Maternal recognition of the (semi) allogeneic fetus during implantation and pregnancy

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Chapter 11

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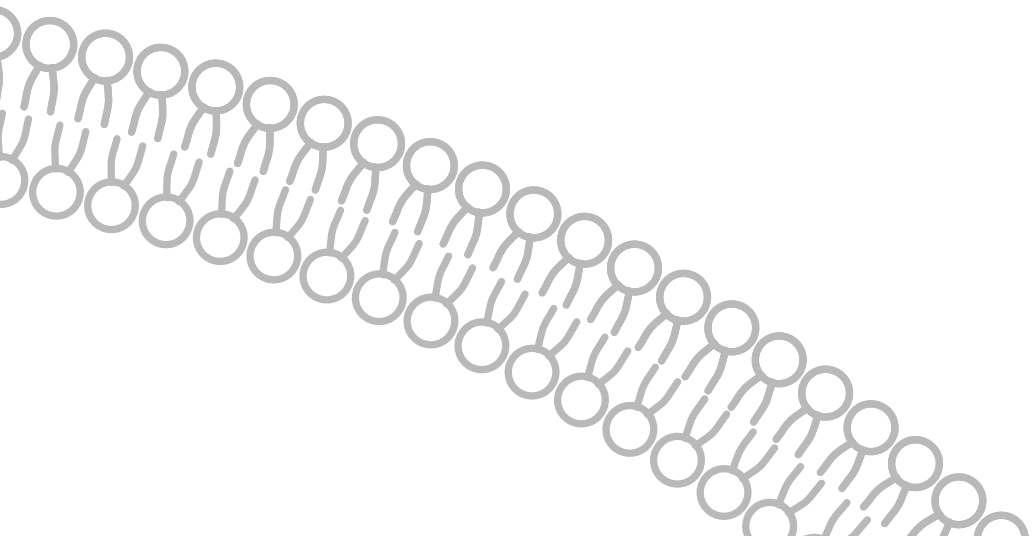

Nederlandse Samenvatting

1 Immunologische paradox

Tijdens de zwangerschap bestaat er een bijzondere immunologische situatie. De foetus heeft zowel maternale als paternale genen en is dus gedeeltelijk lichaamsvreemd voor de moeder, ook wel semi-allogeen genoemd. Gedurende de zwangerschap wordt een foetus echter getolereerd door het immuunsysteem van de moeder en niet afgestoten. Dit in tegenstelling tot een orgaantransplantatie, waarbij levenslange afweer-onderdrukkende medicatie en een uitvoerig zoektocht naar een geschikte donor noodzakelijk zijn om afstoting te voorkomen.
De bijzondere immunologische situatie tijdens zwangerschap wordt de 'immunologische paradox' genoemd en er zijn verschillende mechanismen geopperd die de maternale tolerantie zouden verklaren. Eén van de verklaringen is dat tijdens zwangerschap het afweersysteem onderdrukt is. Inmiddels weten we echter dat zowel de aangeboren als de verworven afweer actief zijn tijdens de zwangerschap en dat de herkenning van de moeder van haar ongeboren kind essentieel is voor het verloop van de zwangerschap.

Herkenning van lichaamseigen en lichaamsvreemd is een van de belangrijkste mechanismen van het afweersysteem om een specifieke afweerreactie te beginnen. Deze herkenning vindt plaats middels Humane Leukocyten Antigenen (HLA), moleculen welke op het membraan van alle cellen voorkomen. HLA kent een buitengewoon polymorfisme, wat wil zeggen dat er een grote individuele verscheidenheid bestaat. Specifieke afweercellen, T cellen, zijn in staat lichaamsvreemd MHC van bijvoorbeeld bacteriën te herkennen. Wat volgt is een immunologische reactie met als doel de vreemde cellen te verwijderen. Ook cellen van de foetus kunnen worden herkend als lichaamsvreemd en een afweerreactie uitlokken. Tijdens de zwangerschap blijken er echter allerlei aanpassingen van het maternale afweersysteem plaats te vinden waardoor een reactie tegen de foetus wordt onderdrukt, maar tegen andere indringers intact blijft. Niet of onvoldoende onderdrukking van de afweerreactie is mogelijk geassocieerd met een aantal zwangerschapscomplicaties, zoals herhaalde miskramen, zwangerschapsvergiftiging (pre-eclampsie) of verminderde vruchtbaarheid. In dit proefschrift bestuderen we daarom de immunologische herkenning en de afweerreactie van de moeder tijdens innesteling- en zwangerschapscomplicaties.

In dit proefschrift onderzoeken we bovendien de eiceldonatie zwangerschap. Zoals beschreven is tijdens een 'normale' zwangerschap de foetus gedeeltelijk lichaamsvreemd; na een eiceldonatie heeft het kind geen genen van de moeder en is het dus totaal allogeen. Immunologisch is deze situatie te vergelijken met een orgaantransplantatie waarbij ook een totaal lichaamsvreemd orgaan in het lichaam wordt gebracht. Kennis van immunologische

mechanismen verantwoordelijk voor een ongecompliceerde eiceldonatiezwangerschap zou gebruikt kunnen worden om een succesvolle orgaantransplantatie te bewerkstelligen. Aan de andere kant kan men een gecompliceerde eiceldonatiezwangerschap zien als een afstotingsreactie. Procedures die gevolgd worden om afstoting van een orgaan te minimaliseren, zoals selectie van een geschikte donor, zouden mogelijk voordelig effect hebben op het verloop van de zwangerschap na eiceldonatie.

2 Dit proefschrift

In **hoofdstuk 1** worden algemene aspecten van de immunologie met de betrokken afweercellen en eiwitten ingeleid. Tevens worden verschillende maternale en foetale mechanismen beschreven welke een rol spelen in de tolerantie tijdens zwangerschap en worden de zwangerschapscomplicaties welke in dit proefschrift zijn bestudeerd geïntroduceerd.

Verschillen in de specifieke afweerreactie tussen zwangere en niet-zwangere vrouwen werden onderzocht in **hoofdstuk 2**. In het bloed van deze vrouwen is gekeken naar percentages van diverse afweercellen zoals T cellen en B cellen. Daarnaast is onderzocht hoe de T cellen reageren wanneer ze lichaamsvreemd HLA herkennen middels een MLC (mixed lymphocyte culture) test. Hiervoor werden T cellen van de zwangere of niet-zwangere vrouw in een laboratorium setting samen gebracht met cellen van haar eigen kind, of met een vreemd kind. Wij vonden dat de mate waarin de T cellen vermenigvuldigen tijdens de herkenningsfase gelijk is tussen zwangere en niet-zwangere vrouwen. Wel vonden we verschillen in de samenstelling van afweercellen en in de productie van cytokines, eiwitten betrokken bij de communicatie tussen afweercellen. Deze resultaten tonen dat zowel de aangeboren als de verworven afweer intensiever zijn tijdens de zwangerschap, maar dat dit niet leidt tot een andere afweerreactie wanneer gekeken wordt naar de proliferatie.

De afweerreactie die optreedt na herkenning van vreemd HLA kan cellulair of humoral zijn. De humorale reactie wordt geïnitieerd door B cellen en leidt tot de productie van antistoffen tegen het vreemde antigen. Ook tijdens de zwangerschap worden er antistoffen gevormd. Wat de gevolgen zijn van deze antistoffen op het verloop van de zwangerschap, is echter niet bekend. In **hoofdstuk 3** hebben we een literatuurstudie en meta-analyse gedaan naar onderzoeken die de associatie tussen HLA antistoffen en zwangerschapscomplicaties onderzochten. De onderzoeken toonden echter een grote mate van klinische heterogeniteit, wat wil zeggen dat de geïncludeerde patiënten en controle personen tussen de studie niet vergelijkbaar zijn. Vooralsnog kunnen we dus niet concluderen dat HLA antistoffen een (positief of negatief) effect hebben op de zwangerschap.

Zoals beschreven, is een kind na eiceldonatie totaal lichaamsvreemd ten opzichte van de moeder. In **hoofdstuk 4** is onderzocht of deze hogere mate van genetisch verschil invloed heeft op de productie van antistoffen gericht tegen het HLA van het kind. We vonden dat 69% van de vrouwen zwanger na eiceldonatie HLA antistoffen produceert, tegen 24-25% van de vrouwen zwanger na spontane conceptie of na IVF. De productie van antistoffen was positief gecorreleerd met het aantal HLA verschillen (mismatches) en epitoop verschillen. Ondanks de hoge mate van antistof productie waren alle eiceldonatie zwangerschappen geïncludeerd in deze studie ongecompliceerd. We suggereren dat, in overeenstemming met andere literatuur, extra activatie van de T helper 2 (Th2) cel nodig is om deze zwangerschappen ongecompliceerd te houden.

De vraag is uiteraard, hoe de immuun activatie is in gecompliceerde eiceldonatie zwangerschap. Mogelijk speelt de onnatuurlijk hoge mate van HLA verschil een rol in het onderliggen mechanisme van complicaties in eiceldonatie zwangerschappen. In spontane zwangerschappen worden zwangerschapscomplicaties als preeclampsie en herhaalde miskramen echter geassocieerd met een laag HLA verschil en hoge mate van 'HLA sharing', een situatie die op kan treden in bijvoorbeeld inteelt populaties. Het onderliggend mechanisme verantwoordelijk voor de preeclampsie is dus mogelijk verschillend in eiceldonatie zwangerschappen. In **hoofdstuk 5** onderzochten we aspecten van de aangeboren afweer, de complement cascade, in vrouwen met preeclampsie zwanger na eiceldonatie, of na IVF met gebruik van eigen eicellen. Hoewel we in beide groepen een verhoogd percentage van placenta's met C4d depositie (marker van complement activatie) vonden, lijkt het mechanisme verantwoordelijk voor deze complement activatie te verschillen. In de groep vrouwen zwanger na eiceldonatie met preeclampsie kwamen namelijk geen groei vertraagde kinderen voor en werd geen op-regulatie van complement regulatoire eiwitten gevonden, eiwitten die de activatie van complement kunnen verminderen. Het lijkt dus dat de C4d depositie in eiceldonatie zwangerschappen gecompliceerd door preeclampsie meer aspecifiek is, veroorzaakt door schade in de placenta maar niet de schade veroorzakend.

In natuurlijke zwangerschappen lijkt er een selectie te zijn naar een optimaal aantal HLA matches en mismatches tussen moeder en foetus. In **hoofdstuk 6** vroegen wij ons af of er ook in ongecompliceerde eiceldonatiezwangerschappen een selectie is voor een bepaalde mate van HLA matching. Hiervoor berekenden we het bestaand aantal HLA matches en mismatches tussen moeder en foetus in eiceldonatie zwangerschappen met een ongerelateerde donor, en het aantal matches en mismatches als we de foetussen 'at random' zouden verdelen onder de moeders. We vonden meer gelijkenis tussen moeder en foetus dan bij een at random verdeling en deze gelijkenis was met name voor HLA klasse I. Mogelijk betekent dit dat selectie van een geschikte donor, met een optimaal aantal matches tussen donor en moeder, de uitkomst na eiceldonatie verbeterd. Hiervoor

is echter grootschalig onderzoek noodzakelijk, waarbij ook gecompliceerde eiceldonatie zwangerschappen worden onderzocht.

Voor het verloop van de zwangerschap is herkenning door het maternale afweersysteem van de foetus van belang voor het verloop van de zwangerschap. De situatie waarin er een weinig HLA verschil is tussen moeder en kind zou kunnen resulteren in weinig aanpassing van het maternale immuunsysteem tijdens de zwangerschap, wat mogelijk is geassocieerd met zwangerschapscomplicaties zoals herhaalde miskramen. Eerdere onderzoeken naar de invloed van HLA 'sharing' tussen partners en herhaalde miskramen lieten echter inconsistente resultaten zien. Reden voor deze inconsistentie zijn waarschijnlijk de verschillende definitie van herhaald miskramen en controle groepen en het gebruik van verschillende HLA typeringsmethoden. In **hoofdstuk 7** hebben we daarom alle onderzoeken vergeleken die gekeken hebben naar HLA allelen en HLA sharing in herhaald miskramen en die strikte inclusiecriteria handhaafden. We hadden echter te maken met hoge selectie en informatie bias en daardoor kunnen we, ondanks dat we in de meta-analyse vonden dat maternale dragerschap van bepaalde HLA allelen en sharing van bepaalde HLA antigenen een verhoogd risico gaven op herhaald miskramen, geen conclusies trekken.

In **hoofdstuk 8 en 9** richtten we ons op koppels met een verminderde vruchtbaarheid en herhaald implantatie falen. In **hoofdstuk 8** onderzochten we de naast de mate van HLA sharing, of er een verhoogde frequentie is voor een bepaalde groep van HLA-C in patiënten die *in vitro* fertilisatie hebben ondergaan maar ≥3 opeenvolgende mislukte terugplaatsingen hebben gehad. HLA-C komt voor op het celmembraan van placentacellen en gaat lokaal een interactie aan met maternale afweercellen. Eerder onderzoek heeft aangetoond dat een bepaalde combinatie tussen moederlijke NK cellen en HLA-C van de foetus nadelig kan zijn op het verloop van de zwangerschap. Wij vonden dat maternaal HLA-C2 geassocieerd was met implantatie falen. Tevens werd een genetische variant van HLA-G onderzocht, waarbij de invoeging van een extra stukje DNA (14 bp) nadelige effecten zou hebben op de vruchtbaarheid. Inderdaad vonden wij deze insertie vaker bij vrouwen met herhaaldelijk implantatie falen.

Tenslotte onderzochten we in **hoofdstuk 9** het percentage en de functie van T cellen in bloed van vrouwen die IVF hebben ondergaan vanwege onverklaarde infertiliteit en vrouwen die een spontane zwangerschap hebben doorgemaakt. We richtten ons met name op de rol van de 'regulatoire T cel', een afweercel die mogelijk belangrijk is om de maternale afweerreactie tegen de foetus te onderdrukken. Hiervoor onderzochten wij de vermenigvuldiging en cytokine productie van T cellen in een MLC, waarbij de cellen werden gestimuleerd met cellen van de eigen partner, of van een vreemde partner. Vervolgens herhaalden wij deze test met een fractie T cellen waar de regulatoire T cel uit

was verwijderd. We vonden dat T cellen van de IVF patiënten meer vermenigvuldigden na stimulatie, en dat een verminderde suppressieve capaciteit van de regulatoire T cel hier mogelijk verantwoordelijk voor is.

3 Conclusie

Tijdens de zwangerschap zijn alle onderdelen van het afweersysteem actief en wordt een foetus herkend als gedeeltelijk lichaamsvreemd. Het afweersysteem is echter aangepast om afstoting van de foetus te voorkomen. Onvoldoende aanpassing kan resulteren in een gecompliceerd verloop, of einde, van de zwangerschap en kennis van deze maladaptatie is van belang in het ontwikkelen van therapeutische en diagnostische mogelijkheden.
Zoals echter ook duidelijk wordt in dit proefschrift, is de aanpassing van het maternale immuunsysteem tijdens de zwangerschap complex en spelen verschillende genen, celtypen en eiwitten een rol. Daarnaast hebben ook andere factoren een belangrijke invloed, zoals milieufactoren, hormonen en epigenetica. Wij toonden aan dat genetische variaties (14 bp insertie in HLA-G) en regulatoire T cellen belangrijk zijn gedurende de implantatie en conceptie. Aanvullend onderzoek is echter noodzakelijk om de exacte bijdrage van deze factoren in de aanpassing van het maternale immuunsysteem tijdens zwangerschap te ontrafelen. Voor het doen van deze immunologische bepalingen, en bepalingen als screening naar HLA antistoffen of meten van HLA sharing tussen koppels, als diagnostiek bij vrouwen met bepaalde zwangerschapscomplicaties, bestaat vooralsnog onvoldoende bewijs en zal in de dagelijkse praktijk niet moeten worden aangeboden. Ook het aanbieden van bepaalde immunotherapie onder het mom van 'baat het niet dan schaadt het niet', blijkt echter weldegelijk meer schade aan te richten dan te helpen, en zou pas bij voldoende immunologisch bewijs kunnen worden gegeven. Hoewel dus steeds meer bekend wordt over het afweersysteem tijdens de zwangerschap zal verder onderzoek noodzakelijk zijn om de immunologische tolerantie naar de foetus te kunnen begrijpen.
Ook voor de bijzondere immunologische situatie die bestaat in eiceldonatie zwangerschappen geldt dat de gevonden resultaten verder zullen moeten worden onderzocht en ook in de gecompliceerde eiceldonatie zwangerschap, om meer inzicht te geven in het onderliggende mechanisme. Dit kan van belang zijn voor de toekomst van eiceldonatie, maar ook voor andere onderzoeksgebieden, zoals de transplantatie immunologie.

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Curriculum Vitae

Lisa Lashley was born on the 1st of December 1980 in Dordrecht, the Netherlands. She graduated in 1998 from secondary school at the Gymnasium Camphusianum in Gorinchem. In the same year, she started with Bio-pharmaceutical Sciences at Leiden, a study focusing on research-oriented training in pharmaceutical sciences and medicine development. She graduated in 2003 and started in the third year of the curriculum of Medicine at the Leiden University. During her study she worked at the Center for Human Drug Research (CHDR) as research assistant and at the emergency department of the Leiden University Medical Center (LUMC). In 2007 she graduated and worked as a physician at the Obstetrics and Gynecology department of the Haga hospital in the Hague and of the LUMC. She became involved in the research on immunology in pregnancy at the Reproductive Immunology laboratory, LUMC, under the guidance of Prof. dr. F.H.J. Claas. She was assigned a grant from ZonMW, NWO, which gave her the opportunity to start a research project, resulting in the current thesis.

In 2010 she started her residency training in Obstetrics and Gynecology at the Haga hospital (head: dr. B.W.J. Hellebrekers) and after two years of research, she continued her training at the LUMC (head: Prof. dr. J.M.M. van Lith).

Lisa lives together in the Hague with Jaap Vestjens and their daughter Lotte.

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Abbreviations

3p	third party
APC	antigen presenting cell
ART	assisted reproductive techniques
BCR	B cell receptor
CD	cluster of differentiation
CDC	complement dependent cytotoxicity
CPM	counts per minute
DC	dendritic cell
ELISA	enzyme linked immunosorbent assay
EVT	extravillous trophoblasts
FACS	fluorescent activated cell sorting
HELLP	hemolysis elevated liver enzymes, low platelets
HLA	human leukocyte antigen
ICSI	intra cytoplasmatic sperm injection
IDO	indolamine 2,3-dioxygenase
IFN-γ	interferon-γ
IL	interleukin
IVF	in vitro fertilization
KIR	killer immuno-globulin like receptor
MFI	median fluorescence intensity
MHC	major histocompatibility complex
MLC	mixed lymphocyte culture
MLR	mixed lymphocyte reaction
NK	natural killer
OD	oocyte donation
PBL	peripheral blood leukocyte
PBMC	peripheral blood mononuclear cell
PE	preeclampsia
PHA	phytohaemagglutinin
RIF	recurrent implantation failure
RSM	recurrent spontaneous miscarriages
SAB	single antigen beads
SI	stimulation index
sIVF	success after one IVF or ICSI treatment
SP	spontaneously conceived pregnancy
SUI	suppression index
TCR	T cell receptor
TGF	transforming growth factor

Th	T helper
TNF	tumor necrosis factor
Treg	regulatory T cell
UCB	umbilical cord blood

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