The influence of pregnancy on CD8 cell subsets in women.

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Primary Objective: The main objective of this study is to analyse the effects of pregnancy on levels and percentages of CD8 cell subsets in peripheral blood both during and after pregnancy.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON38830

Source
ToetsingOnline

Brief title
CD8 cells and subsets in pregnancy

Condition

- Immune disorders NEC
- Maternal complications of pregnancy

Synonym
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: CD8, Immunology, Memory, Pregnancy

Outcome measures

Primary outcome

Primary outcomes of the study will be the percentages and levels of CD8 cell subsets. These levels will be analysed and compared between the different population groups.

Secondary outcome

Not applicable

Study description

Background summary

Adaptation of the maternal immune system to accommodate the semi-allogeneic fetus is necessary for pregnancy success. Dysregulation of the maternal immune adaptation is implicated in reproductive disorders such as infertility, recurrent miscarriage, fetal growth restriction, and preeclampsia, which together affect at least 25% of women seeking to reproduce.

The exact mechanisms being responsible for fetal tolerance are not known, however T cells, natural killer (NK) cells, monocytes, and macrophages are all regarded as important players in the adaptation of the maternal immune response. Especially regulatory T cells (Treg) cells are thought to have an important role in pregnancy. Treg cells are a subset of T cells with immunosuppressive capacities, and are able to regulate immune responses and regulate other immune cell subsets. Altered levels of Treg cells are associated with adverse pregnancy outcomes, both in human and animal studies, and furthermore, Treg based therapies improved pregnancy outcomes in animal studies.

Interestingly, incidences of immune related pregnancy disorders are higher in first pregnancies, with lower rates of for example preeclampsia, in second and third pregnancies. These epidemiologic findings could be explained by a priming mechanism of the maternal immune system during pregnancy, which remains intact after pregnancy. Which enables the maternal immune system to respond more adequate to a possible following pregnancy .

Recently, both human and mouse studies have shown the effect of parity on the maternal immune system. Depletion of Treg cells is known to cause fetal resorptions in mice. A recent study shows lower rates of fetal resorptions in second pregnancies compared to first pregnancies after depletion of Treg cells. This study showed that in a second pregnancy T cells accumulate with accelerated kinetics in lymph nodes compared with the first pregnancy. An effect of previous pregnancies may also exist in women, as nulliparity was associated with lower percentages of Treg cells in blood compared with parous women.

The role of CD8 cytotoxic T cells in pregnancy is of recent interest, but remains to be defined. CD8 cells are important in the cytotoxic immune reaction. This immune reaction starts after a cell presents a foreign antigen. Allogenic peptides derived from for example microbes are presented on cells by specialised proteins called major histocompatibility complexes (MHC). In MHC class I associated immunity MHC class I molecules express peptides derived from intracellular antigens. The antigens are processed intracellularly, after which they are presented on MHC class I molecules. CD8+ cells bind to the MHC class I expressing cells, the CD8+ cytotoxic T cells become activated and kill the antigen-expressing cells. This mechanism is very important for the immune system in recognising foreign cells out of *own* cells. Interestingly, in human pregnancy there is absence of classical MHC class I expression on trophoblasts cells (the cells which invade the uterus), which causes partial prevention of immune attack by maternal T cells. However, trophoblast cells do express HLA-C and also the non-classical MHC molecules HLA-E and HLA-G, these molecules bind to CD8 cells.

CD8 cells can be divided into subsets based on their function and phenotype; naïve, effector, memory, and (recently) regulatory CD8+ cells. Till now there is not a lot known about CD8 cell subsets in pregnancies, previous studies found altered levels of activated CD8 cells in decidual tissue, but no differences in peripheral CD8 cells between pregnant and non pregnant women. These studies only analysed certain subsets of CD8 cells, and did not compare former pregnant women with non pregnant women.

We hypothesise that pregnancy alters levels of CD8 subsets, not only during pregnancy but also after pregnancy, preparing the maternal immune system for any subsequent pregnancies.

Study objective

Primary Objective: The main objective of this study is to analyse the effects of pregnancy on levels and percentages of CD8 cell subsets in peripheral blood both during and after pregnancy.

Study design

This study is an observational study. Levels of CD8 cell subsets will be analyzed in peripheral blood in 3 subject groups. Namely, early gestational pregnant women (n=15), former pregnant women (at least 6 months post partum) (n=15), and non pregnant women (n=15) at a single moment. In the pregnant group blood samples will be taken (10 ml) at weeks 11-13 of pregnancy during routine blood sampling. In the former pregnant women blood will be taken at least 6 months post partum. Blood samples will also be taken from non pregnant healthy women without any pregnancies in their medical history. In whole blood we will measure levels of CD8 cell subsets and monocytes using standard techniques which are operational in our laboratory.

Study burden and risks

If possible blood samples will be taken by means of an extra blood sample taken at a routine sampling moment or blood will be taken at an extra blood sample moment at a suitable time point. This will not pose any risk on the individuals. This study investigates the pregnancy related immune chances in normal pregnancy, eventually these chances might not happen in immune related disorders of pregnancy, and therefore could potentially lead to therapies. Subjects have no direct benefits of this study..

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- healthy
- written informed consent
- 18-40 years ;Depending on the group subjects must either meet criteria 1,2, or 3
1. Pregnant in first pregnancy between 11-13 weeks (pregnant women)
2. 6 months after uncomplicated pregnancy (former pregnant women)
3. Non pregnant (former pregnant and non pregnant women)in the follicular phase of their cycle

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- smoking
- immune related disorders
- fever / illness within the last month
- infertility
- body mass index <18 or >30
- medication use other than folic acid ;Depending on the group a subject will be excluded meeting one of the following criteria
- Medical history of complicated pregnancy (former pregnant women)

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):	20-01-2014
Enrollment:	45
Type:	Actual

Ethics review

Approved WMO

Date:	27-11-2013
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	NL46127.042.13
Other	nog under review