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Babies Galore; or recent findings and future perspectives of pregnancy cohorts with a focus on immunity

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ABSTRACT

Population-based pregnancy cohorts recruiting women before or at the moment of childbirth allow a longitudinal follow-up on children's health later in life. Important findings arising from pregnancy cohorts are discussed in the present review. These insights have led to revised guidelines on how to minimize disease risks in children, e.g., in the context of chronic immune diseases including allergies and asthma. Moreover, insights from pregnancy cohorts also unveiled a collateral effect of pregnancy on maternal immunity, mirrored by an ameliorated course of certain autoimmune diseases, but also an increased risk of infection with influenza A virus. Future pregnancy cohort studies are still required to close gaps in knowledge on how parameters involved in the developmental origin of health or poor immunity observed in children later in life are operational. We discuss here features that should be covered by future pregnancy cohort studies. Expected insights from such studies will then lay the foundation for biomarker discovery and offer opportunities for interventions to ameliorate adverse immune responses in humans.

1. Previous findings arising from pregnancy cohorts with regard to the immunity of offspring

Population-based pregnancy cohort studies have become pivotal in the identification of pre- or perinatal environmental factors affecting children's health and the increase in children's disease risk. The initiation of pregnancy cohort studies over the past three decades has been significantly fostered by the pioneering epidemiological work of the late David Barker, who showed that individuals born with a low birth weight are at a greater risk of developing coronary heart disease later in life. Based on these findings, the "fetal origins hypothesis" or "Barker hypothesis" was proposed in the 1990s (Barker et al., 1989, 1993).

Recent epidemiological studies unveil increased incidence of chronic immune diseases, such as multiple sclerosis (MS), diabetes type I, or asthma and allergies (Okada et al., 2010). This increased incidence occurs especially in Western societies, progressively affecting younger individuals. For example, asthma currently has a childhood incidence of 2.65–4 cases/1000 children per year in industrialized countries. In Germany, approximately 10% of all children suffer from asthma and the frequency of eczema, rhinitis, and food allergies is even higher (Keil et al., 2006). The incidence of juvenile MS is – depending on the study – between 0.6 and 2.6 (Pohl et al., 2007; Achiron et al., 2012) and the incidence of type I diabetes has been increasing as well (Patterson et al., 2009). Whilst a hereditary component accounts for an increased risk of chronic immune

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diseases, genetic factors do not suffice as a sole explanation for the recent steady increase in immune diseases. This reinforces the notion that environmental factors, including those occurring pre- or perinatally, may account for the increased incidence of chronic immune diseases, underscoring the need for pregnancy cohorts to confirm this association and to identify individuals at risk.

To date, intriguing findings linking pre- and perinatal factors to the risk of chronic immune diseases in children have arisen from such pregnancy cohorts. One impressive example is the large, population-based Avon Longitudinal Study of Parents and Children, also known as Children of the 90s, to which pregnant women were recruited in 1991 and 1992 in the UK. This study has led to the publication of over 700 articles (Pearson, 2012) and findings include the identification of a link between the use of acetaminophen in late pregnancy and an increased risk in asthma in the children later in life (Allmers et al., 2009; Shaheen et al., 2002).

A pregnancy cohort initiated in Canada (Pole et al., 2010) unveiled that prenatal steroid therapy, which is generally administered during preterm labor to accelerate fetal lung maturation, does in fact increase the risk of developing asthma during early childhood. In Germany, the risk of preterm delivery (before gestation week 37) is still among the highest within Europe (Schleussner, 2013) and prenatal steroids are routinely applied. The limited evidence available to date with regard to the advantages (lung maturation) versus the disadvantages (asthma risk, poor immunity) of prenatal steroids for children's health has fostered ongoing research endeavors aiming to identify the effect of prenatal steroids on the developing fetal immune system.

In the Netherlands, another pregnancy cohort, the Generations R Study, has contributed to the recognition that accelerated early infant growth is associated with an increased risk of asthma symptoms (Jaddoe et al., 2006; Sonnenschein-van der Voort et al., 2012). In a subsequent meta-analysis of European birth cohorts, including the Danish National Birth Cohort, the German multicenter allergy study (MAS) and others, younger gestational age at birth and higher infant weight gain could be associated with childhood asthma (Sonnenschein-van der Voort et al., 2014). Also, preterm birth was positively associated with an increased risk of preschool wheezing and school-age asthma. These epidemiological findings have sparked a number of research projects aiming to identify prenatal markers indicative of an increased risk of poor fetal development and preterm birth. Work from our own groups on the Berlin Pregnancy Cohort amends these observations. In this study, although smaller than the meta-analysis, which included the large epidemiological or Danish registry-based studies described above (Sonnenschein-van der Voort et al., 2014), we had biological samples available from first-trimester pregnant women. These samples were used to identify serum levels of pregnancy hormones, which revealed that maternal progesterone levels during the first trimester inversely correlated with birth weight in girls (Hartwig et al., 2013). Moreover, low levels of maternal progesterone during pregnancy predicted an increased risk of eczema in the children at the age of three years (Pincus et al., 2010) and for allergic airway diseases by the age of five (Hartwig et al., 2014a). The Berlin Pregnancy Cohort further revealed that the lack of social support during the first trimester constitutes an important risk factor for low birth weight (Elsenbruch et al., 2007).

Recently, our group assessed the impact of more moderate prenatal life events during pregnancy, such as financial or partner problems, on the subsequent risk of asthma in the children. These assessments were carried out in the Western Australian Pregnancy Cohort (Raine) Study. We showed that children of mothers who had experienced moderately adverse life events during the second half of gestation were also at an increased risk of asthma and eczema at the age of 14 (Hartwig et al., 2014b). These observations strongly reinforce the notion that the prenatal modulation of future allergy risk is not restricted to the small group of pregnant women experiencing severe life events. Strikingly, we observed a stronger increase in the risk of developing asthma upon moderate prenatal life events in children without a hereditary risk of asthma (Hartwig et al., 2014b), which strengthens the role of epigenetic pathways in modulating the risk of diseases upon prenatal challenges (Martino et al., 2014).

It is noteworthy, as outlined by the Children of the 90s study and other birth cohorts, that genetic variants are associated with fetal growth and birth weight (Freathy et al., 2010) or alter the risk of allergic diseases (Henderson et al., 2008). Interestingly, novel evidence further suggests an interaction between asthma susceptibility genes and prenatal environmental challenges, e.g., smoking (Scholtens et al., 2014). The Life Child Birth Cohort, recruiting women in the vicinity and city of Leipzig, Germany (Quante et al., 2012), aims to assess interactions between gestational environmental factors (e.g., maternal diet) and susceptibility genes in the development of non-communicable diseases, such as obesity, cardiovascular disease, and atopy. In this prospective, longitudinal population-based study prenatal examinations are conducted during the 24th–26th and 34th–36th weeks of gestation.

In addition, substantial evidence supports the importance of the pre- and perinatal microbiome with regard to the risk of chronic immune diseases later in life. This aspect has been reviewed extensively elsewhere (Sly et al., 2008; Renz et al., 2011; Legatzki et al., 2014) and hence, shall not be addressed here. Similarly, potential mediators involved in the development of poor immunity and chronic immune diseases, focusing on the role of pregnancy-related hormones and immune cells, have also recently been reviewed and hence, will thus not be addressed in the present article either (Arck and Hecher, 2013; Hsu and Nanan, 2014).

2. Previous findings arising from pregnancy cohorts on maternal immunity

Clearly, pregnancy cohorts such as the examples described above are generally initiated in order to prospectively follow up on children's health. However, pregnancy cohorts have also provided seminal insights into pregnancy-associated advantages for maternal health. A striking example is given by the study by Confavreux and