In vitro activation of monocytes from pregnant women by different types of bacterial lipopolysaccharides leads different immunological pathways

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON32389

Source
ToetsingOnline

Brief title
Changed immunological response to oral micro-organisms during pregnancy

Condition

- Bacterial infectious disorders
- Maternal complications of pregnancy

Synonym
immune response during pregnancy

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: Immune response, Monocytes, Oral micro-organisms, Pregnancy

Outcome measures

Primary outcome

Expression of toll-like receptors on monocytes during pregnancy.

Cytokine production of monocytes during pregnancy after stimulation with

sonicates from different oral pathogenic micro-organisms and LPS of E. coli and

P. gingivalis.

Secondary outcome

Not applicable.

Study description

Background summary

Recent studies show a relationship between complications during pregnancy and the presence of an maternal infection during pregnancy, like for instance the association between bacterial vaginosis and preterm birth. There is growing evidence that maternal periodontal disease during pregnancy is a risk factor for preterm birth or preeclampsia. Periodontal disease is a severe and destructive infection of the periodontium (tissues surrounding the teeth), caused mainly by gramnegative micro-organisms. Althought more than 500 species have been identified in the oral cavity, only a small group of periodontopathic micro-organisms (like Fusobacterium nucleatum, Tannerella forsythensis, Prevotella intermedia, Treponema denticola, Micromonas micros en Porphyromonas gingivalis) seems to play a role in the development of periodontal disease. Gramnegative micro-organisms contain cell wall components like lipopolysaccharides (LPS) which trigger the immune system to produce proinflammatory cytokines, like IL-1 and TNF-alfa. Especially P. gingivalis seems to be capable of producing large amounts of LPS. The role of LPS in the

immune response during pregnancy is subject of interest. Conducted studies show that extreme low-dose infusion of E. coli LPS into pregnant rats leads to a preeclampsia-like syndrome, characterized by hypertension and proteinuria. This syndrome is pregnancy-specific: identically treated non-pregnant rats don't develop these symptoms. This shows that pregnant rats are more susceptible to LPS than non-pregnant rats. In our recently conducted study *The effect of Porphyromonas gingivalis lipopolysaccharides in pregnant rats: a pilot study*we investigated the possible role of P. gingivalis-LPS in the pathogenesis of preeclampsia. The results show that LPS of P. gingivalis does lead to growth-restriction of the placenta and the fetus, and also leads to hypertension, but doesn't induce a preeclampsia-like syndrome in the pregnant rat. LPS of different types of micro-organisms seem to have different effects on pregnancy. Whether or not pregnant rats are more susceptible for P. gingivalis-LPS compared with non-pregnant rats is subject of further investigation.

The immune system recognizes LPS of different micro-organisms through pattern recognition receptors (toll-like receptors) on the cell wall of monocytes. At present, 13 different types of toll-like receptors have been identified, of which TLR-4 and TLR-2 have been studied most frequently. TLR-4 recognizes LPS of gramnegative micro-organisms, like E. coli. TLR-2 mainly recognizes peptidoglycan of grampositive micro-organisms. Recent studies however show that LPS of the gramnegative bacteria P. gingivalis activates TLR-2 but not TLR-4. This might be explained by the fact that the chemical structure of P. gingivalis lipid A differs from the lipid A produced by bacteria such as E. coli. Activation of a specific toll-like receptor will trigger the monocyte to a modulated immune response. Activation of TLR-4 leads to the production of Th1 cytokines like IL-1, IL-6 en TNF-alfa, which stimulates the cellular immune response. Activation of TLR-2 leads to the production of Th2 cytokines, like PGE2, IL-4, IL-5, IL-10 and IL-13, which stimulates the humoral immune response. Succesful pregnancy induces an immune bias toward a Th2-immune response. It has been postulated that Th1-immunity is not compatible with pregnancy. A pathological pregnancy, like preeclampsia, is associated with a Th1-Th2 shift, toward Th1-immunity. The mechanisms responsible for this pathological shift in cytokine production in preeclamptic pregnancies are not understood. It is possible that activation of different toll-like receptors (induced by a mixed infection, like periodontal disease) initiates different kinds of immunological pathways. The results of our animal experiments suggest that LPS of gramnegative bacteria which activates TLR-4 is capable of inducing preeclampsia-like symptoms (hypertension and proteinuria), while LPS of gramnegative bacteria which activates TLR-2 induces growth-restriction and hypertension, but not proteinuria.

The aim of this project is to test if the expression of TLR-4 and TLR-2 on monocytes changes during pregnancy. We also want to study whether different types of LPS (of different types of bacteria, like E. coli and P. gingivalis) trigger the monocytes to produce Th1 or Th2 cytokines. Since pregnant women are more susceptibility to LPS, we also would like to study if the cytokine production of monocytes changes during pregnancy after stimulation with

different types of LPS.

Study objective

Objective of this study is to investigate cytokine production and expression of toll-like receptors on monocytes in blood samples from pregnant and non-pregnant women using sonicates from different types of oral pathogenic micro-organisms and isolated LPS.

Study design

Two blood samples, drawn from the antecubital vein, will be taken from pregnant patients during routine vein puncture at 30 weeks of pregnancy. Two blood samples will be taken from age-matched controls during the follicular fase of their menstrual cycle. The expression of TLR-2 and TLR-4 on the monocyte in unstimulated whole blood samples of both groups (pregnant and non-pregnant)will be measured using fluorescent antibodies. The total amount of monocytes expressing these TLR's and the density of expression will be measured using flow cytometry. Blood samples will be stimulated in vitro with sonicates from different oral periodontopathic micro-organisms and different doses of LPS of E. coli and P. gingivalis to determine to cytokine production of pregnant and non-pregnant monocytes. The production of different cytokines (like IL-1 beta, IL-6, IL-10, IL-13, IL-18 and TNF-alfa) will be measured after stimulation (flow cytometry/ELISA). We will also investigate the recently discovered, new interleukins IL-23 and IL-29 (of the IL-12 family) which are associated with a Th1-immune response and a disturbed placental implantation.

Study burden and risks

Two extra blood samples, drawn from the antecubital vein, will be taken from pregnant patients during routine vein puncture at 30 weeks of pregnancy. Two blood samples will be taken from controls during the follicular fase of their menstrual cycle. In order to exclude patients with severe periodontal disease and patients with oral pathogenic micro-organisms, all participants will be submitted to a quick periodontal screening (DPSI-screening) and a microbiological screening. No risks are to be expected.

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

Age < 40 years
Caucasian origin

Exclusion criteria

Multiple pregnancy
Growth restriction of the fetus
Hypertension
Chronical diseases
Age > 40 years
Smoking
Influenza or fever within two weeks prior to bloodsampling
Severe periodontal disease
Presence of P. gingivalis

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):	01-09-2008
Enrollment:	40
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
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

No registrations found.

In other registers

Register	ID
CCMO	NL23423.042.08