The role of immunology in diabetes mellitus and pregnancy

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Primary Objective: To determine the local and peripheral immune response in diabetic pregnancies in comparison to healthy controls. Immune response will be measured by counting Th1/Th2-cells, Tregs, NK-cells, monocytes and granulocytes. Produced...

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

Summary

ID

NL-OMON36546

Source
ToetsingOnline

Brief title
Immunology in diabetes mellitus and pregnancy

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Autoimmune disorders
- Obstetric and gynaecological therapeutic procedures

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: Diabetes mellitus, Immunology, Pregnancy

Outcome measures

Primary outcome

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

- Age
- Body weight
- 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
- Medication
- Co morbidity
- Pregestational RR
- End-organ damage (i.e. retinopathy, nephropathy, neuropathy and cardiovascular events)
- Parameters of pregnancy (i.e. course of pregnancy, birth weight, height and weight of placenta)

Main study parameter/endpoint:

Peripheral immune response:

- Number of Th1/Th2-cells

- Number of cytotoxic T-cells

- Number of Tregs

- Number of NK-cells

- Number of monocytes

- Number of granulocytes

- Number of produced cytokines by the different cells

Local immune response:

- Number of monocytes

- Number of granulocytes

- Number of cytotoxic T-cells

- Number of T-helper cells

- Number of NK-cells

- Number of Tregs

All of these results will be compared to the different control groups and a difference of 10% will be considered as physiologic significant.

Secondary outcome

- Obstetric complications:

o 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.

o Preterm delivery (defined as delivery <37 weeks gestation).

o Caesarean section

o Postpartum haemorrhage (defined as blood loss >500 ml)

o Maternal mortality

- Perinatal outcome

o Large for gestational age (defined as birth weight >90th percentile)

o Small for gestational age (defined as birth weight <10th percentile for gestational age and sex)

o Congenital abnormalities (those responsible for death, those causing a significant future disability, or those requiring major surgery for correction)

o Spontaneous abortion

o 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.

- Neonatal outcome

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

o Infant respiratory distress syndrome (defined according to Giedion et al and according to clinical symptoms of respiratory stress)

o Neonatal jaundice (defined as hyperbilirubinemia requiring phototherapy)

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, 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 are higher in pregnancies complicated by DM2 compared with DM1. In both DM1 and DM2 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. This hypothesis is subject of the present study. One important mechanism may be the altered immune response during diabetes, since in both DM1 as well as in DM2 patients the immune response has changed. These changes may not always be compatible with pregnancy, since for a normal pregnancy the normal immune response has to shift to a type 2 T-helper cell (Th2) type immune response. Next to it, it is important that the numbers of Tregs are increased during pregnancy. These changes of pregnancy are necessary to accommodate the semiallogenic fetus. Deviations from these adaptations are associated with pre-eclampsia, pre-term delivery and/or abortion. So, adequate and strict regulation of the immune responses is essential for a normal pregnancy also. Such an adequate and strict regulation of the immune responses is especially important at local level at the time of implantation. Local infiltration of immune cells is seen into the decidua and the endometrium around the implantation site during the implantation. By producing cytokines, chemokines and growth factors, these cells are important in creating the local environment in the endometrium for implantation of the blastocyst and subsequent placentation. The balance between the various immune cells present and the factors produced by these cells is critical for normal placentation and therefore normal foetal growth and normal pregnancy.

Immune response in DM1: Due to the fact that DM1 is an autoimmune disease, the immune response of diabetic women differs from the immune response of healthy women. Various changes in immune responses have been found in patients with DM1, on peripheral as well as on local level. On peripheral level, a shift towards a type 1 T-helper cell (Th1) immune response and a decreased number and/or functions of regulatory T-cells (Tregs), decreased numbers of Natural Killer cells (NK) and activation of monocytes have been found. Some of these changes are opposite to the changes occurring in normal pregnancy, so it may be possible that adequate adaption of the immune response to pregnancy may not occur in these patients. An autoimmune-induced dysregulated immune response and pregnancy complication has been shown in women with rheumatoid arthritis. They showed increased pregnancy complications, such as pre-eclampsia and decreased

birth weight, although data about disease severity and medication use was not available. So, this association is more an indication than a strict relation.

Immune response in DM2: In case of DM2, a low grade general inflammatory response has been observed often. This low grade inflammation and activated inflammatory cells may contribute to the insulin resistance in these patients. The presence of a low level of inflammation in DM2 patients may interfere with pregnancy, since pregnancy itselves is also associated with activation of the inflammatory system. Further activation of the inflammatory response during normal pregnancy may result in pregnancy complications, like pre-eclampsia. So, low levels of inflammation in DM2 patients may aggravate the normal pregnancy induced activation of the inflammatory response, possibly resulting in preeclampsia.

The present study is a pilot study in order to investigate the adaptations of the immune response to pregnancy in women with DM1 or DM2 in comparison with normal controls. In a observational study design, the immune responses in peripheral blood and placenta will be studied in healthy pregnant women and pregnant women with DM1 or DM2 and in control non-pregnant women. We hypothesize that the peripheral and local immune responses are different compared to healthy controls. We expect that the shift towards a Th2-response will be hampered, the numbers of Tregs will be decreased and monocytes and granulocytes will be further activated in comparison with normal pregnancy. We hypothesize also that the changes in immune responses in diabetic pregnancy are associated with the increased numbers of complications during diabetic pregnancies.

Study objective

Primary Objective: To determine the local and peripheral immune response in diabetic pregnancies in comparison to healthy controls. Immune response will be measured by counting Th1/Th2-cells, Tregs, NK-cells, monocytes and granulocytes. Produced cytokines by different cells will be measured as well.

Secondary Objective: To determine the maternal and foetal outcome of diabetic pregnancies in comparison with healthy controls in association with the local and peripheral immune response.

Study design

Design: observational study.

Peripheral immune response will be studied in whole blood from pregnant women in the third trimester of pregnancy. Blood will be taken during routine blood sampling. Blood samples of pregnant and non-pregnant women with DM1 or DM2 (see in- and exclusion criteria) will be collected. Diagnosis of DM1 or DM2 has been

established before pregnancy. Controls will be healthy pregnant women without diabetes mellitus and non-pregnant women (healthy, DM1 and DM2). Blood samples will be used to evaluate the number of the various leukocytes, i.e. lymfocytes and lymphocyte subpopulations (for instance regulatory T cells), monocytes, granulocytes, as well as their state of activation, using flow cytometry. The production of type 1 and type 2 cytokines will be evaluated after stimulation of the lymphocytes in order to evaluate the balance between Th1 and Th2 responses. Plasma will be frozen for additional measurement of inflammation markers, such as hCRP, vWF and VCAM-1.

Local immunological changes will be studied. The placentas of all women included will be collected and biopsies will be taken in situ of the decidua. Moreover, tissue biopsies of the placental bed will be obtained after caesarean section. These biopsies from approximately 0.3 x 0.3 cm in diameter will be obtained from the placenta bed from the uterus after delivery of the placenta during caesarean delivery by pfannenstiel incision. All of these tissue biopsies will be fixed (liquid nitrogen and formalin) immediately after resection and stored until further analysis. Parameters of the immune response will be evaluated at the protein level (immunohistochemistry). Previous research from Dr. R.B. Donker (METc-registrationnr 2003/026) and Dr. M.M. Faas (ABR-25930) has shown that this procedure does not pose any risk to the patients.

Study burden and risks

Blood sampling as well as the placental biopsies procedure does not carry any risk for the women. As far as blood sampling in diabetic pregnant and healthy women is concerned, this will be done during routine blood sampling in the hospitals during the third trimester of pregnancy. Two tubes of 10 ml of extra blood will be sampled at that time. Control pregnant women will be asked to give two times of 10 ml of blood during the third trimester as well.
Non-pregnant women with DM1 or DM2 will be asked to give two times of 10 ml of blood during the follicular phase of the menstrual cycle. In case of use of oral contraception*s: the blood samples will be taken at the end of the stopweek. These samples will be sampled during routine blood sampling for serum glucose measurement. From the control healthy non-pregnant women, blood will be taken at 1 occasion during the follicular phase of the ovarian cycle. For placental biopsies, this will be done after delivery of the placenta, which is part of the normal delivery of pregnant women. It will not harm in any way mother or the fetus, beacuse previous research from Dr. R.B. Donker (METc-registrationnr 2003/026) and Dr. M.M. Faas (ABR-25930) has shown that this procedure does not pose any risk to the patients.
Participation in this study will not benefit the women personally. However, the present study about immunology in diabetic pregnancies and the pathogenesis of diabetic complications may in the long term benefit any pregnant women.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Group 1: Pregnant women with DM1 >18 en <40 yrs
Group 2: Pregnant women with DM2 >18 en <40 yrs
Group 3: Healthy pregnant women >18 en <40 yrs
Group 4: Non-pregnant women with DM1 >18 and <40 yrs
Group 5: Non-pregnant women with DM2 >18 and <40 yrs
Group 6: Healthy non-pregnant women >18 en <40 yrs

Exclusion criteria

Group 1,2:
- HbA1c >7,5% after 30 weeks of gestation

- Renal failure (serum creatinine >120 µmol/L)
- Active treatment for auto-immune disease, except substitution therapy for primary hypothyroidism with TBII <1. ;Group 3:
- Gestational diabetes mellitus
- Intrauterine growth restriction (defined as foetal weight <10th percentile for gestational age).
- >2 times of miscarriage (defined as loss of pregnancy during the first 23 weeks of gestation)
- All other maternal and foetal complications
- Known active disease;Group 4, 5:
- HbA1c >7,5%
- Renal failure (serum creatinine >120 µmol/L)
- Active treatment for auto-immune disease, except substitution therapy for primary hypothyroidism with TBII <1. ;Group 6:
- Known active disease, except substitution therapy for primary hypothyroidism with TBII <1.

Study design

Design

Study type:	Observational 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):	07-04-2010
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO

Date:	19-02-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2012
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: 23378
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL30779.042.09
OMON	NL-OMON23378