

Pregnancy and the risk of autoimmune disease

An exploration

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Fetal microchimerism is the study of persisting fetal cells in the mother years after pregnancy and the purported implications for her health and longevity. Due to the association between pregnancy and autoimmune disease (AID), and the preponderance of these diseases in women, laboratory studies have for years attempted to link microchimeric fetal cells with the onset of AID after pregnancy. This new study gave us the opportunity to examine for the first time if this theory could be proven clinically in a large cohort of women. By examining whether different types of delivery affected the onset of AID, we also aimed to indirectly relate this finding to fetal microchimerism. The results did suggest an association between pregnancy and the risk of subsequent maternal AID, with increased risks noted after caesarean section (CS) and decreased risks after abortion. This is the first epidemiological study on the risk of AID following pregnancy.

Fetal Microchimerism and Autoimmune Disease

Autoimmune diseases, which include more than 70 different disorders, are more common among women and increase in incidence after their childbearing years. Clinicians accept this occurs but the reasons behind it are far from clear. Whether pregnancy itself or the number and/or type of pregnancies influences the development of autoimmune disease (AID) also remains controversial.

Trafficking of fetal cells into the maternal circulation begins very early in pregnancy and the effects of this cell traffic are

long lasting.¹ Fetal cells can also be located in maternal tissues after pregnancy, and persist for decades in marrow and other organs, in a phenomenon referred to as fetal microchimerism.^{1,2} While persisting fetal cells were first implicated in the pathogenesis of AID, subsequent reports that routinely found microchimeric cells in healthy tissues queried this theory.^{3,4} Nonetheless, the “fetal microchimerism” hypothesis of autoimmune disease is supported by similarities of chronic graft-versus-host-disease to some autoimmune conditions, their predilection for women of childbearing-age with an increased incidence after the reproductive years, and experimental animal models of AID showing fetal cells in diseased tissues.⁵⁻⁷

Factors predisposing to the development of fetal microchimerism are much debated.^{6,7} There is more fetal cell traffic across the placenta in certain complications of pregnancy such as pregnancy loss or pre-eclampsia, and it is hypothesised that there is greater fetal cell traffic with operative delivery compared to normal vaginal delivery.^{8,9} It is accepted that even short-term microchimerism can lead to AID. Further, microchimerism should be established in greater amounts after CS and this might increase the exposure of these mothers in particular to develop autoimmune disorders.⁸

“Pregnancy and the Risk of Autoimmune Disease”

In this study, we aimed to find out whether the risk of new onset AID was higher after delivery by caesarean section compared to vaginal delivery and we also aimed to

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quantify the risk of AID after abortion. The study cohort consisted of all women born in Denmark between January 1, 1962 and December 31, 1992—and it is thus quite a homogenous group. The main strength of the paper is the large cohort used and the fact that the study was population based, which avoids the problem of selection bias.¹⁰

If fetomaternal cell trafficking is to be implicated in the aetiology of AID after pregnancy, we expected the highest increase in AID diagnosis following CS, due to increased fetomaternal hemorrhage, and following abortion, as fetal loss is the only pregnancy complication significantly influencing microchimerism.⁹ The first year after pregnancy should be most relevant, being the time closest to the fetomaternal hemorrhage occurring at delivery.

In the cohort studied, women who were pregnant had a higher incidence of AID than those who had no pregnancy records and women who had singletons had slightly higher incidence of AID than those who had multiple gestation. We found the risk of AID *during* pregnancy was significantly reduced in relation to vaginal delivery and significantly increased in relation to CS. In contrast, the risk of AID during pregnancy in relation to abortion was not significantly changed. Of greater interest, we found the risk of AID was significantly higher in the first year *after* vaginal delivery and CS but significantly lower in the first year following abortion. The risk of AID in the first year following CS appeared to be higher in older women (>35 years) and there was a non-significant increase in risk of AID in their second year after CS. However overall, the risk of AID was not significantly changed after the first year apart from a reduction of the risk between year three and year ten after vaginal delivery.¹⁰

Limitations of this Approach

The limitations of this approach are detailed in the paper and largely relate to the focus on the first pregnancy as well as the limited details on each individual

autoimmune disease.¹⁰ As we included data on the first pregnancy only, we did not account for the effect of subsequent pregnancies on the risk of AID. However, the effect observed on the risk of AID was manifest in the first year after pregnancy, which precludes subsequent pregnancies being responsible in the vast majority of women.

It is possible that the increased risk of AID that we reported in the study is linked to the increased risk of AID presenting during pregnancy—although in clinical practice, few diseases seem to develop in this way. Also, women may be more likely to be tested for some conditions during pregnancy, due to reaching medical attention—presuming they have access to antenatal care. Further, women with symptoms related to AID might experience a complicated pregnancy and require delivery by CS, although these numbers should be small. It is difficult to conceive a study design that would exclude these concerns entirely.

Speculation and Future Work

The results of this paper suggest an association between pregnancy and the risk of subsequent maternal AID.¹⁰ Increased risks of AID after CS may be explained by amplified fetal cell traffic at CS delivery, while decreased risks after abortion may be due to the transfer of more primitive fetal stem cells in early pregnancy.^{8,10}

The cohort studied consisted of women born between 1962 and 1992 now aged from 19 to 49 years—and longer follow up when available may reveal more information about the impact of pregnancy. We would like to explore the impact of further pregnancies on the overall risk of autoimmune disease and to detail the effect of parity and gravidity on AID. This might also clarify the relationship between individual AID and pregnancy. We would also like to investigate further the impact of miscarriage. In the paper, we report only the risk of AID after induced abortion. There is some evidence from other work that fetal cell traffic is increased after induced compared to spontaneous

abortion, but that the type of cells persisting are more ‘stem-cell’ like with different implications for maternal health and disease.^{2,8,9} Finally, children delivered vaginally might also have a different prevalence of AID compared to those delivered by CS.

Understanding why autoimmune disease develops after pregnancy may be of use when designing future treatments for these varied disease processes.^{6,7} If the ‘missing link’ is fetal cells persisting in the mother after pregnancy, then while fetal cell traffic cannot be prevented, it could be manipulated or influenced. The slightly higher risk of AID developing after delivery by CS has relevance for the reported increase in CS rates worldwide and must be balanced against any proposed benefits of fetal microchimerism for long-term maternal health and longevity.^{8,10}

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