The effects of intra uterine exposure to Tumor Necrosis Factor alpha inhibitors in infants on the development of the immune system

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Primary ObjectiveIn order to assess the effects of anti TNFα on the development of adaptive and innate immunity, children exposed to anti TNFα (with or without other immunosuppressive drugs) will be compared to children exposed to immunosuppressive...

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

Summary

ID

NL-OMON54516

Source
ToetsingOnline

Brief title
PETIT study

Condition

- Immune disorders NEC
- Neonatal and perinatal conditions

Synonym
immunodeficiency after intra exposure to TNF alpha inhibitors; immune disorder after use of anti-inflammatory drugs during pregnancy

Research involving
Human

Sponsors and support

Primary sponsor: HagaZiekenhuis
Source(s) of monetary or material Support: deel van het onderzoek valt binnen reguliere follow up;waarvoor geen extra financiering nodig is;voor overig onderzoek subsidie van Dr CJ Vaillant fonds

Intervention

Keyword: immune system, infant, pregnancy, tumor necrosis factor alpha inhibitors

Outcome measures

Primary outcome

In order to assess the effects of anti-TNFα on the development of adaptive and innate immunity, children exposed to anti-TNFα (with or without other immunosuppressive drugs) will be compared to children exposed to immunosuppressive drugs (but no anti-TNFα) to evaluate for differences in:

1) immunological markers in relation to anti TNFα level (immunophenotyping of T and B cell subsets (in particular memory B cells at 12 months), presence of hypogammaglobulinaemia at 12 months)

2) the frequency of infections

Secondary outcome

1) Differences in other immunological markers (response to routine vaccinations (Tetanus, H Influenzae type B, Pertussis, pneumococcal conjugate vaccine), immunoglobulin levels, presence of hypogammaglobulinemia at birth, 2 and 6 months, proteomics) between children exposed to anti-TNFα (with or without other immunosuppressive drugs) and children exposed to immunosuppressive drugs (but no anti-TNFα)

In order to further assess the effects of anti TNFα on the development of adaptive and innate immunity, children exposed to anti TNFα (with or without other immunosuppressive drugs) will be compared to children exposed to immunosuppressive drugs (but no anti-TNFα) and to healthy children for differences in:

2) innate and adaptive immunity by measuring immunological markers in relation to anti TNFα level (immunophenotyping of T and B cell subsets, immunoglobulin levels, presence of hypogammaglobulinemia, response to routine vaccinations (Tetanus, H Influenzae type B, Pertussis, pneumococcal conjugate vaccine), proteomics)

3) the frequency of infections

4) persistent /long term effects on the immune system by detecting epigenetic changes in mononuclear cells

5) gut microbiome

Explorative objectives

Infants with intra uterine exposure to immunomodulating drugs because of maternal COVID-19 will be included in a separate cohort. The objectives in this cohort will be explorative and descriptive:

1) innate and adaptive immunity: measurement of immunological markers in relation to concentration of immunomodulating drug: immunophenotyping of T and B cell subsets, immunoglobulin levels, response to routine vaccinations (Tetanus, H Influenzae type B, Pertussis, (including maternal pertussis

vaccination) pneumococcal conjugate vaccine), and proteomics.

2) the frequency of infections

3) persistent /long term effects on the immune system by detecting epigenetic

changes in mononuclear cells

4) gut microbiome analysis

Study description

Background summary

Relapse of inflammatory bowel disease (IBD) activity during conception and pregnancy is associated with a negative pregnancy outcome; prematurity and low birth weight. Therefore disease remission during this period is of utmost importance and it is advised to maintain drugs such as Anti- Tumor Necrosis Factor alpha (anti TNFα), thiopurines and 5-aminosalicylic acid. IBD is a disease often diagnosed in the reproductive years and most often diagnosed before the first pregnancy. With a disease prevalence of 5-500 per 100000, this means a considerable number of infants are born to mothers with IBD and are possibly exposed to these drugs. Most IBD drugs are of low risk during pregnancy, since no increase of congenital malformations has been reported so far. However the effects on the developing immune system, after intra-uterine exposure, remain unknown. Anti-TNF drugs are increasingly used in the treatment of IBD. These drugs are effectively transferred through the placenta resulting in high levels in the new-borns. Some anti-TNF drugs might even be detectable after one year of age. It is known that live vaccines must be avoided until the levels of anti-TNF are undetectable, as there has been one report of an infant, who died after a BCG vaccination associated with exposure to anti TNFα in utero. In addition, some authors have observed a higher risk of infection, hypogammaglobulinaemia, decreased response to vaccination, neutropenia and changes in T and B cell phenotype in a small cohort of children. In small case series following intra uterine exposure to thiopurines and other immunosuppressive drugs a variety of immunological chances has also been described. Since studies are scarce and most of the data were collected retrospectively, there is an urgent need for prospective studies focussing on the impact of exposure to biologicals, especially anti-TNFα, in utero on the development of the immune system and the potential risk of clinical complications.
During the Sars-Cov2 pandemic pregnant women with severe Coronavirus disease 2019 (COVID-19) are being treated with immunomodulating drugs, like tocilizumab. Tocilizumab, a monoclonal anti-IL6 IgG antibody is also

effectively transferred through the placenta resulting in detectable levels in the new-borns. As is the case with anti-TNFα, the effects on the developing immune system, after intra-uterine exposure to tocilizumab or other immunomodulating drugs, remain unknown. But given the potential severity of COVID-19 in pregnant women and the increasing incidence of COVID-19 in pregnant women there is an urgent need to gain more knowledge on the effect of these drugs on the developing immune system and the need for follow up of these infants.

Study objective

Primary Objective
In order to assess the effects of anti TNFα on the development of adaptive and innate immunity, children exposed to anti TNFα (with or without other immunosuppressive drugs) will be compared to children exposed to immunosuppressive drugs (but no anti-TNFα) to evaluate for differences in
1) immunological markers in relation to anti TNFα level (immunophenotyping of T and B cell subsets (in particular memory B cells at 12 months), presence of hypogammaglobulianemia at 12 months)
2) the frequency of infections

Secondary Objective(s):
1) Differences in other immunological markers (response to routine vaccinations (Tetanus, H Influenzae type B, Pertussis, pneumococcal conjugate vaccine), immunoglobulin levels, presence of hypogammaglobulinemia at birth, 2 and 6 months, proteomics) between children exposed to anti TNFα (with or without other immunosuppressive drugs) and children exposed to other immunosuppressive drugs (but no anti-TNFα)

In order to further assess the effects of anti TNFα on the development of adaptive and innate immunity, children exposed to anti TNFα (with or without other immunosuppressive drugs) will be compared to children exposed to immunosuppressive drugs (but no anti-TNFα) and to healthy children for differences in:

2) innate and adaptive immunity by measuring immunological markers in relation to anti TNFα level (immunophenotyping of T and B cell subsets, immunoglobulin levels, presence of hypogammaglobulinemia, response to routine vaccinations (Tetanus, H Influenzae type B, Pertussis, pneumococcal conjugate vaccine), proteomics)
3) the frequency of infections
4) persistent /long term effects on the immune system by detecting epigenetic changes in mononuclear cells
5) gut microbiome

Explorative objectives
Infants with intra uterine exposure to immunomodulating drugs because of

maternal COVID-19 will be included in a separate cohort. The objectives in this cohort will be explorative and descriptive:
1) innate and adaptive immunity: measurement of immunological markers in relation to concentration of immunomodulating drug: immunophenotyping of T and B cell subsets, immunoglobulin levels, response to routine vaccinations (Tetanus, H Influenzae type B, Pertussis, (including maternal pertussis vaccination) pneumococcal conjugate vaccine), and proteomics.
2) the frequency of infections
3) persistent /long term effects on the immune system by detecting epigenetic changes in mononuclear cells
4) gut microbiome analysis

Study design

Prospective longitudinal observational cohort study

Study burden and risks

Given the previous observations on possible immunosuppression it seems necessary to perform follow up on the immunological function of all children who have been exposed to immunosuppressive drugs in utero. Currently a national or international guideline is lacking.In the Haaglanden Medical Center (HMC) and the Juliana Children*s hospital (JKZ) a local guideline has been used for follow up of children who have been exposed to anti-TNFα since 2013. In the local HMC and JKZ guideline clinical follow up and performing immunological studies of immunoglobulin levels, flow cytometry and vaccination response are advised. For this study 1ml extra blood will be necessary at follow up visits. For epigenetic studies 2 ml extra blood will be drawn at the regular follow up visit at the age of 12 months. In most other hospitals follow up of children who have been exposed to anti-TNFα is not part of standard care. In these hospitals follow up and blood tests will be for study purposes. In children who have been exposed to immunosuppressive drugs other than anti-TNF α the same follow up will be performed. Currently there is no guideline concerning follow up of children exposed to immunosuppressive drugs other than anti-TNF α. However, there is some evidence of an effect of these drugs on the developing immune system, underpinning the need for a control group of these patients and supporting the idea that some follow up might be necessary in these patients as well. Since there is currently no guideline, blood tests in these patients are primarily for study purposes. A biopsy of the placenta will be taken and preserved for pharmacological studies on immunosuppressive drugs and immunological study purpose. Mothers who breastfeed will be asked for breastmilk samples of 10 ml shortly after birth (nutritional intake of the neonate has to be guaranteed) and twice between 2 and 6 months after birth. Samples will be asked to collect just before and shortly after receiving immunosuppressive medication for future pharmacological studies on immunosuppressive drugs and immunological study purposes. For epigenetic

studies and proteomics cord blood and blood from healthy children aged 12 months, in whom a venipuncture for other reasons (such as minor surgery) is necessary, will be drawn after parental informed consent. Blood volume restrictions will comply with the recommendations of the European Commission and the World Health Organization (WHO) guidelines. Collecting faecal and breastmilk samples are non-invasive procedures.
Results will be used to guide immunosuppressive strategies during pregnancy in women with IBD or COVID-19. If intra uterine exposure to anti-TNFα or other immunomodulating drugs do indeed lead to abnormalities in the development of the immune system, immunization schedules should potentially be adapted, and long term follow up is warranted to study the presence of potential long-term complications such as susceptibility to infection and immune mediated disease. Given the aim of this study investigating minors is necessary.
No serious adverse events (SAE) are expected in the study, since it is an observational non-interventional study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

Infants with intra uterine exposure to anti-TNFα (with or without other immunosuppressive drugs) for maternal IBD and infants with intrauterine exposed to other immunosuppressive drugs (but no anti-TNFα) for maternal IBD OR infants with intra exposure to immunomodulating drugs because of maternal COVID-19. Parents must have sufficient understanding of the Dutch language and be able to give informed consent.

Exclusion criteria

Infants in which informed consent is not obtained.
Infants with a (possible) HIV infection, infants with an immunodeficiency as part of a known genetic or inherited disease.
Infants of mothers using certolizumab or eternacept are excluded, because they are hardly present in the cohort of pregnant women with IBD. In addition, certolizumab hardly passes the placenta

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-12-2018
Enrollment:	210

Type:	Actual

Ethics review

Approved WMO Date:	22-02-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	04-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	16-06-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	04-10-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-01-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	23-04-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	14-09-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	18-02-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	28-07-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	28-01-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	03-03-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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: 22495
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL63910.098.17