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INTRODUCTION

Beyond the "take-home baby": pregnancy as a modulator of organ-specific immunity in mother and offspring

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The maternal immune system significantly adapts to pregnancy in order to mount immunological tolerance towards the semiallogenic fetus [1]. Insights into how this adaptation is operational have arisen from the last five decades of research in the area of reproductive immunology. This area was significantly fostered once the relevance of acquired immune tolerance was acknowledged, based on the work of Sir Peter Medawar and Sir Frank Macfarlane Burnet [2, 3]. It is now widely accepted that maternal immune adaptation to pregnancy promotes placentation, hereby ensuring nourishment of the unborn child until birth [1]. In the current issue of *Seminars of Immunopathology*, Mori, Szekeres-Barthó and colleagues provide an overview on how the uterine mucosal lining during pregnancy, the decidua, provides the transient scaffolding to enable the temporal and spatial coexistence of semiallogenic fetal cells and maternal immune cells [4]. Clark highlights not only the importance but also the limitations of mouse models towards understanding why these semiallogenic fetal cells are not rejected by the maternal immune system [5]. In this context, Clark also discusses how an impaired maternal immune adaptation to pregnancy triggers pregnancy complications. Pregnancy complications can significantly affect an organ which has long been underappreciated in the field of reproductive immunology, the maternal liver. In the present issue, Tiegs and colleagues illuminate the bi-directionality between pregnancy (and related complications) and liver inflammation [6].

Assisted reproductive technologies have become widely accessible and thus are increasingly used medical treatments for infertility. These medical advances have added a new twist towards understanding how the maternal immune adaptation to pregnancy reduces the risk for the semiallogenic fetus to be rejected. Procedures of assisted reproductive technologies frequently include oocyte donation. From an immunologist's perspective, these third-party oocytes are complete allografts with a greater antigenic dissimilarity to the mother, compared to the implantation of a semiallogenic oocyte. Saito and colleagues highlight that insights from pregnancies resulting from third-party oocyte donations advance our understanding of how the fetus is protected by the maternal immune system [7]. Moreover, Saito et al. also provide a long-overdue summary of the risks for mother and child in pregnancies upon oocyte donations, for which an altered maternal immune adaptation may be accountable.

It is now recognized that pregnancy is a window to women's future health, as it often unmasks predispositions to conditions how an impaired immune adaptation to pregnancy in the context of preeclampsia can account for the increased incidence of cardiovascular disease, diabetes, and other health disadvantages not only in the mother but also in the child later in life [8].

Besides promoting a successful pregnancy outcome, which is often referred to as a "take-home baby", the maternal adaptation to pregnancy can modulate immunity in organs other than in the uterus. The brain, joints, and the liver are such organs, as an amelioration of autoimmune disease activity concurrent with pregnancy has been observed in women with multiple sclerosis [9], rheumatoid arthritis, [10] or autoimmune hepatitis [11]. In fact, greater parity even significantly reduced the odds of multiple sclerosis or rheumatoid arthritis [12]. The amelioration of autoimmunity during pregnancy is considered to be a collateral effect of the maternal immune adaptation to the semiallogenic fetus. This notion is reinforced by the observation that this transient amelioration of autoimmunity during pregnancy is followed by an increased relapse probability after birth, when the maternal

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immune system redresses to the non-pregnant status. Gold and Voskuhl emphasize how pregnancy serves as an intriguing example to understand the pathobiology of autoimmune diseases, primarily multiple sclerosis [13]. This improved understanding may aid the discovery of new therapeutic targets for the treatment of autoimmune diseases.

Besides these maternal health advantages, the immune adaptation to pregnancy can cause organ-specific health disadvantages for the mother, as seen in the context of viral infections. One example is the infection with influenza virus, as strongly reconfirmed during the influenza pandemic in the year 2009, when increased morbidity and mortality were observed worldwide in pregnant women [14]. In this context, Gabriel and colleagues summarize the current knowledge on the clinical observations in influenza virus infected pregnant women and discuss the suitability of animal models to study the underlying molecular influenza disease pathways [15].

Another example for maternal health disadvantages during pregnancy is the infection with human immunodeficiency virus [16], as observed in women in sub-Saharan Africa. Since behavioral risk factors could largely be excluded, Altfeld and Bunders discuss human immunodeficiency virus infection in the turnstile of the maternal immune adaptation to pregnancy along with the effect of prenatal antiretroviral therapies on maternal and offspring's immunity [17].

Moreover, maternal immune adaptation to pregnancy can be challenged, resulting in poor fetal development or preterm birth. Prenatal challenges to which women particularly in Western societies are nowadays frequently subjected to include high levels of stress perception [1, 18, 19], prescription-free self-medication [20], an inadequate nutritional status (obesity) [21], and vitamin deficiencies (folic acid and vitamin D) [22]. These challenges—which are not mutually exclusive—can be associated with an increased risk for the child to suffer from health disadvantages later in life [1]. Hence, it can be proposed that prenatal challenges jeopardize placental function and subsequently fetal growth and organ development. Maternal markers such as cortisol are increased in response to prenatal stress challenges and can cross the placenta. Solano and colleagues discuss not only how these endogenous steroids but also steroids exogenously applied during pregnancy in the context of preterm labor, can alter fetal (organ) development, and interfere with immune ontogeny and long-term immunity [23]. Noteworthy, an unprecedented rise of chronic immune diseases has been observed in Western societies over the past decades [24], which is now recognized as "health emergency in slow motion" by the World Health Organization

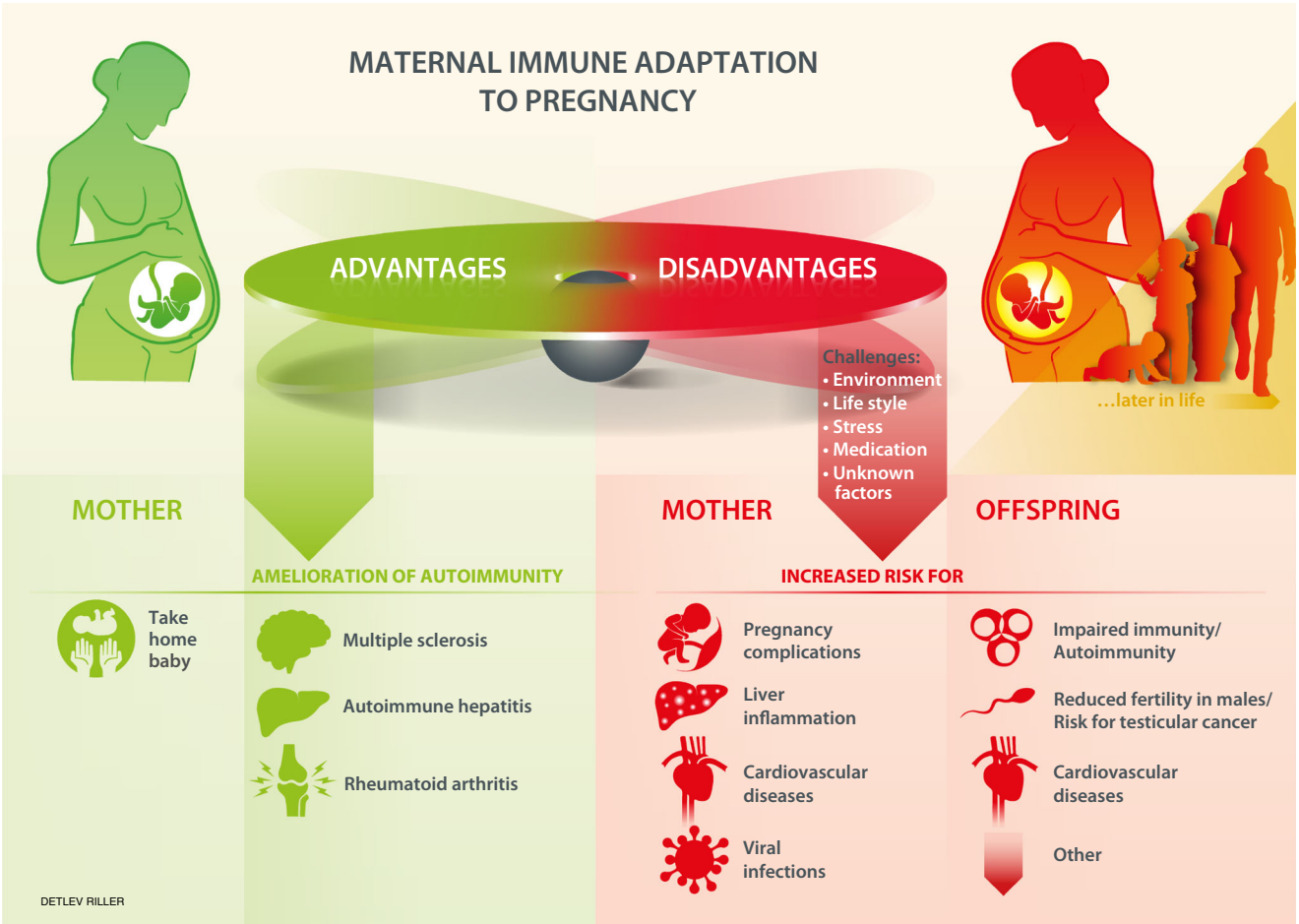

Fig. 1 Scenario depicting that maternal immune adaptation to pregnancy can exert health advantages and disadvantages for mother and offspring

[25], highlighting the urgency to understand the (prenatal) origin of these diseases.

In line with this, there is increasing evidence that a number of adult male reproductive disorders, such as a poor semen quality and an increased risk for testicular cancer in adulthood, have a fetal origin. Meinhardt and colleagues discuss how environmental prenatal challenges can affect the developing reproductive organs of the male fetus via epigenetic pathways, with potential consequences for several generations post-exposure.

Thus, understanding the underlying mechanisms of what is generally termed as "the developmental origin of health and disease" may allow the identification of mother-child dyads at risk for an impaired immunity of poor reproductive success prior to birth or early in life, based on which primary prevention strategies can be developed.

Taken together, the maternal immune adaptation occurring during pregnancy yields to more than the "take-home baby". It can be linked to health advantages, but also disadvantages for mother and child. The health disadvantages are generally treated by different medical disciplines, a fact that limits the concerted approach to understand the role of maternal immune adaptation to pregnancy in the underlying pathogenesis. In the present issue, we sought to overcome this limitation by allying authors from different medical disciplines and taking advantage of the added value of their interdisciplinary expertise and approach to understand health consequences from the perspective of reproduction. Amalgamating their conclusions, it can be proposed that pregnancy can serve as a model to understand organ-specific immunity and as a tool to identify the pathogenesis of a wealth of diseases and disorders, as depicted in Fig. 1.

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