Advanced Glycation Endproducts (AGEs) in pregnancies complicated by diabetes mellitus and the accumulation of AGEs in the neonates

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Primary Objective: To determine the accumulation of AGEs in the skin and serum of pregnant women with DM1, DM2 or GDM, in comparison to healthy pregnant women and non-pregnant women with DM1 or DM2 and to determine the accumulation of AGEs in the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Observational non invasive

Summary

ID

NL-OMON34029

Source
ToetsingOnline

Brief title
Skin autofluorescence in diabetic pregnancies

Condition

- Diabetic complications
- Pregnancy, labour, delivery and postpartum conditions

Synonym
diabetes, Dysglycemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Advanced Glycation End products, Diabetes Mellitus, Pregnancy, Skin autofluorescence

Outcome measures

Primary outcome

The following descriptive parameters of all women included will be evaluated:

- Age

- Body weight during AGE measurement

- Pregestational BMI

- Nulliparous/multiparous

- Family history of diabetes mellitus

- Age at onset of diabetes

- Duration of diabetes

- Smoking (if yes; pack years, if quitted; when stopped and no)

- Serum creatinin

- Co morbidity

- Medication

- Pregestational RR when available

- End-organ damage (i.e. retinopathy, nephropathy, neuropathy and

cardiovascular events)

- Parameters of pregnancy (i.e. course of pregnancy, birth weight, duration

pregnancy, height and weight of placenta)

The following descriptive parameters of all neonates will be evaluated:

- Gestational age

- Birth weight

- Apgar-score after 5*

- Quantity of milk received before AGE measurement

- Mode of birth

- Whether the mother had DM1, DM2, GDM or no diabetes

- Twins/Triplets

- Perinatal asfyxia (pH in umcilical cord [grenswaarde UMCG invoegen])

- Glucose levels 0 to 48 hours post partum/need for glucose infusion.

Main study parameter/endpoint:

SAF level: Skin AF will be assessed on the ventral side of the lower arm or the skin on the dorsal side of the upperleg with an AGE-Reader (DiagnOptics Technologies BV, Groningen, The Netherlands) as described elsewhere. This instrument is quick and easy to operate on any computer with an USB connection and the measurement takes approximately 30 seconds to complete. In short, the AGE-reader consists of a tabletop box, containing a black light excitation light source (peak wavelength ~370 nm). Light emitted from the skin is measured with an integrated spectrometer. Measurement is fully automated, giving an average value over 50 individual scans. Skin AF is calculated by dividing the mean value of the emitted light intensity per nm between 420 and 600 nm y the mean value of the excitation light intensity per nm between 300 and 420 nm, expressed as arbitrary units (AU). The intra-individual Altman error percentage

is 5.0% on a single day and 5.9% for seasonal changes.

sAGEs: serum AGEs (CML, CEL and pentosidine) will be measured in maternal serum, obtained twice during normal routine control of HbA1c. Serum will be stored at -80*C until analysis of sAGEs.

Secondary outcome

Secondary study parameters/endpoints:

Obstetric complications:

- Pre-eclampsia (defined as diastolic blood pressure >=90 mm Hg on two occasions at least four hours apart in the second half of pregnancy in a previously normotensive women and proteinuria (>=300mg/24h). In patients with pre-existing hypertension, pre-eclampsia was diagnosed when proteinuria occurred de novo in the second half of pregnancy.
- Preterm delivery (defined as delivery <37 weeks gestation).
- Caesarean section
- Postpartum haemorrhage (defined as blood loss >500 ml)
- Maternal mortality
- Other obstetric complications

Perinatal outcome:

- Large for gestational age (defined as birth weight >90th percentile)
- Small for gestational age (defined as birth weight <10th percentile for gestational age and sex)
- Congenital abnormalities (those responsible for death, those causing a significant future disability, or those requiring major surgery for correction)

- Spontaneous abortion

- Perinatal mortality (defined as foetal loss from 24 weeks of gestation,

>=500g, or both, together with all postnatal deaths up to seven days after birth.

- Other perinatal complications

Neonatal outcome

- Neonatal hypoglycaemia (defined as blood glucose <2,6 mmol/L)

- Infant respiratory distress syndrome (defined according to Giedion et al and

according to clinical symptoms of respiratory stress31)

- Neonatal jaundice (defined as hyperbilirubinemia requiring phototherapy)

- Other perinatal complications

Other study parameters (if applicable)

In GDM women only, later presence of IGT or DM, according to ADA criteria,

during 75 gram oral 2-hour GTT performed at least 6 weeks after delivery as

part of standard clinical care.

Study description

Background summary

Since the global incidence of diabetes mellitus (DM) in younger people is increasing, there is an increase in number of women at the reproductive age with DM, especially DM2. During diabetic pregnancy, both in type 1 and 2 diabetes and gestational diabetes mellitus (GDM), an increased incidence in birth defects, perinatal complications, but also maternal complications like pre-eclampsia was found. The prevalence of maternal and perinatal morbidity as well as the perinatal mortality is higher in pregnancies complicated by DM2 compared with DM1. In both DM1, DM2 and GDM the number of complications can be

decreased by stringent glycaemic control. However, despite this stringent metabolic control in recent years, complications are still much more present in diabetic pregnancies than in normal pregnancies. This suggests that other mechanisms are involved in the development of diabetes induced pregnancy complications. One important mechanism may be the increased accumulation of Advanced Glycation Products (AGEs) in long-lived tissues, since the accumulation of AGEs is increased in patient with DM1, DM2 or GDM. This hypothesis is subject of the present study.

AGEs are formed when a reducing sugar, such as glucose, react nonenzymatically with free amino groups on polypeptides or lipids, resulting in formation of reversible early glycation end products, so called Amadori products. Further molecular rearrangements result in the formation of virtually irreversible AGEs. Formation of AGEs is a normal physiological process and tissue concentrations of AGE-modified proteins increase slowly with aging. However, during oxidative and/or glycemic stress, AGEs can be formed more rapidly. This accumulation of AGEs is associated with the progression of various chronic diseases, such as atherosclerosis, renal failure and diabetes mellitus. AGEs among others accumulate in the vessel wall, where they may disturb cell structure and function. AGEs have been implicated in both the microvascular and macrovascular complications of diabetes. The general mechanisms of this association are as follows: (1) formation of cross-links between key molecules in the basement membrane of the extracellular matrix (ECM), permanently altering cellular structure; and (2) interaction of AGEs with receptors for AGEs (RAGE) on cell surfaces, altering cellular function and leading to an inflammatory response. This inflammatory response includes the upregulation of nuclear transcription factors, including NF-*B, which transcribes its target genes. Among these are endothelin-1, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), tissue factor and proinflammatory cytokines.

Increased accumulations of AGEs may possibly not always be compatible with pregnancy, since accumulated AGEs contribute to vascular endothelial dysfunction, a hallmark of pre-eclampsia. Above all, preeclampsia share several risk factors with cardiovascular disease, including pre-existent hypertension, thrombophilia (factor II or factor V Leiden mutations), dyslipidemia, obesity, insulin resistance, diabetes mellitus, inflammation, family history of heart disease or stroke, and possibly increased accumulation of AGEs. This leads to increased cardiovascular morbidity and mortality in later life in women with preeclampsia in previous pregnancies. So, AGEs possibly does not only contribute to the development of preeclampsia and other pregnancy induced complications, but also to anchoring of cardiovascular damage and the cardiovascular diseases involved.
In previous research investigators found AGEs in umbilical cord blood, which means AGEs pass the placenta and reach the unborn child during the whole pregnancy durance. Probably AGEs are able to accumulate in the unborn infant during pregnancy. Therefore, the extent of AGE accumulation in the mother may

be reflected in the by skin AF in the newborn. Possibly infants, born after a pregnancy complicated by diabetes, start their life with a higher AGEs accumulation when compared to infants born after an uncomplicated pregnancy and making them more vulnerable for vascular complications.

Tissue AGE levels can be assessed noninvasively by the autofluorescence reader (AFR; patent number PCT/NL99/00607, DiagnOptics BV Groningen, the Netherlands), a recently introduced and validated device that measures skin autofluorescence based on the fluorescent properties of a part of the various AGE molecules. With the AFR, a close relation of skin autofluorescence was established not only with renal failure, diabetes mellitus, and its complications, but also with inflammation and oxidative stress in acute coronary syndromes. But, tissue AGEs are not exactly the same as serum AGEs (sAGEs). For instance, the physical half-life of sAGEs is shorter and they are more unstable than tissue AGEs. Therefore, sAGEs will be assessed as well for two reasons, firstly, to validate the SAF measurements and secondly, to detect short-term variations in accumulation of AGEs.

Our primary aims are to assess skin autofluorescence (SAF) of the lower arm (using the AFR) or the upperleg of a neonate and serum AGEs in pregnant women who are suffering DM1, DM2 or GDM and to investigate the association between increased AGEs and maternal and fetal complications of diabetic pregnancies and to investigate the possible association between SAF, serum AGEs and glycaemic control of the mother and the SAF level in the newborn. We hypothesize that the accumulation of, in both serum and tissue AGEs will be increased in diabetic pregnancies. We expect that women with GDM have a level of accumulation intermediate between healthy pregnant women and women with DM1 or DM2. We will also determine whether the AGEs accumulation in newborn is different between neonates born after a pregnancy complicated by diabetes or neonates born after an uncomplicated pregnancy and if extent of AGEs in the mother will be reflected in the skin autofluorescence of her offspring.
We hypothesize there will be a higher SAF in the neonates born after a pregnancy complicated by diabetes, when compared to neonates born after an uncomplicated pregnancy.
As secondary objectives, we formulated three objectives; (1) the inflammatory response will be assessed, by obtaining maternal serum for measurement of inflammation markers, such as hCRP, vWF and VCAM-1. We hypothesize that these inflammation markers will be increased in comparison to healthy pregnant controls. (2) We hypothesize also that the increased accumulation of AGEs is associated with the increased incidence of maternal and fetal complications during diabetic pregnancies and (3) the relation between SAF in neonates and the SAF of their mothers will be assessed.

The disease GDM requires a further introduction. GDM implies a substantial risk of later diabetes. Diabetes rates are reported to be between 9 and 43% within 5-10 years after the index pregnancy. There is evidence that in women with GDM an underlying pre-existing β-cell defect is unmasked by poor pancreatic β-cell

compensation for physiological insulin resistance in pregnancy. It has been suggested that increased insulin resistance associated with pregnancy may accelerate the depletion of beta cells. If this is the case, it would be expected that increased parity or subsequent pregnancies would increase the risk for development of subsequent diabetes among women with a history of gestational diabetes. However, findings related to the roles of parity and subsequent pregnancies are conflicting.
Recommendations of the 5th Workshop-Conference on GDM38 are that women with GDM undergo postpartum glucose tolerance testing with a 75 gram oral glucose tolerance test (OGTT) at 6-12 weeks, 1 year after delivery, and every 3 years thereafter. The rational for this recommendation is based on the potential to identify women with apparent diabetes as well as women with impaired glucose tolerance (IGT) in whom diabetes can be delayed or prevented by lifestyle intervention or moderate drug therapy. In this study a 75 gram OGTT will be performed at 6-12 weeks after delivery in case of GDM as part of the clinical follow-up.

Study objective

Primary Objective: To determine the accumulation of AGEs in the skin and serum of pregnant women with DM1, DM2 or GDM, in comparison to healthy pregnant women and non-pregnant women with DM1 or DM2 and to determine the accumulation of AGEs in the newborns of the pregnant women who deliver in the UMCG. The accumulation of soft tissue AGEs will be non-invasively measured by the skin autofluorescence reader and sAGES will be measured in maternal serum.

Secondary Objective(s):
1) To asses the inflammatory response by measurement of inflammation markers in maternal serum in pregnant women with DM1, DM2 or GDM. This response will be measured twice, namely firstly in the third trimester and secondly 6-12 weeks after delivery.
2) To asses the relation between skin autofluorescence (SAF) and presence or development of impaired glucose tolerance (IGT) or DM after pregnancy, as assessed by OGTT 6-12 weeks after delivery. Furthermore, the relation between SAF and maternal, fetal and neonatal complications will be assessed.
3) To asses the relation between SAF in neonates and the SAF of their mothers, in perspective of the presence or absence of diabetes during pregnancy.

Study design

Design: Observational study
Participating centers: The diabetes outpatient clinics of the University Medical Centre Groningen and Medical Centre Haaglanden, The Hague.
SAF and sAGEs will be assessed in pregnant women with DM1, DM2 or GDM in comparison to healthy pregnant and non-pregnant women with DM1 or DM2. SAF will be measured by the skin autofluorescence reader (patent number PCT/NL99/00607,

DiagnOptics BV Groningen, the Netherlands) on the ventral side of the lower arm. In their newborn children, only SAF will be assessed, non-invasively, through illumination of the skin on the dorsal side of the upperleg by the AGE-reader and this will only be done in the UMCG.
SAF will be assessed according to a schedule, shown in table. SAF in non-pregnant women with DM1 or DM2 will be performed during routine visits to our outpatient clinics for maximally four times with approximately the same intervals of the pregnant women. sAGEs will be measured twice by taking a venous blood sample in a heparin tube (10 ml) at the same time of the last two SAF measurements during routine HbA1c control. Serum will be separated and stored at -80*C until analysis of sAGEs. The postpartum measurement of AGEs will be obtained to determine the AGE accumulation after the physiological state of pregnancy is ended and will be combined with the postpartum control at the outpatient clinic. This gives us information about the influence of pregnancy on AGE accumulation.
An OGTT 6-12 weeks after delivery in women with GDM during postpartum control will be performed, as part of standard care.

Table 1.
Participants 10-14 weeks of gestation 20-24 weeks of gestation 32-36 weeks of gestation 6-12 weeks postpartum
DM1 x
x
x x
DM2 If possible
x
x x
GDM - If possible x x
Healthy pregnancies x
x x x

All neonates, independent if they are born after a complicated or uncomplicated pregnancy, will have SAF measurements within 24 hours postpartum and between 6-12 weeks postpartum and this part of the study will only be performed in the University Medical Centre Groningen.

Study burden and risks

Not applicable

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Pregnant women with known DM1, DM2, GDM in the age range of 18-40 years. Pregnant women with DM1, DM2 and GDM can only be included when the glucose levels are established in the following range:
- HbA1c <8%, if possible measured during last menstrual cycle, last outpatient visit before pregnancy if within period < 4 months or at first visit after positive pregnancy test.
Controls will be healthy pregnant and non-pregnant women and non-pregnant women with DM1 or DM2 in the age range of 18-40 years and all children of these above mentioned women who deliver in the UMCG. Thereby, we will include a group of control neonates born after an uncomplicated pregnancy.

Exclusion criteria

Pregnant women with DM1 or DM2:
- HbA1c >8%

- Renal failure (serum creatinine >120 µmol/L)
- Fitzpatrick skin type VI (negroid skin colour), or skin reflectance <6% or local skin abnormalities of the volar side of the lower arms
- Recent (< 3 months) serious (requiring hospital admission) infection or cardiovascular event;Pregnant women with GDM:
- HbA1c >7% after 20-24 weeks of gestation
- Treatment of GDM with diet only
- Renal failure (serum creatinine >120 µmol/L)
- Fitzpatrick skin type VI (negroid skin colour), or skin reflectance <6% or local skin abnormalities of the volar side of the lower arms
- Recent (< 3 months) serious (requiring hospital admission) infection or cardiovascular event;Healthy (non-)pregnant women:
- Known active disease
- Fitzpatrick skin type VI (negroid skin colour), or skin reflectance <6% or local skin abnormalities of the volar side of the lower arms
- Recent (< 3 months) serious (requiring hospital admission) infection or cardiovascular event;Non-pregnant women with DM1 or DM2:
- HbA1c >8%
- Pregnancy
- Renal failure (serum creatinine >120 µmol/L)
- Fitzpatrick skin type VI (negroid skin colour), or skin reflectance <6% or local skin abnormalities of the volar side of the lower arms
- Recent (< 3 months) serious (requiring hospital admission) infection or cardiovascular event;Neonates (control group):
- When the mother is excluded
- Congenital malformations
- Gestational age < 37 weeks
- Birth weight < P25 or > P75
- Fitzpatrick skin type VI (negroid skin colour)
- Measurement > 24 hours postpartum

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-11-2010
Enrollment:	550
Type:	Actual

Ethics review

Approved WMO Date:	23-06-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-10-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 23319
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL32041.042.10
OMON	NL-OMON23319