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The role of autoimmunity in women with type 1 diabetes and adverse pregnancy outcome: A missing link

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ABSTRACT

The incidence of pregnancy complications in women with type 1 Diabetes Mellitus (T1D) is greater than in healthy pregnant women. This has mostly been attributed to hyperglycemia. However, despite the implementation of stricter guidelines regarding glycemic control, pregnancy complications remain more common in women with T1D. This may suggest that other etiological factors are involved. We suggest that the immune response may play a role, since the immune response has to adapt during pregnancy in order to facilitate implantation, placental and fetal development, and aberrant immunological adaptations to pregnancy are involved in various pregnancy complications. Since T1D is an autoimmune disorder, the question rises whether the immune response of women with T1D is able to adapt properly during pregnancy. Here we review the current proof and views on the role of aberrant immunological adaptations in pregnancy complications and whether such aberrant adaptations could be involved in the pregnancy complications of T1D patients.

1. Introduction

Pregnancy in women with type 1 Diabetes Mellitus (T1D) is associated with an increased risk of obstetrical and fetal complications like miscarriage, preeclampsia, macrosomia, congenital malformations and even perinatal death (Evers et al., 2004). Up to now, these complications have been attributed mainly to the effects of hyperglycemia (Evers et al., 2004). Therefore strict guidelines have been imposed for the care of diabetic women. These guidelines recommend an HbA1c < 53 mmol/mol before and during pregnancy in order to create advantageous conditions for implantation and fetal development (American Diabetes Association, 2002). Although this approach has indeed resulted in an improved pregnancy outcome, the incidence of pregnancy complications in women with diabetes is still greater than in healthy women (Murphy et al., 2008). The question therefore arises whether other etiological factors are involved.

In healthy pregnancies adaptations in immune responses take place in order to assure successful implantation and placental and fetal development (Svensson-Arvelund et al., 2014). The importance of these immunological adaptations is reinforced by the findings that many pregnancy complications are associated with aberrant immune responses (Raghupathy et al., 2012; Melgert et al., 2012; Saito et al.,

2010; Williams et al., 2009; Tuckerman et al., 2007). Recently we have shown that immunological adaptations to pregnancy are different in women with T1D than in healthy women (Groen et al., 2015a). Therefore, we hypothesized that aberrant immune responses in diabetic pregnancy might play a role in the unfavorable pregnancy outcomes of women with this disease. Here we review the current proof and views on the role of aberrant immunological adaptations in pregnancy complications and whether such aberrant adaptations could play a role in the pregnancy complications of T1D patients.

2. Pregnancy and immune responses

Most pregnancies result in the successful delivery of a healthy child. Major maternal changes in hemodynamics, cardiology and immunology occur during pregnancy, facilitating optimal conditions for development of the fetus, and preparing for delivery and lactation (Svensson-Arvelund et al., 2014; Duvetkot and Peeters, 1994). Aberrant adaptations, especially in immune responses, may result in pregnancy complications like infertility, miscarriage, preeclampsia, prematurity and even perinatal or maternal death (Raghupathy et al., 2012; Melgert et al., 2012; Saito et al., 2010; Williams et al., 2009; Tuckerman et al., 2007). It has been suggested that the placenta plays a prominent regulating role in

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the immunological adaptations during pregnancy (Svensson-Arvelund et al., 2014). In humans, placentation is characterized as hemochorial, indicating that maternal blood is in direct contact with the fetal chorion (Pijnenborg et al., 2011). This poses major challenges to the immune system, since fetal tissue is semi-allogeneic (Svensson-Arvelund et al., 2014). The fact that this semi-allogeneic fetal tissue is tolerated during pregnancy is accomplished both by fetal adaptations and by adaptations of the maternal immune response (Veenstra van Nieuwenhoven et al., 2003a). Here we will focus on these latter adaptations.

2.1. Local immune response during pregnancy

Changes in the local immune response in the uterus (at the implantation site) are necessary for optimal implantation, decidualization, placentation and fetal tolerance (Veenstra van Nieuwenhoven et al., 2003a). The numbers of immune cells in the non-pregnant endometrium fluctuate during the menstrual cycle, which may reflect hormonal changes (King et al., 1989; Moffett-King, 2002). It is thought that these immune cells, consisting mainly of uterine natural killer (uNK) cells, macrophages, regulator T-cells (Treg), and uterine dendritic cells (DCs) are important for the cyclic menstrual bleeding (King et al., 1989; Moffett-King, 2002). In early pregnancy, the numbers of uterine immune cells increase at the endometrial implantation site, which is now called the decidua (King et al., 1989; Moffett-King, 2002). uNK cells are the most abundant immune cells in the decidua during early pregnancy and they are involved in angiogenesis, spiral artery remodeling, and invasion of trophoblast cells into the decidua (King et al., 1989; Moffett-King, 2002). These uNK cells may also play a role in regulating the inflammatory response at the fetomaternal interface by, for instance, suppressing the pro-inflammatory T-helper 17 (Th17) cells (Fu et al., 2013). Another important cell population in the decidua and uterine wall are the macrophages (Faas et al., 2014). These cells are also thought to have a significant function in regulation of trophoblast invasion and spiral artery remodeling (Faas et al., 2014). It has been suggested that Treg play an important role in controlling the function of immune cells in the decidua in early pregnancy, since the number of Treg in the decidua increase during early pregnancy and decrease at the end of gestation (Guerin et al., 2009).

How these local immune adaptations are induced is not exactly known. Various mechanisms may be involved. There is evidence that both hormonal changes and semen may play an important role in the local immunological adaptations (Booker et al., 1994; Remes Lenicov et al., 2012). The increased production of progesterone during the secretory phase of the menstrual cycle induces the influx of leukocytes (Booker et al., 1994). Recent studies have shown that uterine DCs become activated after exposure to semen and fetal antigens, thereby attracting other immune cells, like uNK cells, into the uterus (Remes Lenicov et al., 2012). Furthermore, semen may also cause an accumulation of Treg in the uterus (Guerin et al., 2011). Finally, trophoblast cells are suggested to be involved in the development of fetomaternal tolerance. It has, for instance, been shown that first-trimester trophoblasts are able to recruit uNK cells into the decidua by the CXCL12/CSCR4 axis (Tao et al., 2015).

2.2. Peripheral immune response during pregnancy

Also peripheral immune responses change during pregnancy. Clinically, this is obvious from the observations that symptoms of several autoimmune diseases can exacerbate during pregnancy (e.g. systemic lupus erythematosus), while symptoms of other autoimmune diseases (e.g. rheumatoid arthritis) may decrease (Piccinni et al., 2016).

It has long been known that the number of circulating white blood cells is increased during pregnancy (Siegel and Gleicher, 1981), which is indicative of an inflammatory response. Indeed, monocytes and granulocytes show upregulation of activation markers, produce increased amounts of oxygen-free radicals, and show different production

of cytokines (Sacks et al., 1998; Veenstra van Nieuwenhoven et al., 2003b). Monocyte maturation has also been observed (Melgert et al., 2012; Groen et al., 2015a), which also suggests a proinflammatory state during pregnancy.

Moreover, it has been shown that the specific immune response shifts away from a T-helper 1 (Th1) and Th17 type immune response towards a Th2 type response (Saito et al., 2010). It has been assumed that Treg supports this shift by inhibiting the proliferation and cytokine production of Th1 and Th17 cells (Saito et al., 2010). NK cell numbers, as well as the production of IFN- γ by these cells, are decreased (Borzychowski et al., 2005), suggesting that there is also a shift from a Th1 towards a Th2 type immune response in NK cells. The mechanisms by which all these peripheral immune changes are induced are not completely understood, but have been suggested to be initiated by the presence of the placenta and its production of proinflammatory factors such as hormones, microparticles and cytokines (Svensson-Arvelund et al., 2014).

3. Immunological disturbances and pregnancy outcome

Aberrations in local immunological adaptations during pregnancy are associated with adverse pregnancy outcome (Raghupathy et al., 2012; Melgert et al., 2012; Saito et al., 2010; Williams et al., 2009; Tuckerman et al., 2007). Pregnancy complications associated with aberrant implantation and placentation, such as recurrent pregnancy loss, preeclampsia or intrauterine growth retardation (IUGR), may be associated with altered numbers and function of uNK cells and macrophages in the decidua (Fig. 1). Indeed, uNK cell numbers were decreased in the decidua of women with preeclampsia and IUGR (Williams et al., 2009), while also in women with preeclampsia increased numbers of decidual M1 macrophages (classically activated macrophages) were found (Schonkeren et al., 2011). On the other hand, increased numbers of uNK cells in the decidua have been shown in recurrent pregnancy loss (Tuckerman et al., 2007). Also in women with IUGR a shift towards Th1 type cytokines in the decidua was found (Prins et al., 2012). These data suggest that an optimal number of inflammatory cells need to be present in the decidua in order to ensure normal implantation and placentation.

Aberrant adaptations of the peripheral immune response are also seen in women with pregnancy complications (Fig. 2). Preeclampsia, for instance, is associated with systemic inflammation, characterized by phenotypical activation and functional changes of monocytes and granulocytes (Sacks et al., 1998) as well as changes in monocyte subsets (Melgert et al., 2012; Groen et al., 2015a). In contrast to the shift towards a Th2 response occurring during normal pregnancy, preeclampsia is associated with a Th1 immune response (Saito et al., 2010). Also other pregnancy complications are associated with changes in immune responses. In women with IUGR, as compared to women with normal pregnancy outcome, an increased total lymphocyte count was observed, which coincided with an increased percentage of B-, T-, and helper T-lymphocytes (Bartha and Comino-Delgado, 1999). In women with recurrent miscarriage, increased NK cell numbers in the peripheral blood were observed (Hosseini et al., 2014). Also a predominance of Th1 immunity was often shown in women with IUGR and preterm birth (Raghupathy et al., 2012; Makhseed et al., 2003). As T1D, but also other autoimmune diseases like rheumatoid arthritis (Norgaard et al., 2010) and systemic lupus erythematosus (Cervera et al., 2002), is associated with increased pregnancy complications, the question arises whether T1D during pregnancy is also associated with aberrant immunological adaptations to pregnancy.

4. Type 1 diabetes and pregnancy

T1D is an autoimmune disease in which the pancreatic beta cells are destroyed by a cell-mediated autoimmune process (Wallberg and Cooke, 2013). This autoimmune process is characterized by a Th1/

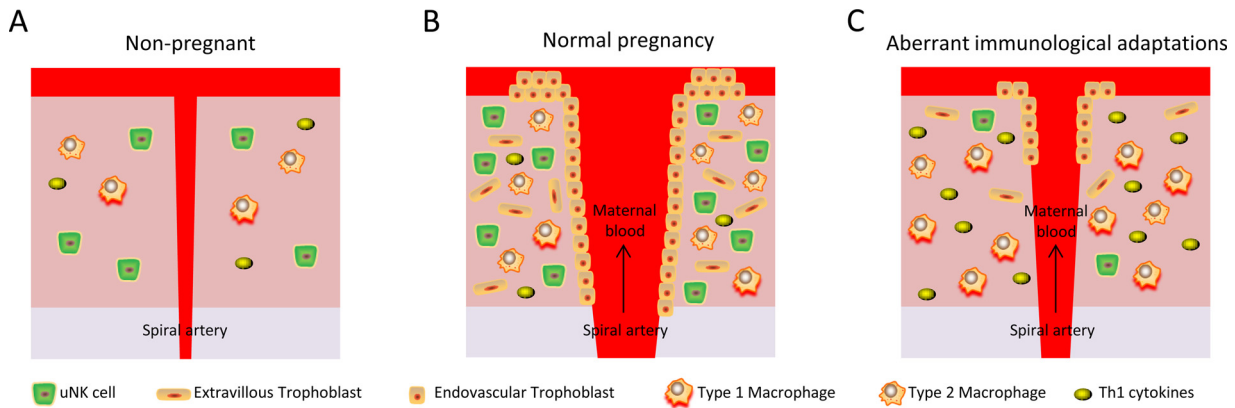


Fig. 1. Immune responses during spiral artery remodeling.

A: Local immune responses at the implantation site in the non-pregnant endometrium. In the endometrium relatively low numbers of uNK cells and macrophages are found. Trophoblast cells are absent.

B: Immunological adaptations in the decidua during normal pregnancy. In the decidua increased numbers of uNK cells and macrophages (mainly type 2) can be found, as well as extravillous trophoblasts. Together, these cells remodel the spiral arteries into large diameter conduit vessels with low resistance, assuring a constant blood supply to the intervillous space of the placenta.

C: Decidua in pregnancy complications such as preeclampsia. The number of uNK cells is decreased and there is less trophoblast invasion. On the other hand, there is an increase of type 1 macrophages and an increased production of Th1 cytokines. As a result, there is less remodeling of spiral arteries. This may result in pregnancy complications like preeclampsia.

Th17 cell-mediated response that involves the innate as well as the specific immune response (Wallberg and Cooke, 2013). The pathogenesis and etiology of T1D is heterogenic. Both genetic predisposition and environmental factors such as viral infections are included in the etiology (Wallberg and Cooke, 2013). Viruses can directly infect beta cells with subsequent damage, upregulation of MHC-I and release of antigens and cytokines, affecting the adaptive and innate immune response, ultimately resulting in autoimmunity against beta cells (Wallberg and Cooke, 2013). Viruses can also affect adjacent cells or cells at other locations, as for instance immune cells (Coppieters and von Herrath, 2011). Infection of immune cells with viruses carrying cross reactive epitopes of beta cells may result in molecular mimicry and therefore also in autoimmunity against beta cells (Coppieters and von Herrath, 2011). It has recently also been speculated that a ‘leaky gut’ may be involved. As a consequence of the elevated permeability of the intestine, macromolecular structures may enter the circulation and induce, via molecular mimicry, immune responses against epitopes present on beta cells (Vaarala, 2012). Animal studies in the diabetes

prone BB rat and non-obese diabetic (NOD) (Kikutani and Makino, 1992; Mordes et al., 2004) have shown that many cell types are involved in the process of beta cell destruction, such as (type 1) macrophages, NK-cells, B and T lymphocytes (Jun et al., 1999; Gur et al., 2010; Noorchashm et al., 1997; Bending et al., 2009). Most of these cells have been shown to be important in immunological pregnancy adaptations.

Not only is the autoimmune response seen in the pancreas of T1D patients, also peripheral immune responses have shown to be different in T1D patients as compared to healthy individuals. A recent study demonstrated that Treg cells are decreased in patients with T1D (Haseda et al., 2013). Further, it has been shown that the peripheral immune response in patients with T1D is characterized by an increased Th1/Th2 ratio, increased Th17 responses, dysfunctional Treg, and increased expression of IFN- γ by NK-cells (Groen et al., 2015a; Haseda et al., 2013; Honkanen et al., 2010). Interestingly, the T1D induced immunological changes seem to be the opposite of the changes needed during pregnancy (Fig. 3).

	Pregnancy	Preeclampsia	T1D P
Innate	Monocyte	↑↑	↑↑
	Activation	↑	↑
	Classical subset	↓↓	↓
	Nonclassical subset	=	=
Adaptive	Intermediate subset	↑	↑
	NK cell	↓	↑
	Activation	↓	↑
	Th1	↓	↑
	Th2	↑	↓
	Treg	↑	↓
	Th17	↓	↑

Fig. 2. Immunological adaptations to pregnancy, preeclampsia and type 1 diabetes.

Immunological adaptations in the peripheral immune response during normal pregnancy, preeclampsia and in pregnant women with type 1 diabetes (T1D P).

It can be observed that many immunological adaptations in T1D pregnancy are similar to the aberrant adaptations in preeclampsia. Arrow up: an increase as compared to healthy non-pregnant women.

Arrow down: a decrease as compared to healthy non-pregnant women.

‘=’ no change as compared to healthy non-pregnant women.

A double arrow indicates a more prominent increase/decrease.

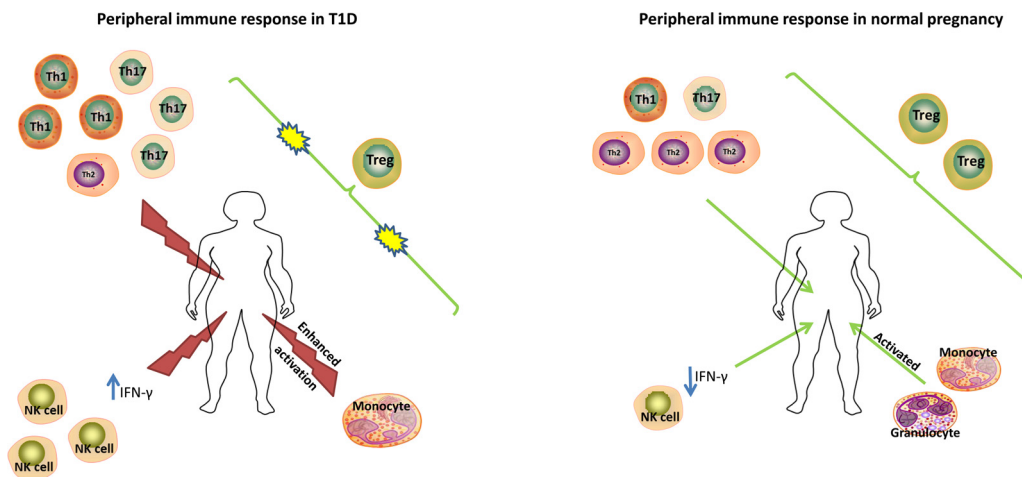


Fig. 3. Peripheral immunological adaptations during pregnancy with and without type 1 diabetes.

Peripheral immune responses in non-pregnant patients with T1D and in normal pregnant women. In patients with T1D the number of Th1, Th17 and NK cells is high, while the number of Th2 cells is low. Monocytes are activated and number and/or function of Treg are decreased. During a normal pregnancy, opposite immunological adaptations are needed, i.e. a decreased Th1/Th2 balance, low numbers of NK cells and low IFN- γ production by NK cells and increased number and/or function of Treg.

T1D is associated with an increased incidence of pregnancy complications (Evers et al., 2004), even when, as outlined in the introduction, glycaemia is strictly controlled. This should not be interpreted as a suggestion that glycaemic control is not of pivotal importance for a healthy pregnancy during T1D. The importance of adequate glycaemic control has convincingly been demonstrated by preconceptional improvement of glycaemic control or continuous glucose monitoring for prevention of congenital malformations and macrosomia (Murphy et al., 2008; Kitzmiller et al., 1991). However, although congenital malformations and macrosomia can be directly related to hyperglycemia, strong evidence for a sole influence of hyperglycemia on recurrent miscarriage, pre-eclampsia, IUGR and preterm birth is largely lacking. As described above, these complications are also influenced by immunological disturbances during pregnancy. Therefore, in a recent series of experiments we tested the hypothesis that immunological adaptations to pregnancy are disturbed in women and rats with T1D.

To this end, we studied peripheral immunological changes during pregnancy in women with T1D and rats with T1D, i.e. diabetic prone BB rats (Groen et al., 2015a, 2013). We showed many peripheral disturbances in the immunological adaptations in both pregnant women and pregnant rats with T1D. The most important differences were found in Th cells, NK cells and monocytes. We observed an increased Th1/Th2 ratio in pregnant women with T1D versus healthy control women (Groen et al., 2015a). NK cells showed an increased cytotoxic potential in pregnant T1D women (Groen et al., 2015a). Our results were in line with a study from Burke et al, who also found in T1D pregnancies a shift towards a Th1 immune response as well as changes in peripheral NK cells (Burke et al., 2015). Moreover, we observed increased numbers of intermediate monocytes, which also showed an increased MHC-II expression (Groen et al., 2015a). In T1D pregnant rats, as compared to non-diabetic pregnant rats, we found similar results, i.e. an increased percentage of NK cells and intermediate monocytes and an increased Th1/Th2 ratio (Groen et al., 2013). Therefore, the immune response in pregnant individuals with T1D may be interpreted as a Th1 type immune response with a general activation of the innate immune response. Immune responses with these characteristics are also observed in non-diabetic women with pregnancy complications like preeclampsia (Fig. 2). In future studies, it would be important to directly compare (local and peripheral) immune responses during T1D pregnancy and preeclamptic pregnancy, since to the best of our knowledge such studies have never been performed.

In diabetes prone BB rats, we studied the local immune response in the placental bed, and also here we observed immunological disturbances. There was an increased number of NK cells and type 1 macrophages in the mesometrial triangle in the uterus (i.e. the placental bed) of T1D pregnant rats as compared to healthy control rats (Groen et al., 2015b). This was associated with decreased trophoblast

invasion and suboptimal spiral artery remodeling in the T1D rats (Groen et al., 2015b). Burke et al. studied NK cells in the decidua basalis of NOD mice (also a model for T1D) and found decreased numbers of uNK cells early in pregnancy (Burke et al., 2007). Differences between our study and the study of Burke may be the timing of pregnancy (day 18 in our study vs days 6–8 in the Burke study) or the location of the uNK cells (Mesometrial triangle vs decidua basalis). Further studies are needed to determine whether similar changes take place in the placental bed of T1D pregnant women.

The immunological changes observed in T1D women and rats are similar to the immunological changes observed in women with pregnancy complications like recurrent miscarriage, preeclampsia, IUGR and preterm birth and are in line with our hypothesis that the pregnancy complications in T1D women may result from aberrant adaptations of the maternal immune response to pregnancy. Besides the fact that the immune response of women with T1D is altered due to the autoimmunity, women with T1D also suffer from chronic vascular inflammation, which might also affect placentation and the mother's vascular response to inflammation or inflammatory factors, resulting in pregnancy complications like preeclampsia (Staff and Redman, 2018).

5. Conclusion

We suggest that the pathophysiology of pregnancy complications in women with pregestational T1D is multifactorial. In addition to hyperglycemia, aberrant adaptations of the immune response during the course of pregnancy may well be responsible for the increased incidence of specific pregnancy complications like recurrent miscarriage, preeclampsia, IUGR and preterm birth. Future research should therefore focus on possible interventions in the immune response of (pre) pregnant T1D women and animals, in order to improve pregnancy outcome.

Disclosures and conflicts of interest

The authors of this review state that the complete article has been written by themselves and that no sponsorship was received for this work. Furthermore, the authors report no conflicts of interest and declare that no pharmaceutical company was involved in the funding of this article.

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