

Natural killer cell profiling in women with recurrent pregnancy loss

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IMPACT

The aim of this thesis was to integrally profile NK cells in women with recurrent pregnancy loss (RPL), an aim for which a unique collaboration was realized between the departments of Obstetrics & Gynecology and Transplantation Immunology in the Maastricht UMC+, for which a specialized outpatient clinic was set up for women with RPL and for which a standardized way of NK cell profiling was developed in the laboratory.

RPL is one of the most complex and challenging scenarios in reproductive medicine. Understanding the mechanisms behind RPL and identifying mediators or effectors and validating targets for prevention or therapy will have a profound impact on the couples' decision making on future family planning. However, identifying immunological factors by NK cell profiling in women with RPL is challenging to say the least. The immune system during early pregnancy is not black and white, it is not on or off, it is driven by a delicate balance of immune tolerance to allow implantation, placentation and growth of the semi-allogenic fetus but also depends on a responsive immune system that can protect both the mother and the fetus against pathogens when necessary.

Given that 50% of the women with RPL do not yet have an explanatory cause for their losses, some cases could perhaps be explained by an immunological etiology. It would be promising if we could uncover this immunological underlying cause, for example to treat these women with immunomodulatory medication. To date, there are no immunological diagnostic or intervention strategies available for women with RPL and current guidelines, such as the NVOG, the ASRM and the ESHRE, do not recommend testing for immune abnormalities in women with RPL due to low level quality of evidence. However, since there is a limited availability of predictors and limited possibilities for diagnosis and treatment for women with RPL, it is very important to investigate novel immunological factors that can offer more perspective for these women. By integrally profiling NK cells we aimed to acquire more insight in whether a poorly balanced regulation of the various effector functions of NK cells may play a role in RPL.

In this thesis we showed that NK cell profiling can be used as a tool to investigate NK cells in peripheral blood and menstrual shed and can be used to identify markers related to RPL that can help patient stratification and prediction of the severity of RPL. Moreover, we showed that genomic analysis, analysis of antibody profiles and viral status analysis, but also overarching analysis between different systems, such as the cardiovascular and metabolic system, could provide more insight in constituents that are important to take into account when profiling NK cells in women with RPL, hereby underlining the importance of complementing NK cell profiles with additional analyses. Although integral NK cell

profiling will not be all encompassing for every woman with RPL, a multidisciplinary approach seems to be the way forward and can certainly be of great value for identifying a subset of women with RPL with an underlying immunological etiology. In the future this could potentially lead to a preconceptional immunological and cardiovascular screening program for the outpatient clinic, unmasking predispositions to disturbances that only become symptomatic later in pregnancy. Such a preconceptional screening program might identify aberrant immunological factors before pregnancy, so that couples at high risk of having a pregnancy loss can make informed reproductive decisions.

However, for the use of integral NK cell profiles as a reliable and predictive biomarker in a preconceptional screening program, our results should first be confirmed in a standardized setting. Furthermore, functional studies are needed to investigate a potential causal relation with pregnancy outcome hereby providing targets for intervention and guiding personalized treatment strategies of a subgroup of women with RPL in the future. Moreover, the added value of NK cell profiling in predicting subsequent loss or healthy pregnancy has not yet been studied well enough. In addition to predictors such as maternal age and the number of previous losses, integral NK cell profiling could be beneficial for predicting pregnancy outcome and is highly needed as prediction is severely limited to date.

Couples who endure RPL are desperate to find an explanation for their repeated losses of pregnancies. The social need for finding diagnosis and treatment strategies for women with RPL is urgent as many general practitioners and also gynecologist often don't have a clue what to offer women with RPL besides care-as-usual. However, there is so much more that can be done, helping these women with a tremendous amount of grief and despair losing pregnancies over and over again. Just because we don't have a validated biomarker or readily available treatment options,

doesn't mean we can't try to help these women in the best way possible. Offering appropriate care supported by scientific research can offer these patients a new perspective for the future as many women sadly experience RPL as a traumatic life event.

Progress is potentially to be achieved when RPL will gain more attention from patient organizations and gynecologist (in training), who will have to first acknowledge the multifactorial nature of the problem and consequently be comprehensive in their approach looking for novel strategies improving diagnosis and treatment by means

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Jaarlijks 23 miljoen miskramen, maar nauwelijks aandacht voor het verdriet

Gewoon uithuilen en opnieuw beginnen. Dat lijkt vaak de algemene teneur van de reacties bij een miskraam, valt op te maken uit een analyse in The Lancet. Miskramen worden gezien als onvermijdelijk, maar dat is onterecht en doet geen recht aan het verdriet van vrouwen die het overkomt.

of scientific research and shared discussion making. It would therefore be relevant to organize a conference for FREYA, a very important Dutch association for people with fertility problems and professionals, where results of our research could be elucidated. Moreover, this thesis could also serve as a wonderful example for education purposes. The immune system during pregnancy is truly unique and new insights in its role should not only be published in articles but also be implemented in a curriculum for biomedical and medicine studies to make future biomedical scientist and physicians aware of the relevance and the importance of the immune system in reproduction. Losing pregnancies recurrently is not inevitable, the grief of these couples is enormous and should certainly not be underestimated.

Furthermore, these couples are extremely vulnerable, which makes it even more important to provide appropriate care. Private fertility clinics do offer immunology testing and treatment for NK cells, selling couples blood tests despite experts warning that there is no proof that the procedure improves the chances of having a baby. The so-called Chicago test costs €1,000 plus a consultation fee. The blood is sent to Chicago to be examined to see if the woman's immune system is attacking embryos and causing pregnancy losses. If elevated levels of the killer cells are found the woman can be prescribed drugs to suppress her immune system, which can cost thousands of euros per dose. However, there are no guidelines for what normal NK cell numbers or activity are and which imbalance of NK cells will lead to pregnancy loss. Although there is a series of scientific studies that find that NK cells are important for normal pregnancy, it's still not clear what the optimal level of NK cells is and more importantly, what is the best way is to correct any imbalance. Integral NK cell phenotypic profiling can hopefully provide more insight whether a mismatched regulation of the various effector functions of NK cells might play a role in some women with RPL, hereby saving them unnecessary costs and disappointment.

This thesis has provided pieces of a puzzle in order to guide preconceptional screening of NK cells by integrally phenotypic profiling as this might not only be valuable for stratifying women with RPL, but also provides a blueprint for future studies for the development of new clinical strategies and for selecting women whose pregnancy losses may be more likely to respond to specific interventions, subsequently targeting these interventions to pre-selected women when the puzzle is complete.