclusion until 6 weeks after delivery) and phase B (from 6 weeks until 1 year after delivery) are the interventional phases, while phase C (from 1 until 20 years after delivery) is the long-term observational phase.
The study will be conducted in the Netherlands and embedded in regular care with multidisciplinary GDM treatment teams usually consisting of a gynaecologist, internist, diabetes specialist nurse, midwife and dietician.

Ethical compliance

The methods employed in this trial were judged and approved by the Central Committee on Research Involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, CCMO, the National Medical Ethical Committee in the Netherlands). EudraCT number is 2015-002148-15. The trial was registered prospectively in the United States Clinical Trial registry (NCT02947503).

Public involvement

The Dutch Diabetes Association was involved in the preparation of this trial and approved the protocol.

Study population

GDM is diagnosed using a 75-gram oral glucose tolerance test (OGTT) according to the national Dutch guidelines.[20] Currently, screening for GDM in the Netherlands occurs based on predisposing risk factors, to be known; BMI > 30 kg/m², a history of a neonate with a birth weight > p95 or > 4500 grams, a first degree family member with diabetes mellitus, ethnic groups with a higher risk of diabetes mellitus (women of South-Asian descent, Afro-Caribbean, Middle-East, Morocco or Egypt), a medical history of unexplained foetal death

and women with polycystic ovary syndrome. Women with these risk factors are tested between 24-28 weeks of gestation. Women with a medical history of GDM are tested at 16 weeks of gestation.[20] The OGTT is also performed in case of clinical features of GDM such as suspected macrosomia or polyhydramnios.
Women are eligible for inclusion in this study if they have a fasting plasma glucose (FPG) ≥ 5.3 mmol/l and/or a 2-hour post-load glucose ≥ 7.8 mmol/l after a 75-gram OGTT. This inclusion strategy is based on national guidelines and the WHO criteria of 1999 and 2013, also including mild cases of GDM given this population also exhibits some degree of chronic insulin resistance and consequently sub-optimal outcome.[15,46]
The inclusion and exclusion criteria are listed in Table 1. The upper gestational age limit for inclusion is set at 32 weeks, to allow at least 6 weeks of metformin exposure during pregnancy. With the current screening policy, we expect that most participants will be treated ≥ 12 weeks during phase A.

Inclusion and randomisation
Eligible women will be informed about the study by either a research nurse, investigator or a healthcare provider (internist, diabetes specialist nurse, midwife or gynaecologist). Prior to participation written informed consent is obtained. Participants are randomised, stratified for age and duration of pregnancy and allocated 1:1 to either metformin and dietary and lifestyle intervention (MDL) or to dietary and lifestyle intervention alone (DL). Randomisation with stratification (for age and pregnancy duration) will be performed in the electronic case report form (eCRF) using Castor EDC.

The flowchart for eligibility, randomisation, intervention and control group and visit frequencies in the three phases of this study is presented in Figure 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Pregnant women with GDM defined as a FPG ≥ 5,3 mmol/l and/or an OGTT with a PG ≥ 7,8 mmol/l, two hours after the oral intake of 75 gram glucose
2. Age 18-45 years
3. Written informed consent
4. Singleton pregnancy
5. Gestational age at inclusion 16-32 weeks
6. HbA1c at inclusion ≤ 48 mmol/mol
Exclusion criteria
1. Diabetes Mellitus before pregnancy, except GDM
2. Proteinuria (UACR > 35 mmol/mol) at screening
3. Chronic liver disease and/or ASAT/ALAT >3x ULN
4. Chronic renal failure with GFR < 45 ml/min/1.73 m2
5. Malignancy during the last 5 years, except non-melanoma skin cancer
6. Psychiatric and/or mood disorders potentially affecting compliance of treatment
7. Chronic pulmonary failure with hypoxia
8. Significantly uncontrolled hypertension (SBP > 160 mmHg despite medical treatment)
9. Chronic treatment with corticosteroids
10. Intolerance for metformin and/or earlier use of metformin in this pregnancy.
11. Involvement in the POEM study
12. Severe foetal anomaly at inclusion
13. Ruptured of membranes (ROM)
14. Inability to understand or read Dutch language
15. Bariatric surgery in medical history
16. Hyperemesis gravidarum

FPG = fasting plasma glucose , OGTT = oral glucose tolerance test, GDM = gestational diabetes mellitus, UACR = urine albumin creatinin ratio, ULN = upper limit of normal, SPB = systolic blood pressure.

Intervention: metformin

The intervention group will receive metformin tablets of 850 mg (TEVA), titrated within approximately 15 days up to three times daily, if tolerated. The maximally tolerated dose will be continued until 1 year after delivery. Metformin will be stopped according to clinical judgement during, for example, severe diarrhoea with dehydration, severe illness with fever and/or sepsis. Additionally, metformin will be stopped in case of fetal growth restriction, as was also done in previous studies.[47] Fetal growth restriction will be defined according to the criteria proposed by Delphi consensus.[48]

Obstetric care

Obstetric care will be performed according to usual practice of the participating centre. Regular ultrasonography with foetal biometry (abdominal circumference, femur length, head circumference, estimated foetal weight and amniotic fluid volume) is performed approximately every four weeks. Timing of delivery will be performed according to usual practice of GDM with dietary and lifestyle intervention without insulin, which is often an expectant approach. If insulin rescue is needed, or in case of expected LGA, it is generally recommended to consider induction of labour around 38-39 weeks.[20]

Diabetes care

All participants will be referred to a diabetes specialist nurse, dietician and internist according to routine GDM care. In both groups, glucose monitoring and dietary and lifestyle intervention will be performed according to usual care with guidance by a diabetic nurse and a dietician. The diabetes specialist or research nurse instructs the participants about measuring procedures according to national guidelines.[49] CareSens^{TM} glucose meters will be used as the standard system for blood glucose measurements in all participants. Dietary and lifestyle interventions are embedded in regular care, and are performed according to the Dutch and WHO guidelines (physical activity and a well-balanced diet with carbohydrate redistribution and (mild) carbohydrate restriction).[50]

The participants will be asked to collect two 7-point blood glucose profiles in the week prior to the research visits. For the other weeks participants will collect 4-point blood glucose profiles according to usual care. The blood glucose levels will be reviewed by a diabetes nurse specialist or medical doctor at least every 1-2 weeks. At inclusion, laboratory safety tests will be performed to exclude e.g., renal- or liver diseases. Glycated haemoglobin (Hba1c), renal and liver function will be checked every 8 weeks in phase A.

In both groups, insulin rescue will be started at the discretion of the internist if the allocated treatment is not sufficient to achieve the target values of glycaemic control at least more than two times (FPG < 5.3 mmol/l and PG < 7.8 mmol/l). According to normal standard of care, the internist may choose to commence insulin rescue only temporarily if there is a reversible factor for dysregulation (medication/food/stress/fever).
If target values are not met more than two times in Phase B or C (FPG < 7.0 mmol/l or PG < 11.1 mmol/l), anti-hyperglycaemic treatment will be started (or extended) according to national guidelines for the treatment of T2DM.[51]

Neonatal care

Neonatal care will be performed according to usual care. Most sites will perform glucose monitoring if the neonate has a birth weight > p90 and/or if mother receives insulin therapy.

Follow-up and data collection

The follow-up and data collection per visit are presented in Table 2. All data will be recorded in the eCRF per site. In phase A, participants will have visits every four weeks until delivery, and 6 weeks after delivery. In phase B, participants will have visits twice a year, at 6 and 12 months after delivery. In phase C, participants will have visits once a year for a duration of 20 years after delivery. Additional blood samples from the mother (research panel) and urine samples from the child will be collected and stored at -80 °C for later analyses and to study the effects of metformin regarding metabolic, development and safety outcomes.

Table 2. Measurements per visit

Phase A										**Phase B**			**Phase C**
		R							**D**				
Visit number	1	2	3	4	5	6	7	8	9	10[1]	11	12	13 to 31
Weeks	-1	0	4	8	12	16	20	24					
Time (mo) after delivery										1,5	6	12	2 to 20 years
Visit window (±days)	7	7	7	7	7	7	7	7	7	7	14	14	14
General													
Baseline characteristics	X												
Medical/obstetric history	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
Physical examination		X								X		X	Every four visits
Vital signs, body weight	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
7 points BGM review		X	X	X	X	X	X	X		X	X	X	
AE/SAE/endpoint report		X	X	X	X	X	X	X	X	X	X	X	Every visit
Check compliance			X	X	X	X	X	X		X	X	X	
Check GOS									X	X			
Check fetal sonography		X	X	X	X	X	X	X					
EQ-5D-5L and WHO-5		X		X		X				X		X	Every other visit
Lactation evaluation										X	X	X	
Development child										X	X	X	Every visit
Samples													
Safety panel mother[2]	X									X		X	
Regular panel mother[3]		X		X		X		X		X	X	X	Every visit
Research panel mother		X		X		X		X		X	X	X	Every visit
OGTT mother[4]	X									X			Every other visit
Morning urine mother		X		X		X		X		X		X	Every four visits
Urinalysis		X		X		X		X					
Morning urine child										X		X	Every four visits
Delivery													
Umbilical cord sampling									X				
Histological samples									X				
Neonatal glucose[5]									X				
First urine child									X				

R = randomisation
D = delivery
[1] Visit 10 is completing phase A and starting phase B
[2] Safety panel (fasting): UACR, blood cell count, haemoglobin, creatinin, urea, sodium, potassium, γGT, AF, ASAT, ALAT, LDH, CRP, TSH, FT4 (if TSH is abnormal).

[3] Regular panel (fasting): Hba1c, haemoglobin, FPG, creatinin, ASAT, ALAT, B12, MMA (if B12 < 220 mmol/l)
[4] When the OGTT is performed prior to visit 1, this data will be used
[5] According standard of care a neonatal plasma glucose can be measured postpartum
BGM = blood glucose monitoring, AE = adverse event, SAE = serious adverse event, GOS = GDM outcome score, OGTT = oral glucose tolerance test

Additional pregnancies

If a new pregnancy occurs during phase B, this pregnancy will be entirely exposed to the allocated treatment strategy. There is no evidence for safety issues concerning metformin exposure in the first trimester.[47,52–56] If a pregnancy occurs during phase C this pregnancy will be treated according to regular clinical practice.

Primary outcome measures

The primary outcome measure during phase A consists of a composite endpoint at delivery and is termed the GDM Outcome Score (GOS). The GOS is an ordinal variable ranging from 0-8 and consists of eight components which are shown in Table 3. Additionally, the dichotomous endpoint GOS positive (1-8) versus GOS negative (0) will be evaluated as a variant of the primary outcome. The incidence of T2DM and weight development in mother and child are the co-primary outcome measures in Phase B and C.

Table 3. Primary outcome measures

Phase A	Phase B and C
GDM Outcome Score (GOS) score (range 0-8):	Incidence of maternal T2DM
1. Pregnancy related hypertension	Weight and BMI (category) development mother
2. Large for gestational age (LGA) at delivery (weight > 90th percentile)	Weight and BMI (percentile) development child
3. Premature delivery (< 37.0 weeks of gestation)	
4. Instrumental delivery	
5. Caesarean delivery	
6. Birth trauma	
7. Neonatal hypoglycaemia (< 2.6 mmol/l)	
8. Admission to the neonatal intensive care unit	

Secondary outcome measures

The secondary outcome measure during phase A consists of two composite endpoints at delivery and is termed the maternal outcome score (MOS) and neonatal outcome score (NOS). Both are ordinal variables consisting of the components shown in Table 4. Moreover, each separate component of the eight components of GOS is a secondary endpoint in Phase A.

The Dutch version of the EuroQol-5D-5L (EQ-5D-5L) and The World Health Organisation-Five Well-Being Index (WHO-5) will be administered to evaluate health-related quality of life. The EQ-5D-5L is a commonly used questionnaire to measure health-related quality of life.[57] This questionnaire can be used to obtain quality-adjusted life years (QALYs). Using the Dutch algorithm,[58] a utility score can be produced ranging from 0 to 1, with 0 indicating the worst imaginable health and 1 indicating the best imaginable health state.[58] The WHO-5 is a 5-item short and non-invasive generic rating scale measuring subjective psychological well-being.[59] The questionnaire consists of five items and the participant is asked to rate how well each of the 5 statements applies to her when considering the last 14 days. It has been used as a screening tool for depression but is also widely used as outcome measure in clinical trials to capture (improvement in) well-being caused by various pharmacological interventions.[59,60]

Finally, biometric, metabolic and hormonal variables collected during the study will be evaluated as a variant to the secondary outcome during phase A and B. During phase C, the secondary outcome concerns the developmental milestones of the child, anthropometric measurements and development of chronic disease for mother and child. A complete overview of secondary outcome measures is presented in appendix 1.

Table 4. Secondary outcome measures

Phase A	
Mother	**Child**
Maternal outcome score (MOS):	*Neonatal outcome score (NOS):*
Caesarean delivery	IRDS requiring oxygen therapy
Pre-eclampsia, eclampsia, HELPP and PIH	Stillbirth and neonatal death
Maternal mortality	Preterm birth
Postpartum haemorrhage	Shoulder dystocia
Thrombosis	Instrumental delivery
Each separate maternal component of GOS	Caesarean delivery
	Neonatal hypoglycaemia < 2.6 mml/l
	Neonatal jaundice needing phototherapy
	NICU admission
	Apgar score as a variable
	Apgar score < 7 at 5 minutes
	Congenital anomaly
	Each separate neonatal component of GOS
Phase B and C	
Mother	**Child**
Hypertension development	Gonadal and gender development
Thrombotic and CVD events	Puberty and maturation
Development of chronic disease	Educational and intellectual development
	Development of chronic disease

Drug safety

Observational studies and randomised trials did not show a drug safety issue in patients with GDM, polycystic ovarian syndrome (PCOS), T2DM and obesity.[21,47,53,54,56,61] Metformin is considered as a safe and non-teratogenic drug.[52,55,56] Limited concentrations of metformin are observed in breast milk (median concentrations ranging between 0,17-0,41 mg/L).[62–64] The mean relative infant dose ranges between 0.20-0.65% of the weight adjusted maternal dose.[62–64] Metformin use during lactation did no show adverse effects on the infants blood glucose levels or on growth, motor and social development.[62–65]

Safety monitoring

According to the risk classification of investigator-initiated research, this study has a small chance to induce minor damage leading to the qualification of a negligible risk study. Nevertheless, we installed a Data and Safety Monitoring Board (DSMB) to secure the safety of the participants. All serious adverse events (SAEs) will be reported. A study monitor will periodically visit all participating centres and ensure the rights and wellbeing of the participating subjects and to assess the quality of data collection and check if the rights, safety and wellbeing of the participants are reassured.

Sample size

The eight components of GOS and their estimated prevalence in GDM patients in the Netherlands are: LGA (16.5-19.9%), preterm delivery (4.4-6.4%), admission to neonatal intensive care (5%), instrumental delivery (7.5-8.2%), birth trauma (3.7%), neonatal hypoglycaemia (3.4-27.1%), caesarean delivery (12.1-23.8%) and pregnancy-related

hypertension (8.8-12.5).[10,13] Metformin added to dietary and lifestyle intervention has never been compared to dietary and lifestyle intervention alone. Several meta-analyses comparing metformin to insulin showed a lower incidence of LGA (pooled risk ratio (RR): 0.80 [0.64-0.99]) and macrosomia (pooled RR: 0.60 [0.45-0.79]), pregnancy induced hypertension (pooled RR: 0.56 [0.37-0.85]), neonatal hypoglycaemia (pooled RR: 0.63 [0.45-0.87]) and NICU admission (pooled RR: 0.72 [0.59-0.88]) [29,30,32,66]. Rates of caesarean section (pooled RR: 0.97 [0.80-1.19]), birth trauma (pooled RR: 0.86 [0.45-1.63]), preterm birth (pooled RR: 1.18 [0.67-2.07]) and assisted delivery (pooled RR: 1.34 [0.65-2.75]) did not differ between the groups.[29,30,32,66,67] By pooling the known effects of metformin versus insulin, so far, the effect size of metformin on GOS can be estimated as a relative risk reduction of 15%. We anticipated the early addition of metformin to dietary and lifestyle intervention results in a relative risk reduction of 25% on the GOS scale compared to the control group.

Based on the Groningen Pregnancy Outcome Database, the distribution of GOS was observed to be distributed according to a Poisson distribution of mean λ (and equal variance) close to 1. Assuming a Poisson parameter of λ=1, a ratio rate of 0.7 and a baseline final correlation in the range 0<R<0.2, we got the following results on several R and λ values in an acceptable pessimistic-optimistic range:

Table 5. Sample size calculation. Rows are values of events. Columns are values of rho.

^	R=0	R=0.2	R=0.4	R=0.6	R=0.8
0.5	442	425	372	283	160
1	221	213	186	142	80
1.5	148	142	124	95	54

The most likely value without considering the decrease of patients due to correlation corresponds to 221 patients per group (Table 5). We expect a drop out in the short-term Phase A of less than 10% after inclusion. Nevertheless, we will include an extra number of 29 patients per group, increasing the total sample size up to 500 patients (250 per group).

Data handling

All data will be recorded in the eCRF Castor EDC. This record will be filled in by the investigator or research nurses. Data will be handled confidentially and accordingly to the guidelines for privacy protection (AVG). The subjects will be identified only by a subject code in the eCRF and any electronic database. Data will be stored for a minimum of 15 years after study closure.

Data analysis

Data will be presented as means with standard deviation and/or 95% confidence interval or as median with interquartile range, depending on distribution. Categorical data will be assessed by comparing the event rates in the two groups using a chi-squared test. For continuous data, differences between groups will be assessed with the Student's t-test if the outcome is normally distributed and with the Mann-Whitney U test if not normally distributed.

The primary analysis will be by intention to treat. The effect of metformin on GOS will be studied using linear models. A list of covariates will be pre-specified prior to code breaking. During the follow-up before the end of the study, and in any event before the final blinded review, this model will be fitted to the on-going data by firstly applying existing predictors, and secondly adding possible variables, currently not investigated.

The aggregated secondary outcome measures MOS and NOS will be analysed similar to the primary outcome measure. Additionally, we aim to perform a stratified analysis based on known GDM phenotypes: predominantly insulin resistant and predominantly insulin deficient

based on OGTT results.[68,69] A p-value of 0.05 will be considered significant in all analyses.

ETHICS AND DISSEMINATION

The study protocol was approved by the Central Committee on Research Involving Human Subjects in the Netherlands and approval of the institutional review board of each participating centre will be obtained. The content authority of this trial was the Dutch Ministry of Public Health, Well-being and Sports (VWS). Changes in the study protocol will be submitted to the CCMO in amendments for approval.
Interim analyses are planned at the end of Phase A, B and C, with their own co-primary endpoints. Results of these interim analyses will be published in peer-reviewed journals. Additional analyses will be reported separately.

Authors' contributions

Study design, protocol and acquisition of data: EGMvH, PRvD, JRP, HLL, KH, JJHME, AK. Drafting of initial manuscript: EGMvH. Critical revision of the manuscript for important intellectual content: PRvD, JRP, HLL, KH, JJHME, AK. Final approval of the version submitted: EGMvH, PRvD, JRP, HLL, KH, JJHME, AK.

Funding statement

The POEM study is supported by grants from ZonMw (Dutch National Ministry of Health, project number 848017010), province of Drenthe (70617), Novo Nordisk BV (reference number 0072016) and Sanofi-Aventis BV (V170120, V160258, V150352). None of the funding partners has or will have any influence on the protocol, performance, data collection, data analysis, interpretation and/or publication of the POEM study.

Competing interests statement

KH received a lecture fee and travel grant from Novo Nordisk. All other authors declare they have no competing interests related to this study.

Legend Figure 1

FPG = fasting plasma glucose , OGTT = oral glucose tolerance test, GDM = gestational diabetes mellitus, MDL = metformin and diet and lifestyle intervention, DL = diet and lifestyle intervention.

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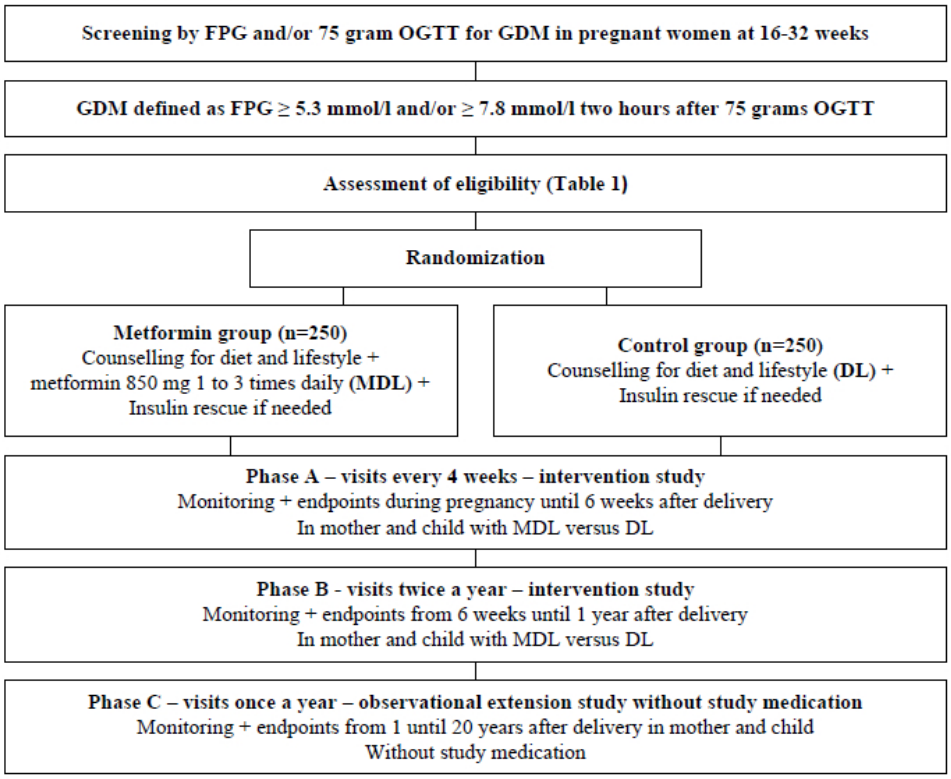
Figure 1. Flowchart



154x129mm (118 x 118 DPI)

Appendix 1: Secondary outcomes

Phase A	
Mother	**Child**
Maternal weight at inclusion, weight gain	Intra-uterine growth measurements by ultrasonography
Maternal glycemic control: FPG and glucose tolerance at GDM diagnosis	Fetal weight and percentile at delivery
	Fetal macrosomia
Proteinuria (UACR)	LGA (neonatal weight > p90)
Insulin rescue and mean daily dose of insulin	
Acceptability of treatment	*Unfavourable neonatal outcome score (NOS)*
Maternal urinary tract infection (no and %)	IRDS needing CPAP, optiflow, mechanical ventilation and/or surfactant replacement
Unfavourable maternal outcome score (MOS)	Stillbirth and neonatal death
Caesarean delivery	Preterm birth (birth < 37.0 weeks)
Pre-eclampsia, eclampsia, HELPP and gestational hypertension	Shoulder dystocia
	Instrumental delivery
Maternal mortality	Caesarean delivery
Postpartum hemorrhage	Neonatal hypoglycaemia < 2.6 mml/l
Thrombosis (in pregnancy and/or childbed)	Neonatal jaundice needing phototherapy
Each separate neonatal component of GOS	NICU admission
	Apgar score as a variable
	Apgar score < 7 at 5 minutes
	Congenital anomaly
	Each separate neonatal component of GOS

Phase B and C	
Mother	**Child**
Incidence of T2DM and pre-diabetes	Growth and weight development
Weight and BMI (category) development	Gonadal and gender development
Incidence of hypertension	Puberty and maturation
Thrombotic and CVD (cardiovascular disease) events	Educational and intellectual development
Development of chronic disease	Development of chronic disease

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11,12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8-9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	In original protocol

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	In original protocol and IC
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n/a
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	8-9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Pregnancy Outcomes: Effects of Metformin (POEM) study: a protocol for a long-term, multicentre, open-label, randomised controlled trial in gestational diabetes mellitus

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056282.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Feb-2022
Complete List of Authors:	van Hoorn, Eline; University of Groningen, University Medical Center Groningen, Department of Endocrinology van Dijk, Peter; University of Groningen, University Medical Center Groningen, Department of Endocrinology Prins, Jelmer; University of Groningen, University Medical Center Groningen, Department of Obstetrics and Gynaecology Lutgers, Helen; Medical Centre Leeuwarden, Department of Internal Medicine Hoogenberg, Klaas; Martini Hospital, Department of Internal Medicine Erwich, Jan Jaap H.M.; University of Groningen, University Medical Center Groningen, Department of Obstetrics and Gynaecology Kooy, Adriaan; University of Groningen, University Medical Center Groningen, Department of Internal Medicine; Bethesda Diabetes Research Centre
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Obstetrics and gynaecology
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, OBSTETRICS, PAEDIATRICS

Pregnancy Outcomes: Effects of Metformin (POEM) study: a protocol for a long-term, multicentre, open-label, randomised controlled trial in gestational diabetes mellitus

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Word Count: 3234

ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is a common disorder of pregnancy with health risks for mother and child during pregnancy, delivery, and further lifetime, possibly leading to type 2 diabetes mellitus (T2DM). Current treatment is focused on reducing hyperglycaemia, by dietary and lifestyle intervention and, if glycaemic targets are not reached, insulin. Metformin is an oral blood glucose lowering drug and considered safe during pregnancy. It improves insulin sensitivity and has shown advantages, specifically regarding pregnancy-related outcomes and patient satisfaction, compared to insulin therapy. However, the role of metformin in addition to usual care is inconclusive and long-term outcome of metformin exposure in utero are lacking. The primary aim of this study is to investigate the early addition of metformin on pregnancy and long-term outcomes in GDM.

Methods and analysis: The POEM study is a multicentre, open-label, randomised, controlled trial. Participants include women with GDM, between 16 and 32 weeks of gestation, who are randomised to either usual care or metformin added to usual care, with insulin rescue in both groups. Metformin is given up to one year after delivery. The study consists of three phases (A-C): A – until 6 weeks after delivery; B – until 1 year after delivery; C – observational study until 20 years after delivery. During phase A, the primary outcome is a composite score consisting of: (1) pregnancy-related hypertension, (2) large for gestational age neonate, (3) preterm delivery, (4) instrumental delivery, (5) caesarean delivery, (6) birth trauma, (7) neonatal hypoglycaemia, (8) neonatal intensive care admission. During phase B and C the primary outcome is the incidence of T2DM and (weight) development in mother and child.

Ethics and dissemination: The study was approved by the Central Committee on Research Involving Human Subjects in the Netherlands. Results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT02947503.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This is the first RCT to investigate immediate initiation of metformin at the start of GDM diagnosis added to dietary and lifestyle intervention versus dietary and lifestyle intervention alone.
- It is the first RCT to study the effects of metformin in GDM on mother and child during pregnancy, at delivery and for 20 years thereafter.
- The POEM study is the first RCT that studies the effects of continuing metformin exposure in the direct post-partum period (during lactation).
- Although the POEM study is a randomized multicentre RCT, the design is incorporated into usual practice. Confounding could be introduced due to variation in usual care.

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common disorders of pregnancy with a prevalence estimated up to 17% worldwide. There is a wide variation between countries, due to different populations, screening approaches and diagnostic criteria.[1–5]

GDM is an expression of chronic insulin resistance, worsened by the hormonal and metabolic physiology of pregnancy and inadequate pancreatic β-cell adaptation.[6–9] Women are often asymptomatic and therefore testing occurs in women with risk factors for GDM with a fasting plasma glucose and an oral glucose tolerance test. GDM is associated with suboptimal maternal and neonatal outcomes such as offspring large for gestational age (LGA), macrosomia, shoulder dystocia, pregnancy-related hypertension, caesarean section, neonatal hyperinsulinemia and hyperbilirubinemia.[10–13] After delivery both mother and child show an increased risk of cardiometabolic disease, specifically obesity and progression to type 2 diabetes mellitus (T2DM) in mothers, and early childhood obesity and development of (pre)diabetes in adolescence.[14–18]

Prior research has shown strong associations between maternal blood glucose levels – even in the near-normal range - and pregnancy-related outcomes as well as childhood adiposity and insulin resistance.[15,18,19] Therefore, current treatment primarily strives to normalize glycaemic levels and consists of dietary and lifestyle interventions with regular self-monitoring of blood glucose levels.[20] If blood glucose levels exceed the target ranges, antihyperglycemic medication is recommended. Most treatment guidelines recommend insulin therapy as the first choice.[20] However, insulin has several disadvantages as it is associated with increased maternal weight gain, maternal and neonatal hypoglycaemia and patients are burdened with storage, intensified self-monitoring and frequent subcutaneous injections.[21] In addition, insulin therapy is costly and burdens the health care system by medical education and frequent contacts. Finally, although insulin administration could compensate for the β-cell dysfunction, insulin sustains the hyperinsulinemia and does not treat the underlying insulin resistance. Perhaps this explains why women with GDM and with optimal glycaemic control still show unsatisfactory (pregnancy) outcomes.[13,22,23]

Mechanisms related to insulin resistance rather than low-grade glucotoxicity may contribute to the pathophysiology of the complications in GDM. This makes metformin a logical option for women with GDM. Metformin (dimethylbiguanide) is an oral blood glucose lowering drug (OBGLD) and has numerous mechanisms of action. It primarily inhibits the gluconeogenesis in the liver and acts as a insulin sensitizer – especially in the liver, and to a lesser extent in muscle and adipose tissue.[24,25] Additionally, it improves glucose sensing in the intestine and mechanisms through the incretin system are also involved.[25–27] Since insulin secretion is unaltered, the risk of hypoglycaemia is negligible.[28] Metformin is widely used in T2DM and to a lesser extent in GDM. In GDM, metformin compared to insulin and other OGBLD, reduces maternal and neonatal weight gain, the risk of pregnancy related hypertension, neonatal intensive care admission and hypoglycaemia.[24,29–32] Additionally, metformin shows anti-inflammatory and anti-thrombogenic effects [33–37] and higher patient satisfaction compared to insulin.[21] Several international treatment guidelines already recommend metformin treatment above insulin therapy if dietary and lifestyle interventions fail to adequately treat hyperglycaemia.[38–40] No studies on the use of metformin prior to considering insulin therapy exist.

Although hyperglycaemia usually resolves between 48 hours post-partum, most GDM patients have a degree of chronic insulin resistance,[41] which persists after delivery and is

not treated adequately with current therapy. It is hypothesized that the addition of metformin to GDM care reduces the risk of developing T2DM.[16,42,43] In mice, metformin exposure in utero and during lactation has shown to improve glucose tolerance and insulin secretion in the adult male offspring.[44,45] Additionally, metformin reduces the incidence of T2DM in pre-diabetic adults with and without a history of GDM.[42,43] Despite these findings, no studies investigated the effects of continued administration of metformin in the direct post-partum period.

Despite the confirmed and theoretical advantages of metformin, its role in treatment guidelines is still inconclusive. This multicentre randomised open-label controlled trial addresses this unmet need and will contribute to the primary treatment of GDM by providing insight into (1) immediate metformin treatment on top of dietary and lifestyle intervention versus dietary and lifestyle intervention, (2) continued metformin exposure in the direct post-partum period and (3) the long-term effects of metformin for both mother and child. As such, results of this study will provide a broad understanding of metformin in GDM and the pregnancy related outcomes as well as provide data on the long-term outcomes concerning safety and efficacy in mother and child.

METHODS AND ANALYSIS

Design and setting

The POEM study is a long-term, multicentre, randomised controlled, open-label, trial comparing usual care to metformin added to usual care. The trial consists of three distinct phases (A, B and C), and has a 20 year follow-up period after delivery. The first patient was included in December 2019 and the planned end date including phase C is in 2043.
Phase A (from inclusion until 6 weeks after delivery) and phase B (from 6 weeks until 1 year after delivery) are the interventional phases, while phase C (from 1 until 20 years after delivery) is the long-term observational phase.
The study will be conducted in the Netherlands and embedded in regular care with multidisciplinary GDM treatment teams usually consisting of a gynaecologist, internist, diabetes specialist nurse, midwife and dietician.

Ethical compliance

The methods employed in this trial were judged and approved by the Central Committee on Research Involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, CCMO, the National Medical Ethical Committee in the Netherlands). EudraCT number is 2015-002148-15. The trial was registered prospectively in the United States Clinical Trial registry (NCT02947503).

Public involvement

The Dutch Diabetes Association was involved in the preparation of this trial and approved the protocol.

Study population

GDM is diagnosed using a 75-gram oral glucose tolerance test (OGTT) according to the national Dutch guidelines.[20] Currently, screening for GDM in the Netherlands occurs based on predisposing risk factors, to be known; BMI > 30 kg/m², a history of a neonate with a birth weight > p95 or > 4500 grams, a first degree family member with diabetes mellitus, ethnic groups with a higher risk of diabetes mellitus (women of South-Asian descent, Afro-Caribbean, Middle-East, Morocco or Egypt), a medical history of unexplained foetal death

and women with polycystic ovary syndrome. Women with these risk factors are tested between 24-28 weeks of gestation. Women with a medical history of GDM are tested at 16 weeks of gestation.[20] The OGTT is also performed in case of clinical features of GDM such as suspected macrosomia or polyhydramnios.
Women are eligible for inclusion in this study if they have a fasting plasma glucose (FPG) ≥ 5.3 mmol/l and/or a 2-hour post-load glucose ≥ 7.8 mmol/l after a 75-gram OGTT. This inclusion strategy is based on national guidelines and the WHO criteria of 1999 and 2013, also including mild cases of GDM given this population also exhibits some degree of chronic insulin resistance and consequently sub-optimal outcome.[15,46]
The inclusion and exclusion criteria are listed in Table 1. The upper gestational age limit for inclusion is set at 32 weeks, to allow at least 6 weeks of metformin exposure during pregnancy. With the current screening policy, we expect that most participants will be treated ≥ 12 weeks during phase A.

Inclusion and randomisation
Eligible women will be informed about the study by either a research nurse, investigator or a healthcare provider (internist, diabetes specialist nurse, midwife or gynaecologist). Prior to participation full written informed consent is obtained for phase A and B (supplemental appendix 1 and 2). At the end of phase B, informed consent will be obtained for phase C. Participants are randomised, stratified for age and duration of pregnancy and allocated 1:1 to either metformin and dietary and lifestyle intervention (MDL) or to dietary and lifestyle intervention alone (DL). Randomisation with stratification (for age and pregnancy duration) will be performed in the electronic case report form (eCRF) using Castor EDC.

The flowchart for eligibility, randomisation, intervention and control group and visit frequencies in the three phases of this study is presented in Figure 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Pregnant women with GDM defined as a FPG ≥ 5,3 mmol/l and/or an OGTT with a PG ≥ 7,8 mmol/l, two hours after the oral intake of 75 gram glucose
2. Age 18-45 years
3. Written informed consent
4. Singleton pregnancy
5. Gestational age at inclusion 16-32 weeks
6. HbA1c at inclusion ≤ 48 mmol/mol
Exclusion criteria
1. Diabetes Mellitus before pregnancy, except GDM
2. Proteinuria (UACR > 35 mmol/mol) at screening
3. Chronic liver disease and/or ASAT/ALAT >3x ULN
4. Chronic renal failure with GFR < 45 ml/min/1.73 m2
5. Malignancy during the last 5 years, except non-melanoma skin cancer
6. Psychiatric and/or mood disorders potentially affecting compliance of treatment
7. Chronic pulmonary failure with hypoxia
8. Significantly uncontrolled hypertension (SBP > 160 mmHg despite medical treatment)
9. Chronic treatment with corticosteroids
10. Intolerance for metformin and/or earlier use of metformin in this pregnancy.
11. Involvement in the POEM study
12. Severe foetal anomaly at inclusion
13. Ruptured of membranes (ROM)
14. Inability to understand or read Dutch language
15. Bariatric surgery in medical history
16. Hyperemesis gravidarum

FPG = fasting plasma glucose , OGTT = oral glucose tolerance test, GDM = gestational diabetes mellitus, UACR = urine albumin creatinin ratio, ULN = upper limit of normal, SPB = systolic blood pressure.

Intervention: metformin

The intervention group will receive metformin tablets of 850 mg (TEVA), titrated within approximately 15 days up to three times daily, if tolerated. The maximally tolerated dose will be continued until 1 year after delivery. Metformin will be stopped according to clinical judgement during, for example, severe diarrhoea with dehydration, severe illness with fever and/or sepsis. Additionally, metformin will be stopped in case of fetal growth restriction, as was also done in previous studies.[47] Fetal growth restriction will be defined according to the criteria proposed by Delphi consensus.[48]

Obstetric care

Obstetric care will be performed according to usual practice of the participating centre. Regular ultrasonography with foetal biometry (abdominal circumference, femur length, head circumference, estimated foetal weight and amniotic fluid volume) is performed approximately every four weeks. Timing of delivery will be performed according to usual practice of GDM with dietary and lifestyle intervention without insulin, which is often an expectant approach. If insulin rescue is needed, or in case of expected LGA, it is generally recommended to consider induction of labour around 38-39 weeks.[20]

Diabetes care

All participants will be referred to a diabetes specialist nurse, dietician and internist according to routine GDM care. In both groups, glucose monitoring and dietary and lifestyle intervention will be performed according to usual care with guidance by a diabetic nurse and a dietician. The diabetes specialist or research nurse instructs the participants about measuring procedures according to national guidelines.[49] CareSens^{TM} glucose meters will be used as the standard system for blood glucose measurements in all participants. Dietary and lifestyle interventions are embedded in regular care, and are performed according to the Dutch and WHO guidelines (physical activity and a well-balanced diet with carbohydrate redistribution and (mild) carbohydrate restriction).[50]

The participants will be asked to collect two 7-point blood glucose profiles in the week prior to the research visits. For the other weeks participants will collect 4-point blood glucose profiles according to usual care. The blood glucose levels will be reviewed by a diabetes nurse specialist or medical doctor at least every 1-2 weeks. At inclusion, laboratory safety tests will be performed to exclude e.g., renal- or liver diseases. Glycated haemoglobin (Hba1c), renal and liver function will be checked every 8 weeks in phase A.

In both groups, insulin rescue will be started at the discretion of the internist if the allocated treatment is not sufficient to achieve the target values of glycaemic control at least more than two times (FPG < 5.3 mmol/l and PG < 7.8 mmol/l). According to normal standard of care, the internist may choose to commence insulin rescue only temporarily if there is a reversible factor for dysregulation (medication/food/stress/fever).
If target values are not met more than two times in Phase B or C (FPG < 7.0 mmol/l or PG < 11.1 mmol/l), anti-hyperglycaemic treatment will be started (or extended) according to national guidelines for the treatment of T2DM.[51]

Neonatal care

Neonatal care will be performed according to usual care. Most sites will perform glucose monitoring if the neonate has a birth weight > p90 and/or if mother receives insulin therapy.

Follow-up and data collection

The follow-up and data collection per visit are presented in Table 2. All data will be recorded in the eCRF per site. In phase A, participants will have visits every four weeks until delivery, and 6 weeks after delivery. In phase B, participants will have visits twice a year, at 6 and 12 months after delivery. In phase C, participants will have visits once a year for a duration of 20 years after delivery. Additional blood samples from the mother (research panel) and urine samples from the child will be collected and stored at -80 °C for later analyses and to study the effects of metformin regarding metabolic, development and safety outcomes.

Table 2. Measurements per visit

Phase A										**Phase B**			**Phase C**
		R							**D**				
Visit number	1	2	3	4	5	6	7	8	9	10[1]	11	12	13 to 31
Weeks	-1	0	4	8	12	16	20	24					
Time (mo) after delivery										1,5	6	12	2 to 20 years
Visit window (±days)	7	7	7	7	7	7	7	7	7	7	14	14	14
General													
Baseline characteristics	X												
Medical/obstetric history	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
Physical examination		X								X		X	Every four visits
Vital signs, body weight	X	X	X	X	X	X	X	X	X	X	X	X	Every visit
7 points BGM review		X	X	X	X	X	X	X		X	X	X	
AE/SAE/endpoint report		X	X	X	X	X	X	X	X	X	X	X	Every visit
Check compliance			X	X	X	X	X	X		X	X	X	
Check GOS									X	X			
Check fetal sonography		X	X	X	X	X	X	X					
EQ-5D-5L and WHO-5		X		X		X				X		X	Every other visit
Lactation evaluation										X	X	X	
Development child										X	X	X	Every visit
Samples													
Safety panel mother[2]	X									X		X	
Regular panel mother[3]		X		X		X		X		X	X	X	Every visit
Research panel mother		X		X		X		X		X	X	X	Every visit
OGTT mother[4]	X									X			Every other visit
Morning urine mother		X		X		X		X		X		X	Every four visits
Urinalysis		X		X		X		X					
Morning urine child										X		X	Every four visits
Delivery													
Umbilical cord sampling									X				
Histological samples									X				
Neonatal glucose[5]									X				
First urine child									X				

R = randomisation
D = delivery
[1] Visit 10 is completing phase A and starting phase B
[2] Safety panel (fasting): UACR, blood cell count, haemoglobin, creatinin, urea, sodium, potassium, γGT, AF, ASAT, ALAT, LDH, CRP, TSH, FT4 (if TSH is abnormal).

[3] Regular panel (fasting): Hba1c, haemoglobin, FPG, creatinin, ASAT, ALAT, B12, MMA (if B12 < 220 mmol/l)
[4] When the OGTT is performed prior to visit 1, this data will be used
[5] According standard of care a neonatal plasma glucose can be measured postpartum
BGM = blood glucose monitoring, AE = adverse event, SAE = serious adverse event, GOS = GDM outcome score, OGTT = oral glucose tolerance test

Additional pregnancies

If a new pregnancy occurs during phase B, this pregnancy will be entirely exposed to the allocated treatment strategy. There is no evidence for safety issues concerning metformin exposure in the first trimester.[47,52–56] If a pregnancy occurs during phase C this pregnancy will be treated according to regular clinical practice.

Primary outcome measures

The primary outcome measure during phase A consists of a composite endpoint at delivery and is termed the GDM Outcome Score (GOS). The GOS is an ordinal variable ranging from 0-8 and consists of eight components which are shown in Table 3. Additionally, the dichotomous endpoint GOS positive (1-8) versus GOS negative (0) will be evaluated as a variant of the primary outcome. The incidence of T2DM and weight development in mother and child are the co-primary outcome measures in Phase B and C.

Table 3. Primary outcome measures

Phase A	Phase B and C
GDM Outcome Score (GOS) score (range 0-8):	Incidence of maternal T2DM
1. Pregnancy related hypertension	Weight and BMI (category) development mother
2. Large for gestational age (LGA) at delivery (weight > 90th percentile)	Weight and BMI (percentile) development child
3. Premature delivery (< 37.0 weeks of gestation)	
4. Instrumental delivery	
5. Caesarean delivery	
6. Birth trauma	
7. Neonatal hypoglycaemia (< 2.6 mmol/l)	
8. Admission to the neonatal intensive care unit	

Secondary outcome measures

The secondary outcome measure during phase A consists of two composite endpoints at delivery and is termed the maternal outcome score (MOS) and neonatal outcome score (NOS). Both are ordinal variables consisting of the components shown in Table 4. Moreover, each separate component of the eight components of GOS is a secondary endpoint in Phase A.

The Dutch version of the EuroQol-5D-5L (EQ-5D-5L) and The World Health Organisation-Five Well-Being Index (WHO-5) will be administered to evaluate health-related quality of life. The EQ-5D-5L is a commonly used questionnaire to measure health-related quality of life.[57] This questionnaire can be used to obtain quality-adjusted life years (QALYs). Using the Dutch algorithm,[58] a utility score can be produced ranging from 0 to 1, with 0 indicating the worst imaginable health and 1 indicating the best imaginable health state.[58] The WHO-5 is a 5-item short and non-invasive generic rating scale measuring subjective psychological well-being.[59] The questionnaire consists of five items and the participant is asked to rate how well each of the 5 statements applies to her when considering the last 14 days. It has been used as a screening tool for depression but is also widely used as outcome measure in clinical trials to capture (improvement in) well-being caused by various pharmacological interventions.[59,60]

Finally, biometric, metabolic and hormonal variables collected during the study will be evaluated as a variant to the secondary outcome during phase A and B. During phase C, the secondary outcome concerns the developmental milestones of the child, anthropometric measurements and development of chronic disease for mother and child. A complete overview of secondary outcome measures is presented in appendix 3.

Table 4. Secondary outcome measures

Phase A	
Mother	**Child**
Maternal outcome score (MOS):	*Neonatal outcome score (NOS):*
Caesarean delivery	IRDS requiring oxygen therapy
Pre-eclampsia, eclampsia, HELPP and PIH	Stillbirth and neonatal death
Maternal mortality	Preterm birth
Postpartum haemorrhage	Shoulder dystocia
Thrombosis	Instrumental delivery
Each separate maternal component of GOS	Caesarean delivery
	Neonatal hypoglycaemia < 2.6 mml/l
	Neonatal jaundice needing phototherapy
	NICU admission
	Apgar score as a variable
	Apgar score < 7 at 5 minutes
	Congenital anomaly
	Each separate neonatal component of GOS
Phase B and C	
Mother	**Child**
Hypertension development	Gonadal and gender development
Thrombotic and CVD events	Puberty and maturation
Development of chronic disease	Educational and intellectual development
	Development of chronic disease

Drug safety

Observational studies and randomised trials did not show a drug safety issue in patients with GDM, polycystic ovarian syndrome (PCOS), T2DM and obesity.[21,47,53,54,56,61] Metformin is considered as a safe and non-teratogenic drug.[52,55,56] Limited concentrations of metformin are observed in breast milk (median concentrations ranging between 0,17-0,41 mg/L).[62–64] The mean relative infant dose ranges between 0.20-0.65% of the weight adjusted maternal dose.[62–64] Metformin use during lactation did no show adverse effects on the infants blood glucose levels or on growth, motor and social development.[62–65]

Safety monitoring

According to the risk classification of investigator-initiated research, this study has a small chance to induce minor damage leading to the qualification of a negligible risk study. Nevertheless, we installed a Data and Safety Monitoring Board (DSMB) to secure the safety of the participants. All serious adverse events (SAEs) will be reported. A study monitor will periodically visit all participating centres and ensure the rights and wellbeing of the participating subjects and to assess the quality of data collection and check if the rights, safety and wellbeing of the participants are reassured.

Sample size

The eight components of GOS and their estimated prevalence in GDM patients in the Netherlands are: LGA (16.5-19.9%), preterm delivery (4.4-6.4%), admission to neonatal intensive care (5%), instrumental delivery (7.5-8.2%), birth trauma (3.7%), neonatal hypoglycaemia (3.4-27.1%), caesarean delivery (12.1-23.8%) and pregnancy-related

hypertension (8.8-12.5).[10,13] Metformin added to dietary and lifestyle intervention has never been compared to dietary and lifestyle intervention alone. Several meta-analyses comparing metformin to insulin showed a lower incidence of LGA (pooled risk ratio (RR): 0.80 [0.64-0.99]) and macrosomia (pooled RR: 0.60 [0.45-0.79]), pregnancy induced hypertension (pooled RR: 0.56 [0.37-0.85]), neonatal hypoglycaemia (pooled RR: 0.63 [0.45-0.87]) and NICU admission (pooled RR: 0.72 [0.59-0.88]) [29,30,32,66]. Rates of caesarean section (pooled RR: 0.97 [0.80-1.19]), birth trauma (pooled RR: 0.86 [0.45-1.63]), preterm birth (pooled RR: 1.18 [0.67-2.07]) and assisted delivery (pooled RR: 1.34 [0.65-2.75]) did not differ between the groups.[29,30,32,66,67] By pooling the known effects of metformin versus insulin, so far, the effect size of metformin on GOS can be estimated as a relative risk reduction of 15%. We anticipated the early addition of metformin to dietary and lifestyle intervention results in a relative risk reduction of 25% on the GOS scale compared to the control group.

Based on the Groningen Pregnancy Outcome Database, the distribution of GOS was observed to be distributed according to a Poisson distribution of mean λ (and equal variance) close to 1. Assuming a Poisson parameter of λ=1, a ratio rate of 0.7 and a baseline final correlation in the range 0<R<0.2, we got the following results on several R and λ values in an acceptable pessimistic-optimistic range:

Table 5. Sample size calculation. Rows are values of events. Columns are values of rho.

^	R=0	R=0.2	R=0.4	R=0.6	R=0.8
0.5	442	425	372	283	160
1	221	213	186	142	80
1.5	148	142	124	95	54

The most likely value without considering the decrease of patients due to correlation corresponds to 221 patients per group (Table 5). We expect a drop out in the short-term Phase A of less than 10% after inclusion. Nevertheless, we will include an extra number of 29 patients per group, increasing the total sample size up to 500 patients (250 per group).

Data handling

All data will be recorded in the eCRF Castor EDC. This record will be filled in by the investigator or research nurses. Data will be handled confidentially and accordingly to the guidelines for privacy protection (AVG). The subjects will be identified only by a subject code in the eCRF and any electronic database. Data will be stored for a minimum of 15 years after study closure.

Data analysis

Data will be presented as means with standard deviation and/or 95% confidence interval or as median with interquartile range, depending on distribution. Categorical data will be assessed by comparing the event rates in the two groups using a chi-squared test. For continuous data, differences between groups will be assessed with the Student's t-test if the outcome is normally distributed and with the Mann-Whitney U test if not normally distributed.

The primary analysis will be by intention to treat. The effect of metformin on GOS will be studied using linear models. A list of covariates will be pre-specified prior to code breaking. During the follow-up before the end of the study, and in any event before the final blinded review, this model will be fitted to the on-going data by firstly applying existing predictors, and secondly adding possible variables, currently not investigated.

The aggregated secondary outcome measures MOS and NOS will be analysed similar to the primary outcome measure. Additionally, we aim to perform a stratified analysis based on known GDM phenotypes: predominantly insulin resistant and predominantly insulin deficient

based on OGTT results.[68,69] A p-value of 0.05 will be considered significant in all analyses.

ETHICS AND DISSEMINATION

The study protocol was approved by the Central Committee on Research Involving Human Subjects in the Netherlands and approval of the institutional review board of each participating centre will be obtained. The content authority of this trial was the Dutch Ministry of Public Health, Well-being and Sports (VWS). Changes in the study protocol will be submitted to the CCMO in amendments for approval.
Interim analyses are planned at the end of Phase A, B and C, with their own co-primary endpoints. Results of these interim analyses will be published in peer-reviewed journals. Additional analyses will be reported separately.

Authors' contributions

Study design, protocol and acquisition of data: EGMvH, PRvD, JRP, HLL, KH, JJHME, AK. Drafting of initial manuscript: EGMvH. Critical revision of the manuscript for important intellectual content: PRvD, JRP, HLL, KH, JJHME, AK. Final approval of the version submitted: EGMvH, PRvD, JRP, HLL, KH, JJHME, AK.

Funding statement

The POEM study is supported by grants from ZonMw (Dutch National Ministry of Health, project number 848017010), province of Drenthe (70617), Novo Nordisk BV (reference number 0072016) and Sanofi-Aventis BV (V170120, V160258, V150352). None of the funding partners has or will have any influence on the protocol, performance, data collection, data analysis, interpretation and/or publication of the POEM study.

Competing interests statement

KH received a lecture fee and travel grant from Novo Nordisk. All other authors declare they have no competing interests related to this study.

Legend Figure 1

FPG = fasting plasma glucose , OGTT = oral glucose tolerance test, GDM = gestational diabetes mellitus, MDL = metformin and diet and lifestyle intervention, DL = diet and lifestyle intervention.

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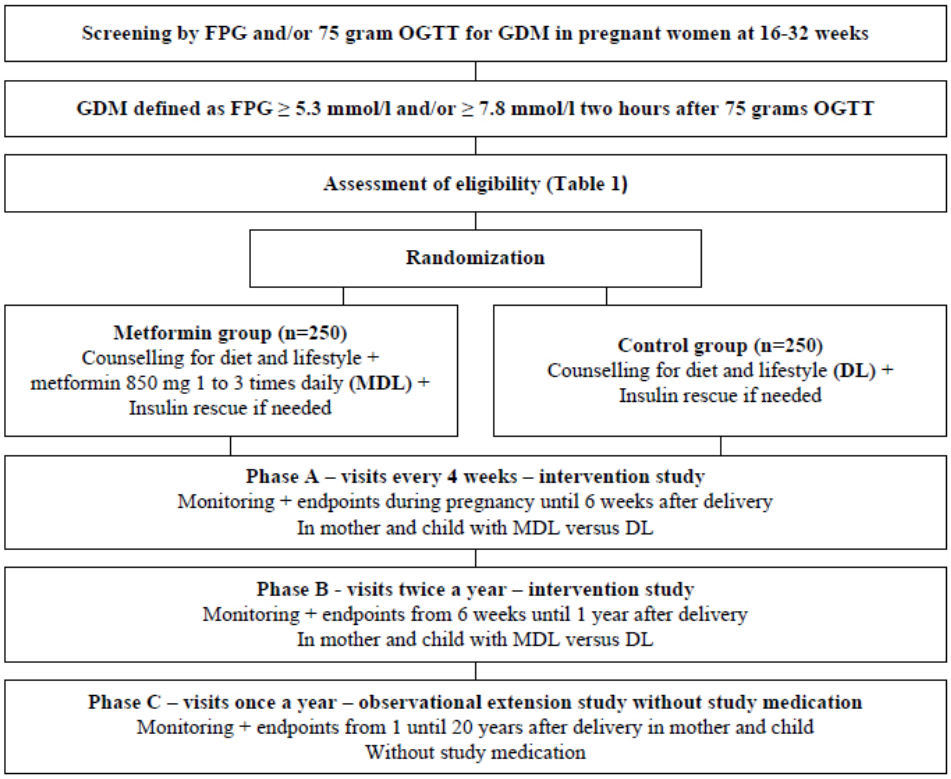
Figure 1. Flowchart



Legend Figure 1
FPG = fasting plasma glucose , OGTT = oral glucose tolerance test, GDM = gestational diabetes mellitus, MDL = metformin and diet and lifestyle intervention, DL = diet and lifestyle intervention

154x129mm (118 x 118 DPI)

Proefpersoneninformatie en toestemmingsformulier voor deelname aan POEM Fase A en B, medisch-wetenschappelijk onderzoek voor de zwangere en jonge moeder.

De POEM studie: *een onderzoek ter verbetering van de behandeling van zwangerschapsdiabetes met een verwachte gezondheidswinst voor moeder en kind*

Inleiding

U ontvangt deze brief omdat bij u zwangerschapsdiabetes is vastgesteld met een suikerbelastingstest. Wij vragen u mee te doen aan een medisch-wetenschappelijk onderzoek naar de behandeling van zwangerschapsdiabetes met het medicijn metformine. Meedoen is vrijwillig. Om mee te doen is wel uw schriftelijke toestemming nodig. Voordat u beslist of u wilt meedoen, krijgt u uitleg over wat het onderzoek inhoudt. Lees deze informatie rustig door en vraag de onderzoeker meer uitleg als u vragen heeft. U kunt er ook over praten met uw partner, vrienden of familie.
Dit onderzoek is opgezet door het Bethesda Diabetes Research Center te Hoogeveen (BDRC).
Er doen in totaal 500 zwangere vrouwen mee aan dit onderzoek in Nederland. De Centrale Commissie Mensgebonden Onderzoek heeft dit onderzoek goedgekeurd. Algemene informatie over meedoen en toetsing van onderzoek vindt u in de brochure 'Medisch-wetenschappelijk onderzoek' (VWS). Deze kunt u downloaden op: https://www.rijksoverheid.nl/documenten/brochures/2014/09/01/medisch-wetenschappelijk-onderzoek-algemene-informatie-voor-de-proefpersoon.

1. Doel van het onderzoek

Zwangerschapsdiabetes is diabetes (= aandoening met te hoge bloedsuikers) ontstaan tijdens de zwangerschap. Zwangerschapsdiabetes verhoogt de kans op hoge bloeddruk tijdens de zwangerschap alsook de kans op overgewicht en type 2 diabetes tijdens het verdere leven bij moeder en kind. Voor het ongeboren kind geeft zwangerschapsdiabetes extra risico's zoals een hoog geboortegewicht, een vroegtijdige geboorte, meer complicaties bij de bevalling en lage bloedsuikers na de bevalling met kans op hersenschade. Op de lange termijn heeft het kind ook een verhoogde kans op overgewicht en diabetes. Al deze risico's willen we helpen verlagen met deze POEM studie.
Zwangerschapsdiabetes wordt nu vooral behandeld met dieet en insuline (injecties). Metformine (pillen) werkt volgens recent onderzoek veilig bij zwangerschapsdiabetes. Bovendien behandelt metformine meer de oorzaak van de diabetes: het pakt de verminderde insulinegevoeligheid aan. Het werkt mogelijk gunstiger voor moeder en kind dan de bestaande behandeling. Vandaar dit onderzoek. Metformine is al geregistreerd voor de behandeling van diabetes. Metformine blijkt de bloedsuikerspiegel én de insulinebehoefte te verlagen. Bovendien voorkomt metformine extra gewichtstoename bij moeder en kind. Vanwege deze gunstige effecten wordt metformine soms al bij zwangerschapsdiabetes gebruikt. Metformine is (nog) niet geregistreerd voor gebruik bij de zwangerschap, maar is wel veilig gebleken in observatiestudies tijdens de zwangerschap. Metformine is een plantaardig product, afkomstig uit de Franse Lelie. Het doel van de POEM studie is om de werkzaamheid en veiligheid van metformine aan te tonen bij de behandeling van zwangerschapsdiabetes met een verwachte gezondheidswinst voor moeder en kind op de korte en lange termijn.

2. Wat meedoen inhoudt

In de studie worden twee groepen gevormd. Een groep die metformine krijgt en een groep die geen metformine krijgt. Via loting wordt bepaald in welke groep u terecht komt. Het onderzoek bestaat uit drie

Proefpersoneninformatie en toestemmingsformulier voor deelname aan POEM Fase A en B, medisch-wetenschappelijk onderzoek voor de zwangere en jonge moeder.

fasen. Fase A start vanaf de vaststelling van zwangerschapsdiabetes en duurt tot 6 weken na de bevalling. Fase B loopt van 6 weken tot 1 jaar na de bevalling. Wij vragen hierbij uw toestemming voor deelname aan Fase A en B. Deelname aan Fase A en B duurt maximaal anderhalf jaar.
Fase C is een vervolgfase zonder studiemedicatie met een jaarlijkse medische beoordeling. In deze fase worden de effecten van metformine op lange termijn vastgesteld. Fase C duurt tot 20 jaar na de bevalling. Voorafgaand aan Fase C zullen wij opnieuw uw toestemming vragen voor deelname. Voor de volledigheid is wel alvast informatie over Fase C opgenomen in deze informatiebrief.

Keuring

Als u met zwangerschapsdiabetes, vastgesteld via de suikerbelastingstest, heeft ingestemd met deelname zal de onderzoeker vragen naar uw medische voorgeschiedenis. U krijgt uitleg hoe u een bloedsuiker dagcurve maakt met 7 bloedsuikermetingen: voor en na de 3 hoofdmaaltijden en voor het naar bed gaan. U meet 2 bloedsuiker dagcurves in één week. Tevens wordt er bloed afgenomen. U wordt ook gevraagd om uw ochtend urine op te vangen en mee te nemen bij het tweede bezoek. Bij dat bezoek wordt er lichamelijk onderzoek gedaan en opnieuw bloed afgenomen. Uw gewicht, lengte, bloeddruk en hartslag worden gemeten en u wordt gevraagd gezondheidsvragenlijsten in te vullen. De onderzoeker stelt daarbij vast of deelname aan de studie voor u van meerwaarde is.

Behandeling

Vanaf visite 2 krijgt de helft van de proefpersonen metformine, de andere helft de gebruikelijke zorg. Loting bepaalt in welke groep u zit. Beide groepen krijgen dieet- en leefstijladviezen.
Als u in de metforminegroep zit, neemt u de eerste week 1 tablet per dag, de tweede week 2 tabletten per dag en vanaf de derde week 3 tabletten per dag. Afhankelijk van hoe goed u de metformine kunt verdragen kan de dosering sneller of juist langzamer opgehoogd worden. U gebruikt metformine tot 1 jaar na de bevalling. Mocht desondanks de bloedsuiker tijdens de zwangerschapsdiabetes te hoog worden, dan volgt een aanvullende behandeling met insuline (injecties). Maar we verwachten dat metforminegebruikers dat niet of minder nodig hebben.
Als u niet in de metforminegroep zit, krijgt u de standaardbehandeling voor zwangerschapsdiabetes onder begeleiding van het onderzoeksteam: dieet- en leefstijladviezen en zo nodig de gebruikelijke insulinetherapie.
Tijdens Fase C gebruikt u geen metformine (meer) vanwege de POEM studie. Tijdens deze fase volgen wij u en uw kind graag voor de mogelijke gezondheidswinst op langere termijn.

Bezoeken en metingen

De frequentie van uw bezoek tijdens de zwangerschap (Fase A) is zoals gebruikelijk bij zwangerschapsdiabetes, ongeveer 1 keer per 4 weken. U komt gedurende Fase A maximaal 10 keer naar het ziekenhuis. Een bezoek duurt ongeveer 30 minuten. Gedurende Fase B bezoekt u het centrum 2 keer.
Tijdens Fase C bezoekt u het centrum 1 keer per jaar.

Tijdens de bezoeken worden de volgende testen en metingen gedaan:

- De Orale Glucose Tolerantie Test (OGTT), ook wel de suikerbelastingstest, is een test waarbij wordt gekeken hoe de bloedwaardes van glucose veranderen na het drinken van een glucosedrank. Door het drinken van de glucosedrank zal de glucosewaarde in het bloed stijgen. Het lichaam reageert hierop, en brengt de glucosewaarde weer naar beneden. Dit gebeurt onvoldoende bij een verstoorde glucosehuishouding. Deze test vindt tijdens deze onderzoeksfase (Fase A en B) 1 keer plaats. *Tijdens Fase C wordt er 10 keer een OGTT gedaan (1x per 2 jaar).*
- Lichamelijk onderzoek bij visite 2 en 6 weken na de bevalling door de arts (-onderzoeker).
- Bloedafname (waar mogelijk op gebruikelijke momenten): in Fase A en B minimaal 5 en maximaal 8 keer. Het aantal keren is afhankelijk van het startmoment van uw deelname aan het onderzoek en het moment van bevallen. (*In Fase C wordt er 1 keer per jaar bloed afgenomen.)* Bloedonderzoek is nodig om de werkzaamheid en veiligheid van metformine te bepalen. Een deel van het bloed wordt bewaard voor aanvullend wetenschappelijk onderzoek.
- Inleveren van urine voor onderzoek: in Fase A en B maximaal 6 keer. (*In Fase C 5 keer.)*
- Invullen van gezondheidsvragenlijsten: in Fase A en B maximaal 5 keer. (*In Fase C 10 keer.)*
- Bloedsuiker 7-punts dagcurves: 2 keer per week voorafgaande aan iedere visite in Fase A, naast de gebruikelijke 4-punts dagcurves op andere dagen volgens de geldende zorgrichtlijn.
- De moederkoek wordt onderzocht en navelstreng bloed wordt afgenomen voor nader onderzoek.

Anders dan bij gebruikelijke zorg

Als u meedoet aan het onderzoek krijgt u dezelfde controles als wanneer u niet mee zou doen. De bezoeken in het kader van zwangerschapsdiabetes kunnen leiden tot een verplichte eigen bijdrage van de ziektekostenverzekering. Dat is ook het geval als u niet deelneemt aan deze studie en u behandeld zou moeten worden voor zwangerschapsdiabetes. Alle kosten die voor dit onderzoek worden gemaakt komen voor rekening van de onderzoeker, bijvoorbeeld extra echo's of bloed- en urineonderzoek. Met de extra metingen verkrijgen we extra informatie over hoe uw zwangerschap en zwangerschapsdiabetes verlopen.

3. Wat wordt er van u verwacht

Het is belangrijk dat u zich aan de volgende afspraken houdt:

- dat u de metformine volgens voorschrift inneemt, als u in de metformine-groep zit;
- dat u geen metformine gebruikt, als u in de controlegroep zit;
- dat u de bloedsuikermetingen volgens de instructies uitvoert;
- dat u uw afspraken voor bezoeken nakomt;
- dat u uw deelnemerskaart van het onderzoek bij u draagt. Laat deze kaart zien als u bij een andere arts komt.
- dat u niet tegelijkertijd aan een ander medisch-wetenschappelijk onderzoek meedoet.

Het is belangrijk dat u contact opneemt met de onderzoeker:

- voordat u andere geneesmiddelen gaat gebruiken (ook homeopathische middelen, natuurgeneesmiddelen, vitaminen of geneesmiddelen van de drogist);
- als u in een ziekenhuis wordt opgenomen of behandeld;
- als u plotseling gezondheidsklachten krijgt;
- als u niet meer wilt meedoen aan het onderzoek;
- als uw contactgegevens wijzigen.

Zwangerschap tijdens Fase B en C

Wordt u tijdens het onderzoek opnieuw zwanger? Laat dit dan direct weten aan de onderzoeker. U kunt gewoon blijven deelnemen aan de POEM studie.

4. Mogelijke bijwerkingen, mogelijke nadelige en voordelige effecten

Metformine is al geregistreerd voor de behandeling van diabetes. Zeer vaak voorkomende tijdelijke bijwerkingen zijn maag- darmklachten. Meer informatie staat in de bijsluiter.

Metformine is tot op heden veilig gebleken bij het kind tijdens de zwangerschap. Metformine helpt tijdens de zwangerschap overmatige lichaamsgroei van het kind tegen te gaan zodat baby's minder zwaar worden. Dit kan mogelijke complicaties door een (te) groot kind bij de bevalling voorkomen, metformine verlaagt het risico op een hoge bloeddruk tijdens de zwangerschap. Metformine wordt in kleine hoeveelheden uitgescheiden in de moedermelk. Er zijn geen bijwerkingen gevonden bij baby's of jonge kinderen die borstvoeding kregen.

5. Mogelijke voor- en nadelen van deelname aan onderzoek

Zwangerschapsdiabetes wordt nu vooral behandeld met dieet en insuline (injecties). Voordeel van meedoen aan het onderzoek is, dat er een grotere kans bestaat dat u geen insuline hoeft te spuiten als u in de groep zit die metformine krijgt. Metformine leidt mogelijk tot gunstigere zwangerschapsuitkomsten voor u en uw kind. Tijdens de POEM studie wordt u zorgvuldig begeleid.
Bij deelname aan Fase C zelfs tot 20 jaar na de bevalling.

Deelname aan een onderzoek als de POEM studie gaat veelal gepaard met gunstigere gezondheidsresultaten dan bij een reguliere behandeling buiten de studie. Mogelijk komt dit door de extra begeleiding en de grotere bewustwording van de gunstige maatregelen voor de behandeling zwangerschapsdiabetes.

Nadelen van meedoen aan het onderzoek kunnen zijn dat u tijd kwijt bent aan de bezoeken die u moet afleggen. De (extra) testen kunnen leiden tot mogelijke ongemakken en u kunt last krijgen van mogelijke bijwerkingen van metformine (tijdelijke diarree, misselijkheid). Bloedafnames kunnen pijn doen of een bloeduitstorting geven. In totaal wordt 5 tot 8 keer bloed bij u afgenomen in Fase A en B. Van de orale glucosetest kunt u tijdelijk wat misselijk worden.

6. Als u niet wilt meedoen of wilt stoppen met het onderzoek

U wordt tweemaal om toestemming gevraagd om deel te nemen aan het totale onderzoek. Eenmaal voorafgaand aan Fase A en Fase B en eenmaal voorafgaand aan Fase C. Deelname is vrijwillig. Als u niet wilt meedoen, wordt u op de gebruikelijke manier behandeld voor uw zwangerschapsdiabetes. Als u wel meedoet aan het onderzoek, dan kunt u zich altijd bedenken. U mag tijdens het onderzoek stoppen. U wordt dan weer op de gebruikelijke manier behandeld voor uw zwangerschapsdiabetes. U hoeft niet te zeggen waarom u stopt. Wel moet u dit direct melden aan de onderzoeker om uw behandeling goed voort te kunnen zetten buiten het onderzoek om. De gegevens die tot dat moment zijn verzameld, worden gebruikt voor het onderzoek. Als u wilt, kan verzameld lichaamsmateriaal, zoals bloed of urine, worden vernietigd. Als er voor u nieuwe belangrijke informatie over het onderzoek is, dan laat de onderzoeker dit aan u weten. U wordt dan gevraagd of u wilt blijven meedoen.

7. Einde van het onderzoek

Uw deelname aan het onderzoek stopt als:

- alle bezoeken voorbij zijn;
- u zelf kiest om te stoppen;
- het einde van het hele onderzoek is bereikt;
- de onderzoeker het beter voor u vindt om te stoppen;
- de ethische toetsingscommissie of de overheid besluit om het onderzoek te stoppen.

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn. Mocht u metformine of een andere behandeling na Fase B nodig hebben, dan zal de onderzoeker dat met u bespreken.

8. Gebruik en bewaren van uw gegevens en lichaamsmateriaal

Voor dit onderzoek is het nodig dat uw lichaamsmateriaal en uw medische en persoonsgegevens worden verzameld en gebruikt. Elke proefpersoon krijgt een code die op het lichaamsmateriaal en de gegevens komt te staan. Uw naam wordt weggelaten. Uw privacy is zo gewaarborgd.

Uw gegevens

Al uw gegevens blijven vertrouwelijk. Alleen het onderzoeksteam (arts en verpleegkundigen) weten welke code u heeft. Wij geven uw gegevens door aan de opdrachtgever van de POEM studie, maar alleen met die code, nooit met uw naam. De sleutel voor de code blijft bij de onderzoeker. Ook in rapporten over het onderzoek wordt alleen die code gebruikt.

Sommige mensen mogen uw medische- en persoonsgegevens inzien. Dit is om te controleren of het onderzoek goed en betrouwbaar is. Algemene informatie hierover vindt u in de brochure ‘Medisch-wetenschappelijk onderzoek’ van VWS.

Mensen die uw gegevens kunnen inzien zijn: het onderzoeksteam, een deskundig controleur en de Inspectie voor de Gezondheidszorg. Zij houden uw gegevens geheim. Als u de toestemmingsverklaring ondertekent, geeft u toestemming voor het verzamelen, bewaren en inzien van uw medische en persoonsgegevens. De onderzoeker bewaart uw gegevens tot 15 jaar na afronding van het onderzoek.

Uw lichaamsmateriaal

Uw lichaamsmateriaal bewaren we gecodeerd en zorgvuldig. Het lichaamsmateriaal wordt gebruikt om de effecten van het metformine te kunnen vaststellen. Er wordt gekeken naar veranderingen in de stofwisseling die kunnen leiden tot het krijgen of voorkomen van chronische ziekten (zoals diabetes, hoge bloeddruk, hart en vaatziekten en kanker). Het lichaamsmateriaal zal uiterlijk tot 15 jaar na afronding van het onderzoek worden bewaard.

Later gebruik gegevens en/of lichaamsmateriaal

Wij willen de ingevroren bloed- en urinemonsters bewaren om nieuwe inzichten over de lange termijn effecten van metformine bij zwangerschapsdiabetes te verkrijgen.
Op het toestemmingsformulier kunt u aangeven of u hiermee akkoord gaat. U kunt deze toestemming altijd weer intrekken. Uw bloed- en urinemonsters worden dan vernietigd. Als er al metingen in uw monsters zijn gedaan, worden de resultaten daarvan wel gebruikt.

De POEM studie is officieel geregistreerd in een wetenschappelijk onderzoeksregister (www.clinicaltrial.gov). Deze website bevat geen informatie die herleidbaar is tot u als persoon. Wel kan de website een samenvatting van de resultaten tonen.

9. Verzekering voor proefpersonen

Voor iedere zwangere die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering dekt schade door het onderzoek. In **bijlage B** vindt u meer informatie over de verzekering.

10. Informeren huisarts en/of behandelend specialist en/of apotheker

Wij sturen uw behandelaar een brief om te laten weten dat u meedoet aan het onderzoek. Dit is in uw belang en een voorwaarde om mee te kunnen doen. U kunt niet deelnemen aan het onderzoek als u geen huisarts heeft.

11. Vergoeding voor meedoen

De bezoeken in het kader van het onderzoek in Fase A vallen samen met de bezoeken die u zou hebben in het kader van controle van uw zwangerschapsdiabetes. Deze bezoeken komen dan ook ten laste van de ziektekostenverzekering en vallen dus mogelijk onder uw verplicht eigen risico.
Kosten die speciaal voor dit onderzoek worden gemaakt komen voor rekening van de onderzoeker, zoals extra echo's en bloed- en urineonderzoek en de metformine tijdens Fase A en Fase B.
Voor de bezoeken in het kader van het onderzoek in Fase B ontvangt u een reiskostenvergoeding, parkeergeld en eventuele kosten voor een maaltijd.

12. Heeft u vragen?

Bij vragen kunt u contact opnemen met het onderzoeksteam. Voor onafhankelijk advies over meedoen aan dit onderzoek kunt u terecht bij de onafhankelijke arts. Deze arts weet veel over het onderzoek, maar heeft niets te maken met dit onderzoek. Bij klachten kunt u altijd terecht bij ons studieteam of zo nodig extern bij de Klachtenfunctionaris. Alle gegevens hiervoor vindt u in **bijlage A**: Contactgegevens.

Proefpersoneninformatie en toestemmingsformulier voor deelname aan POEM Fase A en B, medisch-wetenschappelijk onderzoek voor de zwangere en jonge moeder.

13. Bijlagen bij deze informatie

A. Contactgegevens

B. Informatie over de verzekering

C. Toestemmingsformulieren proefpersoon Fase A en B

Proefpersoneninformatie en toestemmingsformulier voor deelname aan POEM Fase A en B, medisch-wetenschappelijk onderzoek voor de zwangere en jonge moeder.

Bijlage A: Contactgegevens voor Treant

Hoofdonderzoeker:
Onderzoekslocatie:
Adres:
Telefoonnummer:

In spoedgevallen buiten kantooruren kunt u contact opnemen met het telefoonnummer van de huisartsenpost 0528 – 286222 (of: de huisartsenpost van uw woonplaats).

Onderzoeksverpleegkundige:
Onderzoekslocatie:
Adres:
Telefoonnummer:

Onafhankelijk arts:
Locatie:
Adres:
Telefoonnummer:

Onafhankelijk arts:
Locatie:
Adres:
Telefoonnummer

Als u klachten heeft met betrekking tot dit onderzoek kunt u dit melden aan het onderzoeksteam of contact opnemen met de Klachtenfunctionaris.

Klachtenfunctionaris:

Proefpersoneninformatie en toestemmingsformulier voor deelname aan POEM Fase A en B, medisch-wetenschappelijk onderzoek voor de zwangere en jonge moeder.

Bijlage B: Informatie over de verzekering

Voor iedere zwangere die meedoet aan dit onderzoek, heeft verrichter een verzekering afgesloten. De verzekering dekt schade door deelname aan het onderzoek. Dit geldt voor schade tijdens het onderzoek of binnen vier jaar na het einde ervan. Schade moet u binnen die vier jaar aan de verzekeraar hebben gemeld.

De verzekering dekt niet alle schade. Onderaan deze tekst staat in het kort welke schade niet wordt gedekt.
Deze bepalingen staan in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Dit besluit staat op www.ccmo.nl, de website van de Centrale Commissie Mensgebonden Onderzoek (zie: 'Bibliotheek' en dan 'Wet- en regelgeving').

De verzekeraar van het onderzoek is:
Naam: Onderlinge waarborgmaatschappij Centramed B.A
Adres: Appelgaarde 4, 2272 TK Voorburg
Telefoonnummer: 070 301 7070
E-mail: info@centramed.nl
Polisnummer 626.107.132

De verzekering biedt een dekking van € 650.000 per proefpersoon en € 5.000.000 voor het hele onderzoek € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever).

De verzekering dekt de volgende schade **niet**:

- schade door een risico waarover u in de schriftelijke informatie bent ingelicht. Dit geldt niet als het risico zich ernstiger voordoet dan was voorzien of als het risico heel onwaarschijnlijk was;
- schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan;
- schade door het niet (volledig) opvolgen van aanwijzingen of instructies;
- schade aan uw nakomelingen, als gevolg van een negatief effect van het onderzoek op u of uw nakomelingen;
- schade door een bestaande behandelmethode bij onderzoek naar bestaande behandelmethoden.

Proefpersoneninformatie en toestemmingsformulier voor deelname aan POEM Fase A en B, medisch-wetenschappelijk onderzoek voor de zwangere en jonge moeder.

Bijlage C: Toestemmingsformulier proefpersoon Fase A en B

POEM studie: *een lange termijn, gerandomiseerd onderzoek ter verbetering van de behandeling van zwangerschapsdiabetes.*

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn voldoende beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen of te stoppen met het onderzoek. Daarvoor hoef ik geen reden te geven.
- Ik geef toestemming om mijn huisarts/specialist(en) die mij behandelt te informeren dat ik meedoe aan dit onderzoek.
- Ik geef toestemming om informatie op te vragen bij huisarts/specialist(en) die mij behandelt.
- Ik weet dat sommige mensen mijn gegevens kunnen inzien. Die mensen staan vermeld in deze informatiebrief.
- Ik geef toestemming voor gebruik van de bloed- en urinemonsters op de manier en voor de doelen die in de informatiebrief staan.
- Ik geef toestemming om mijn gegevens nog 15 jaar na dit onderzoek te bewaren.
- Ik geef ☐ **WEL**
  ☐ **GEEN**
  toestemming om mijn urine- en bloedmonsters nog 15 jaar na dit onderzoek te bewaren.
  Mogelijk kan dit later nog voor meer onderzoek worden gebruikt, zoals in de informatiebrief staat.
- Ik wil meedoen aan **Fase A en B** (dat is tot en met 1 jaar na de bevalling)
- Ik geef ☐ **WEL**
  ☐ **GEEN**
  toestemming om mij na dit onderzoek opnieuw te benaderen voor een vervolgonderzoek (Fase C).

Naam proefpersoon:
Handtekening: Datum·: __ / __ / __

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.
Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik haar daarvan tijdig op de hoogte.

Naam onderzoeker:
Handtekening:
Datum: __ / __ / __

Aanvullende informatie is gegeven door: (Naam en functie):
Handtekening:
Datum: __ / __ / __

De proefpersoon krijgt een volledige informatiebrief mee, samen met een origineel getekend toestemmingsformulier.

Proefpersoneninformatie en toestemmingsformulier voor de ouders van een kind dat in aanmerking komt voor deelname aan de POEM studie Fase A en B, een medisch-wetenschappelijk onderzoek

De POEM studie: *een onderzoek ter verbetering van de behandeling van zwangerschapsdiabetes met een verwachte gezondheidswinst voor moeder en kind*

Geachte ouders/wettelijke vertegenwoordiger/ voogd,

U ontvangt deze brief omdat u meedoet aan de POEM studie en uw kind na de geboorte ook vrijwillig mee kan doen aan deze studie. Daarvoor is schriftelijke toestemming nodig van beide ouders. Voordat u beslist of u toestemming geeft om uw kind mee te laten doen, krijgt u uitleg over wat het onderzoek voor uw kind inhoudt. Lees deze informatie rustig door en vraag de onderzoeker meer uitleg als u vragen heeft. U kunt het uiteraard ook bespreken met uw partner, vrienden of familie.
Er doen in totaal 500 zwangere vrouwen mee aan dit onderzoek in Nederland. De Centrale Commissie Mensgebonden Onderzoek heeft dit onderzoek goedgekeurd. Algemene informatie over meedoen en toetsing van onderzoek vindt u in de brochure 'Medisch-wetenschappelijk onderzoek' (VWS). Deze kunt u downloaden op: https://www.rijksoverheid.nl/documenten/brochures/2014/09/01/medisch-wetenschappelijk-onderzoek-algemene-informatie-voor-de-proefpersoon.

1. Doel van het onderzoek met betrekking tot het kind

Het doel van de POEM studie is om de veiligheid, het gemak, de meerwaarde en de gezondheidswinst van metformine aan te tonen bij de behandeling van zwangerschapsdiabetes op korte en lange termijn bij moeder en kind. Metformine is al geregistreerd voor de behandeling van diabetes, maar nog niet bij zwangerschapsdiabetes.
De POEM studie bestaat uit 3 fasen. Fase A start vanaf de vaststelling van zwangerschapsdiabetes tot 6 weken na de bevalling. Fase B loopt van 6 weken tot 1 jaar na de bevalling. U heeft aangegeven mee te willen doen aan fase A en B. In deze fasen gebruikt de helft van de deelnemende moeders aan de studie metformine. De andere helft is de controlegroep, die de bestaande behandeling voor zwangerschapsdiabetes krijgt.
Om ook de effecten van metformine op het kind te onderzoeken volgen we ook graag vanaf de geboorte de ontwikkeling van het kind. Hiervoor vragen wij nu uw toestemming. Dit betreft dus de laatste 6 weken van Fase A en Fase B.
Tot slot observeren we in Fase C wat het gebruik van metformine in Fase A en B door moeder op lange termijn voor effect heeft op zowel moeder als kind. Er wordt in Fase C geen studiemedicatie meer gebruikt. Aan het eind van Fase B zullen wij u om toestemming vragen om mee te doen aan Fase C, zowel voor moeder als kind. Voor de volledigheid wordt in deze informatiebrief wel informatie gegeven over Fase C, waarin we u en uw kind graag 1 keer per jaar zien om na te gaan hoe het met u en uw kind gaat tot en met de puberteitsontwikkeling en volwassenwording tot 20 jaar na de bevalling.

Voordelen voor het kind van de behandeling met metformine die de moeder heeft ontvangen kunnen zijn: minder aangeboren afwijkingen, minder kans op overgewicht, minder kans op type 2 diabetes, een gezondere geslachtsrijping en schoolontwikkeling. We verwachten geen nadelige effecten voor moeder en kind.

Proefpersoneninformatie en toestemmingsformulier voor de ouders van een kind dat in aanmerking komt voor deelname aan de POEM studie Fase A en B, een medisch-wetenschappelijk onderzoek

2. Wat meedoen voor uw kind betekent

De volgende handelingen en metingen worden gedaan bij uw kind in het kader van het onderzoek:

- Afname navelstrengbloed voor nader onderzoek. (Fase A)
- Opvang eerste urine na de geboorte voor nader onderzoek. (Fase A)
- Bezoek bij onderzoeker samen met moeder: 1 keer in Fase A, 2 keer in Fase B ter beoordeling van de ontwikkeling van het kind. *In Fase C eenmaal per jaar.*
- Inleveren van urine: 1 keer in Fase A, 2 keer in Fase B. *In Fase C 5 keer.*

3. Wat wordt er van u verwacht

Om het onderzoek goed te kunnen uitvoeren is het belangrijk dat u contact opneemt met de onderzoeker:

- als uw kind in een ziekenhuis wordt opgenomen of behandeld;
- als u niet meer wilt dat uw kind meedoet aan het onderzoek;
- als uw kind geneesmiddelen gaat gebruiken (ook homeopathische middelen en natuurgeneesmiddelen);
- als de contactgegevens wijzigen.

Ook verwachten wij dat u en uw kind zich aan de volgende afspraken houden:

- er kan niet meegedaan worden aan een ander medisch- wetenschappelijk onderzoek gedurende dit onderzoek;
- de afspraken voor de bezoeken worden nagekomen;
- de deelnemerskaart van het onderzoek laat u zien als u bij een andere arts komt.

4. Mogelijke voor- en nadelen van deelname aan onderzoek

Deelname aan dit onderzoek betekent dat u met uw kind jaarlijks het onderzoekscentrum bezoekt. Uw eigen bezoeken worden gecombineerd met de bezoeken van uw kind aan het onderzoekscentrum. Nadelen van meedoen aan het onderzoek kunnen zijn dat u en uw kind tijd kwijt zijn aan de bezoeken die u moet afleggen.

5. Als u niet wilt meedoen of wilt stoppen met het onderzoek

Deelname is altijd vrijwillig. De toestemming van beide ouders is nodig voor deelname van uw kind aan dit onderzoek. Als uw kind de leeftijd bereikt heeft van 12 jaar zal uw kind ook zelf toestemming moeten geven, naast uw toestemming. Als uw kind de leeftijd van 16 jaar heeft bereikt is zijn toestemming toereikend, u hoeft dan als ouders niet meer mee te tekenen.
Gedurende het onderzoek wordt het gedrag van uw kind op verzet beoordeeld. Blijkt dat het verzet groter is dan normaal in soortgelijke situaties, dan is dat een reden om de handelingen voor het onderzoek niet uit te voeren of te stoppen met het onderzoek. De gegevens die tot dat moment zijn verzameld, worden gebruikt voor het onderzoek. Als u dat wilt, kan verzameld lichaamsmateriaal van uw kind zoals urine, worden vernietigd.

Proefpersoneninformatie en toestemmingsformulier voor de ouders van een kind dat in aanmerking komt voor deelname aan de POEM studie Fase A en B, een medisch-wetenschappelijk onderzoek

6. Einde van het onderzoek

Deelname van uw kind aan het onderzoek stopt als:

- alle bezoeken in het kader van dit onderzoek zijn uitgevoerd;
- uw kind hevig verzet vertoond groter dan normaal in afwijkende situaties;
- ouders besluiten om te stoppen;
- het einde van het hele onderzoek is bereikt;
- de onderzoeker het beter voor uw kind vindt om te stoppen;
- de ethische toetsingscommissie of de overheid besluit om het onderzoek te stoppen.

Het hele onderzoek is afgelopen als alle deelnemers klaar zijn.

7. Gebruik en bewaren van gegevens en lichaamsmateriaal

Voor dit onderzoek is het nodig dat lichaamsmateriaal (urinemonsters) en medische en persoonsgegevens van uw kind worden verzameld en gebruikt. Uw kind krijgt een code die op het lichaamsmateriaal en de gegevens komt te staan. De naam van uw kind wordt weggelaten. De privacy van uw kind is zo gewaarborgd.

Uw gegevens

Alle gegevens blijven vertrouwelijk. Alleen het onderzoeksteam (arts en verpleegkundigen) weten welke code uw kind heeft. Wij geven de gegevens van uw kind door aan de opdrachtgever, het onderzoekscentrum van de POEM studie, maar alleen met die code, nooit met de naam. De sleutel voor de code blijft bij de onderzoeker. Ook in rapporten over het onderzoek wordt alleen die code gebruikt. Sommige mensen mogen uw medische- en persoonsgegevens inzien. Dit is om te controleren of het onderzoek goed en betrouwbaar is. Algemene informatie hierover vindt u in de brochure ‘Medisch-wetenschappelijk onderzoek’ van VWS.

Mensen die uw gegevens kunnen inzien zijn: het onderzoeksteam, een deskundig controleur en de Inspectie voor de Gezondheidszorg. Zij houden uw gegevens geheim. Als u de toestemmingsverklaring ondertekent, geeft u toestemming voor het verzamelen, bewaren en inzien van uw medische en persoonsgegevens. De onderzoeker bewaart de gegevens minstens 15 jaar na afronding van het onderzoek.

Lichaamsmateriaal

Verkregen lichaamsmateriaal (urine) bewaren we gecodeerd, zorgvuldig en geanonimiseerd. Het lichaamsmateriaal wordt gebruikt om de effecten van metformine te kunnen vaststellen. Er wordt gekeken naar veranderingen in de stofwisseling die kunnen leiden tot het krijgen of voorkomen van chronische ziekten (zoals diabetes, hoge bloeddruk, hart en vaatziekten en kanker) en van belang zijn in belangrijke ontwikkelingen (puberteit, hormonale, geestelijke en intellectuele ontwikkeling). Het lichaamsmateriaal zal minstens 15 jaar na afronding van het onderzoek worden bewaard.

Proefpersoneninformatie en toestemmingsformulier voor de ouders van een kind dat in aanmerking komt voor deelname aan de POEM studie Fase A en B, een medisch-wetenschappelijk onderzoek

Later gebruik gegevens en/of lichaamsmateriaal

Wij willen ook urinemonsters invriezen en bewaren om nieuwe inzichten over de lange-termijn effecten van metformine bij zwangerschapsdiabetes te verkrijgen. Op het toestemmingsformulier kunt u aangeven of u hiermee akkoord gaat. U kunt deze toestemming altijd weer intrekken. De urinemonsters worden dan vernietigd. Als er al metingen in de monsters zijn gedaan, worden de resultaten daarvan wel gebruikt.
De POEM studie wordt gesteund door het Ministerie van VWS en is officieel geregistreerd in een internationaal erkend wetenschappelijk onderzoeksregister (www.clinicaltrial.gov). Deze website bevat geen informatie die herleidbaar is tot u als persoon. Wel kan de website een samenvatting van de resultaten tonen. Algemene informatie over de registratie van onderzoeken vindt u in de brochure 'Medisch-wetenschappelijk onderzoek' van het Ministerie van VWS.

8. Verzekering voor proefpersonen

Omdat het kind zelf geen medicatie tot zich neemt en het opvangen van urine geen risico's kent, is een proefpersonenverzekering voor het kind niet noodzakelijk.

9. Informeren huisarts en/of behandelend specialist en/of apotheker

Wij sturen uw huisarts een brief om te laten weten dat uw kind meedoet aan het onderzoek. Dit is in het belang van uw kind en een voorwaarde om mee te doen. Uw kind kan niet deelnemen als u geen huisarts heeft.

10. Vergoeding voor meedoen

U of uw kind wordt niet betaald voor het meedoen aan dit onderzoek. De testen van het onderzoek kosten u niets. Voor uw bezoeken in het kader van het onderzoek krijgt u een reiskostenvergoeding, parkeergeld en eventuele kosten voor een maaltijd.

11. Heeft u vragen?

Bij vragen kunt u contact opnemen met het onderzoeksteam. Voor onafhankelijk advies over meedoen aan dit onderzoek kunt u terecht bij de onafhankelijke arts. Hij weet veel over het onderzoek, maar heeft niets te maken met dit onderzoek. Bij klachten kunt u altijd terecht bij ons studieteam of zo nodig extern bij de Klachtenfunctionaris. Alle gegevens hiervoor vindt u in **bijlage A**: Contactgegevens.

12. Bijlagen bij deze informatie

A. Contactgegevens
B. Toestemmingsformulier ouders Fase A en B

Proefpersoneninformatie en toestemmingsformulier voor de ouders van een kind dat in aanmerking komt voor deelname aan de POEM studie Fase A en B, een medisch-wetenschappelijk onderzoek

Bijlage A: Contactgegevens voor

Hoofdonderzoeker:
Onderzoekslocatie:
Adres:
Telefoonnummer:

In spoedgevallen buiten kantooruren kunt u contact opnemen met het telefoonnummer van de huisartsenpost 0528 – 286222 (of: de huisartsenpost van uw woonplaats).

Onderzoeksverpleegkundige:
Onderzoekscentrum:
Adres:
Telefoonnummer:

Onafhankelijk arts:
Locatie:
Adres:
Telefoonnummer:

Onafhankelijk arts:
Locatie:
Adres:
Telefoonnummer

Als u klachten heeft met betrekking tot dit onderzoek kunt u dit melden aan het onderzoeksteam of contact opnemen met de Klachtenfunctionaris.

Klachtenfunctionaris:

Proefpersoneninformatie en toestemmingsformulier voor de ouders van een kind dat in aanmerking komt voor deelname aan de POEM studie Fase A en B, een medisch-wetenschappelijk onderzoek

Bijlage B: Toestemmingsformulier ouders of voogd Fase A en B kind

POEM studie: *een lange termijn, gerandomiseerd onderzoek ter verbetering van de behandeling van zwangerschapsdiabetes.*

Ik ben gevraagd om toestemming te geven voor deelname van mijn kind aan dit medisch-wetenschappelijke onderzoek:

Naam proefpersoon (kind):* Geboortedatum: __ / __ / __ *

<verplicht>

- Ik heb de informatiebrief voor de proefpersoon ouders/ verzorgers gelezen. Ook kon ik vragen stellen. Mijn vragen zijn voldoende beantwoord. Ik had genoeg tijd om te beslissen of ik wil dat mijn kind meedoet.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen dat mijn kind toch niet meedoet. Daarvoor hoef ik geen reden te geven.
- Als sprake is van verzet van mijn kind bij het onderzoek, vervalt mijn toestemming voor verdere deelname aan het onderzoek.
- Ik geef toestemming om de huisarts die mijn kind behandelt te informeren dat mijn kind meedoet aan dit onderzoek.
- Ik weet dat sommige mensen de gegevens van mijn kind kunnen inzien. Die mensen staan vermeld in deze informatiebrief.
- Ik geef toestemming voor gebruik van de urinemonsters op de manier en voor de doelen die in de informatiebrief staan.
- Ik geef toestemming om de gegevens van mijn kind nog 15 jaar na dit onderzoek te bewaren.
- Ik geef ☐ **WEL**
  ☐ **GEEN**

  toestemming om het lichaamsmateriaal nog 15 jaar na dit onderzoek te bewaren. Mogelijk kan dit later nog voor meer onderzoek worden gebruikt, zoals in de informatiebrief staat.
- Ik ga ermee akkoord dat mijn kind meedoet aan
  ☐ Fase A en B (leeftijd 0 -1 jaar)
- Ik geef ☐ **WEL**
  ☐ **GEEN**

  toestemming om mij na dit onderzoek opnieuw te benaderen voor een vervolg onderzoek (Fase C).

Naam ouder/voogd**:
Handtekening: Datum: __ / __ / __

Naam ouder/voogd**:
Handtekening: Datum: __ / __ / __

Ik verklaar hierbij dat ik bovengenoemde persoon/personen volledig heb geïnformeerd over het genoemde onderzoek. Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de ouder of voogd zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Proefpersoneninformatie en toestemmingsformulier voor de ouders van een kind dat in aanmerking komt voor deelname aan de POEM studie Fase A en B, een medisch-wetenschappelijk onderzoek

Naam onderzoeker:

Handtekening: Datum: __ / __ / __

Aanvullende informatie is gegeven door:

Naam:

Functie:

Handtekening Datum: __ / __ / __

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* Deze informatie wordt na de geboorte aangevuld op dit toestemmingsformulier.

** Doorhalen wat niet van toepassing is.

De ouders en/ of voogd van de proefpersoon krijgen een volledige informatiebrief mee, samen met een origineel getekend toestemmingsformulier.

Secondary outcomes

Phase A	
Mother	**Child**
Maternal weight at inclusion, weight gain	Intra-uterine growth measurements by ultrasonography
Maternal glycemic control: FPG and glucose tolerance at GDM diagnosis	Fetal weight and percentile at delivery
	Fetal macrosomia
Proteinuria (UACR)	LGA (neonatal weight > p90)
Insulin rescue and mean daily dose of insulin	
Acceptability of treatment	*Unfavourable neonatal outcome score (NOS)*
Maternal urinary tract infection (no and %)	IRDS needing CPAP, optiflow, mechanical ventilation and/or surfactant replacement
Unfavourable maternal outcome score (MOS)	Stillbirth and neonatal death
Caesarean delivery	Preterm birth (birth < 37.0 weeks)
Pre-eclampsia, eclampsia, HELPP and gestational hypertension	Shoulder dystocia
	Instrumental delivery
Maternal mortality	Caesarean delivery
Postpartum hemorrhage	Neonatal hypoglycaemia < 2.6 mml/l
Thrombosis (in pregnancy and/or childbed)	Neonatal jaundice needing phototherapy
Each separate neonatal component of GOS	NICU admission
	Apgar score as a variable
	Apgar score < 7 at 5 minutes
	Congenital anomaly
	Each separate neonatal component of GOS

Phase B and C	
Mother	**Child**
Incidence of T2DM and pre-diabetes	Growth and weight development
Weight and BMI (category) development	Gonadal and gender development
Incidence of hypertension	Puberty and maturation
Thrombotic and CVD (cardiovascular disease) events	Educational and intellectual development
Development of chronic disease	Development of chronic disease

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11,12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8-9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	In original protocol

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	In original protocol and IC
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n/a
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	On request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	8-9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.