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# Immunology of pregnancy and systemic consequences: an update

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## Abstract

Pregnancy has, for many years, been considered to be an immunological paradox, with renowned Nobel-prize winning transplantation biologist Sir Peter Brian Medawar the first to introduce this concept back in 1953. This concept considers how the maternal immune system can tolerate the developing fetus, which is 50% antigenically foreign to the uterus, however, given the significant advances in our understanding of the immune system in regulating fertility, pregnancy and in complications of these, can we truly still think of this as a paradox? Indeed, the complexity of the maternal-fetal interface, along with our ever-advancing knowledge of immune cells and mediators means that we have a much clearer understanding of these interactions, however, there are areas we have still to fully understand. This chapter will summarise the key aspects of the role of the immune system at each stage of pregnancy and highlight the recent advances in our knowledge.

## Introduction

The female reproductive tract is abundant with immune cells and mediators, and there are many factors which can modulate their production, recruitment, and mechanism of action. In the absence of pregnancy, the immune system serves to protect the female reproductive tract from infection. In every region of the female reproductive tract and at every stage of the uterine cycle (Monin et al., 2020), as well as in response to coitus, through pregnancy, to post-partum uterine involution, components of the immune system are present and function to provide an environment suitable for the establishment of a successful pregnancy and ensure the return of the uterus to a pre-pregnancy state.

Recently, the concept of the pregnant uterus as a sterile environment has also been challenged. For decades it has been assumed that the developing fetus does not have a natural microbiome and the presence of microorganisms within the uterus before birth is associated with disease and creation of a potential threat to the success of pregnancy. In recent times, this has been questioned with the investigation of the presence of some microorganisms within the amniotic fluid, meconium and placenta. Table 1 summarises some of the key studies in this area, highlighting the sample types studied and major organism types identified. Indeed, this is an interesting and developing area of reproductive research, with consideration now being given to the possibility that the microbiome of the uterus can influence fertility, conception and pregnancy success (Bardos et al.,

2019, Chen et al., 2017, Moreno et al., 2016). This, however, this remains a controversial and ongoing area of study with debate around true detection of species versus contamination of samples (Blaser et al., 2021, Fricke and Ravel, 2021, Bushman, 2019, Perez-Munoz et al., 2017).

It is therefore widely acknowledged that the female reproductive tract is a unique mucosal environment, but we must also consider the fluctuation in immune function which arises in response to cyclical changes in hormonal levels. In chapter 2, we learned about the influence of sex hormones in driving differential responses in immunity between females and males. For the first 8 weeks of pregnancy, progesterone, which is often described as the pregnancy hormone, is produced by corpus luteum of the ovary. After this time, progesterone production is taken over by the placenta and it continues to rise dramatically until birth. Estrogens are produced primarily by developing follicles and the corpus luteum. Estradiol is the main estrogen in women of fertile age, estriol is produced by the placenta during pregnancy and estrone is produced in women of menopausal age (Kuijper et al., 2013). Levels of estrogens in maternal serum and urine increase dramatically during pregnancy, but falling after delivery of the fetus (Kuijper et al., 2013). In this chapter, we will also consider how these powerful systemic increases in estrogens and progesterone, required to sustain pregnancy, can act as a mechanism to modulate the maternal immune system (Oertelt-Prigione, 2012, Pennell et al., 2012, Robinson and Klein, 2012, Menzies and Henriquez, 2009, Druckmann and Druckmann, 2005). While these hormonal changes occur to support pregnancy, they can have consequences for the pathogenesis of infections or autoimmune diseases.

### **The impact of seminal fluid on the uterine environment**

The delivery of spermatozoa to the female reproductive tract is aided by the seminal plasma in which they are found. Seminal plasma is much more than a transport medium, it makes up 95-98% of semen contents (Rodriguez-Martinez et al., 2011), providing nourishment and protection for sperm, and containing a multitude of peptides and proteins that influence sperm function and preparation of the uterine epithelia for pregnancy (Schjenken and Robertson, 2020, Rodriguez-Martinez et al., 2011) through inducing changes in gene expression and cellular composition (Robertson, 2005). Seminal plasma contains an array of biologically and immunologically active compounds including hormones, such as estrogen and progesterone as well as prostaglandin E2 and an array of cytokines (Hampl et al., 2013, Robertson, 2005, Maegawa et al., 2002), including interferon-gamma (IFN $\gamma$ ), tumour necrosis factor-alpha (TNF $\alpha$ ), interleukins (IL)-1 $\beta$ , -6, -8, -10, -12 and TGF- $\beta$  (Bromfield, 2014). Most notably the cytokine TGF- $\beta$ , which is abundant within seminal plasma of both mice (Tremellen et al., 1998) and humans (Loras et al., 1999), is present in all three isoforms (TGF- $\beta$ 1, TGF- $\beta$ 2, TGF- $\beta$ 3), and can induce proinflammatory cytokine production by cervical cells (Sharkey et al., 2012a). Interestingly,

studies have shown that levels of TGF- $\beta$  in human seminal plasma fluctuates, with abstinence impacting on content of TGF- $\beta$ 1 and TGF- $\beta$ 2, and TGF- $\beta$ 1 correlating inversely with age (Sharkey et al., 2016). These findings, along with the suggestion that other semen contents may also demonstrate patterns of fluctuation, have potential implications for semen analysis and understanding the content and quality of semen for assisted conception practices.

The presence of immunomodulatory molecules within seminal plasma are required for the success of pregnancy, whether it is via natural conception or assisted reproduction. Indeed, the importance of the inflammatory response to mating is demonstrated by studies showing that *In Vitro* Fertilisation (IVF) is more successful in women who are exposed to semen at the time of embryo transfer (Tremellen et al., 2000). Identifying the role of individual components of seminal plasma, and their role in immunomodulation of the uterus for pregnancy, is an area of fertility research which has gained considerable ground in recent years. For example, recently, it has been shown in an *in vitro* study, that expression of CD25 and IL-10 by female T cells is modulated by exposure to seminal plasma, with differences observed between seminal plasma donated from males who experience recurrent pregnancy losses and their control counterparts (du Fosse et al., 2022).

In humans, deposition of semen results in the influx of macrophages, dendritic cells (DCs) and T cells into the epithelial and stromal compartments of the ectocervix, accompanied by an increase in gene expression for the cytokines granulocyte macrophage colony stimulating factor (GM-CSF), IL-1 $\alpha$ , IL-6, and the chemokine CXCL8 (Sharkey et al., 2012b). Macrophages and DCs remain within the stromal region of the cervix, while increases in T cells are found in both the epithelium and stroma, with a greater proportion of these being CD8+ than CD4+ (Sharkey et al., 2012b).

This immunomodulation of the uterine epithelium prepares the site for implantation, but also serves to prime the uterus and create a hospitable environment for the introduction of paternal antigens. After mating, there is a substantial increase in the cellularity of the uterine draining (para-aortic) lymph nodes (dLNs) in mice (Johansson et al., 2004), the main site of cross-presentation of paternal antigen (Moldenhauer et al., 2009). Recent studies have shown that in mice, the DC populations within the uterus and dLNs change significantly in the period between mating and implantation (Yasuda et al., 2020). Interestingly, these studies suggest that most of the DCs found within the uterus migrate to the site just prior to implantation. As summarised in Figure 1, seminal plasma drives the activation and expansion of specific CD4+ and CD8+ T cells, with maternal Antigen Presenting Cells (APCs) cross-presenting paternal antigens to CD8+ T cells in a TAP-dependent manner (Moldenhauer et al., 2009). Another T cell population considered to be importance for the establishment of tolerance are T regulatory cells (Tregs) (Aluvihare et al., 2004). Studies in mice show that as the female approaches the estrus phase of the cycle, Tregs accumulate in the uterine horn,

and this is accompanied by expression of T cell specific chemokines CCL3, CCL4, CCL22 and CX3CL1 (Kallikourdis and Betz, 2007). More specifically, studies have shown that CCL19 is likely to be a key recruiter of Tregs to the uterus (Guerin et al., 2011), and this is driven by seminal fluid (Shima et al., 2015, Kahn and Baltimore, 2010, Robertson et al., 2009a) and priming by tolerogenic APCs in the uterus (Shima et al., 2020). While Treg populations increase both systemically and locally during pregnancy in humans, paternal-antigen specific T cells have not yet been identified (Tsuda et al., 2019). The importance of Treg cells in maintaining an environment suitable for pregnancy, as it progresses, will be discussed in later sections.

### **Maternal rejection of semen**

The importance of the immunomodulation induced by seminal plasma within the female uterus is highlighted by consideration of the consequences of the rejection of semen. Immune infertility is estimated to impact 20% of couples of reproductive age (Brazdova et al., 2016) with many potential underlying causes, affecting both male and female reproductive systems. One such cause impacting on fertility is through the production of anti-sperm antibodies (ASA), and it is well recognised that multiple ASAs will be involved in causing infertility (Brazdova et al., 2016). Indeed, fertile women (and men) are also thought to produce ASAs as a normal physiological process, however this does not necessarily lead to infertility (Vickram et al., 2019). In some women, for unknown reasons, there can be a failure of tolerance to the complex antigenic milieu of the sperm, leading to pathological production of ASAs and therefore fertility issues. Pathologic ASA production by women impacts on several aspects of sperm function. Incubation of ASA from infertile women with normal sperm for 1 hour *in vitro* leads to a reduction in sperm motility, viability and membrane integrity (Pujianto et al., 2018). Recent advances in this area are now considering the potential of ASAs to create vaccines that can be utilised as a form of contraception (Vickram et al., 2019, Baldeon-Vaca et al., 2021).

### **Mechanisms involved in preventing fetal rejection**

#### *What is the implantation window?*

In humans, implantation occurs approximately 8 to 10 days post-ovulation (Wilcox et al., 1999), with the chance of conception approximately 30% per cycle (Zinaman et al., 1996). With such a low chance of success, it is unsurprising that around 75% of early losses attributed to implantation failure (Wilcox et al., 1988). Indeed, it can be considered that early pregnancy loss (before 10 weeks gestation) is the default consequence of fertilisation (Annual Capri Workshop, 2020). As advances in

reproductive technology have developed, so too has our understanding of the underlying molecular, biochemical and immunological mechanisms associated with successful pregnancy outcomes, and our appreciation that uterine and embryological and factors equally contribute to success.

The uterine endometrium goes through a remodelling process of decidualization to become receptive to the blastocyst, creating a period of 48 hours within the luteal phase of the ovarian cycle known as the “implantation window”. What is interesting to note is that decidualization occurs irrespective of the presence of a blastocyst. During decidualization, endometrial fibroblast-like stromal cells change to become larger, more rounded decidual stromal cells (DSCs) (Dunn et al., 2003), which can be characterised by their secretion of prolactin (Telgmann and Gellersen, 1998, Wu et al., 1995, Daly et al., 1983), insulin-like growth factor binding protein-1 (Matsumoto et al., 2008) and tissue factor (Lockwood et al., 1993) as well as expression of transcription factors such as FoxO1 (Adiguzel and Celik-Ozenci, 2021). The timing of the expression of these molecules is also crucial, as exemplified by studies showing that premature expression of prolactin is associated with repeated implantation failure (Berkhout et al., 2020). Adequate decidualization is a critical point for the fate of the pregnancy. Either decidualization continues in preparation for blastocyst implantation, or it breaks down to begin menstruation. Creation of the environment in preparation for the implantation window is dependent on a number of morphological, biochemical and hormonal changes (Aghajanova et al., 2008, Ng et al., 2020), but is also influenced by the immune environment (Murata et al., 2021).

#### *Implantation as an immunological event*

Implantation requires inflammation as a normal adaptation, involving various immune cells and mediators to support the preparation of the endometrial lining for receiving the blastocyst (Sehring et al., 2022). Contrary to this, excessive or aberrant inflammation can lead to implantation failure or miscarriage (Pantos et al., 2022). To understand the role of inflammation during implantation, it is first necessary to consider the presence of immune cells in the non-pregnant uterus.

#### *Macrophages during implantation*

Macrophages are mononuclear phagocytic cells which are key players of the innate immune system. Macrophages constitute approximately 20% of the total number of decidual leukocytes at the maternal-fetal interface (Zhang et al., 2017, Ning et al., 2016), playing a number of key roles at implantation. In addition, these cells are highly responsive to the female sex hormones, adapting their role and distribution accordingly even in the non-pregnant state (De and Wood, 1990, Ning et al., 2016). Both progesterone and estrogen modulate the inflammatory activities of macrophages (Jones et al., 2008, Menzies et al., 2011, Liu and Wang, 2013).

At implantation, macrophage numbers increase within the decidua to aid in the clearance of cellular debris (Abrahams et al., 2004) and degradation of artifacts present after mating (De et al., 1991). Murine studies utilising a macrophage depletion model have confirmed the necessity for these cells at implantation through disruption of progesterone production by the corpus luteum (Care et al., 2013). Subsequent studies have shown that during the implantation period, macrophages of the M2 subtype are present in the stromal region and in close proximity to the lumen and glands (Ono et al., 2020).

Beyond implantation, macrophages are also found within the placenta as two distinct populations; decidual macrophages and Hofbauer cells (Mezouar et al., 2021) with the ability to isolate and study these independent cell types only recently becoming a possibility (Lasch et al., 2022). Classification of placental macrophages as M1 or M2 is proving somewhat more difficult for researchers to ascertain, however studies suggest first and early second trimester macrophages resemble M1-types macrophages (Zhang et al., 2017) and late second and third trimester macrophages resemble the M2-type (Gustafsson et al., 2008). CD14+ macrophages within the term placenta are of both maternal (30%) and fetal (70%) origin (Mezouar et al., 2019) and exhibit characteristics of M1 macrophages (Mezouar et al., 2021, Gustafsson et al., 2008).

#### *Tregs as master regulators within the pregnant uterus*

Tregs have been the subject of much study and review in both humans and mice over the past 15 or so years and are considered to be pregnancy-protective (Muralidhara et al., 2022, Tsuda et al., 2021, Krop et al., 2020, Shigeta et al., 2020, Zhang and Sun, 2020, Jorgensen et al., 2019, Tsuda et al., 2019, La Rocca et al., 2014, Teles et al., 2013, Leber et al., 2010, Zenclussen et al., 2010, Guerin et al., 2009, Aluvihare et al., 2004). As mentioned earlier, Tregs accumulate within the endometrium during the pre-implantation period (Kallikourdis and Betz, 2007) and offer a protective role at the implantation site. Murine studies of allogeneic and syngeneic matings demonstrate Tregs become activated against self-antigens early after embryo implantation to create a tolerant environment (Chen et al., 2013). Fetal-antigen specific Treg cells are not present at embryo implantation, however their number increases as pregnancy progresses (Rowe et al., 2012). Decidual Tregs increase with advancing gestation (Somerset et al., 2004) and there is preferential recruitment of fetus-specific Treg cells from the maternal blood to the decidua (Tilburgs et al., 2008). Interestingly, decidual Treg numbers are reduced in pre-eclamptic women compared to normal pregnancies (Quinn et al., 2011), suggesting a key role in regulation of the maternal-fetal interface and a developing area of research (Robertson et al., 2019).

This leads to the question as to how Tregs regulate the immune response during pregnancy? Tregs modulate the activities of T cells. Culturing T cells in the presence of medium conditioned by placental trophoblasts demonstrated a skewing towards the production of Th2 associated transcription factors and cytokines, and inhibition of those associated with Th1 and Th17 (Liu et al., 2011). Traditionally, pregnancy was considered a Th2-associated phenomenon, with the placenta and uterine environment skewed towards an abundance of Th2-type cytokines (Lin et al., 1993, Wegmann et al., 1993), however this well-accepted paradigm has now been amended to include Th17 and Tregs into this (Saito et al., 2010). Indeed, the balance between Th17 cells and Treg cells is critical for the outcome of pregnancy in humans. During healthy pregnancy the ratio of circulating Treg cells to Th17 cells is increased significantly compared to non-pregnant controls, however in pre-eclamptic women this skewing away from Th17 cells is not observed (Santner-Nanan et al., 2009).

#### *The specialties of uterine Natural Killer (NK) cells*

Natural Killer (NK) cells are a type of innate lymphoid cell (ILC) crucial in the early innate defences against various pathogens, viruses in particular. In humans, two main populations of blood, or peripheral, NK cells can be defined based on expression of the surface molecule CD56, CD56<sup>dim</sup> or CD56<sup>bright</sup>. 90% of peripheral NK cells are defined as CD56<sup>dim</sup> and these cells are characterised by a high level of spontaneous lytic activity (Dosiou and Giudice, 2005). Contrary to this, CD56<sup>bright</sup> NK cells have little lytic activity. A third type of NK cells can be identified, unique to the uterus. The phenotype and regulation of uterine NK (uNK) cells within the pregnant uterine environment is crucial for pregnancy success (Faas and de Vos, 2017, Giuliani et al., 2014, Manaster and Mandelboim, 2010, Vacca et al., 2013, Vacca et al., 2011). This is demonstrated by the link between recurrent pregnancy loss and dysregulation between uNK cells and peripheral NK cells (Mahajan et al., 2022, Giuliani et al., 2014, Tang et al., 2011).

uNK cells differ from both of the peripheral NK phenotypes, CD56<sup>dim</sup> and CD56<sup>bright</sup>, but have more in common with this latter phenotype, including weak lytic activity and lack of expression of FCγRIII (CD16) (Manaster and Mandelboim, 2010). Binding of IgG to CD16 results in activation of antibody-dependent cell-mediated cytotoxicity (ADCC) by NK cells (Bryceson et al., 2006), and so the absence of CD16 on uNK cells demonstrates another tolerogenic feature of these cells. Endometrial uNK cells are fairly inactive in the non-pregnant uterus (Manaster et al., 2008). uNK cells constitute 50-70% of immune cells within first trimester decidua near to the blastocyte implantation site (Manaster and Mandelboim, 2010, Bulmer et al., 2010, Mahajan et al., 2022). These decidual uNK cells still express many activating NK receptors, but rather than inducing cytotoxicity and potentially a reaction towards the fetally-derived cells, these uNK cells act to support trophoblast invasion and



angiogenesis (Hanna et al., 2006) as well as regulation of Th17 cell function at the fetal-maternal interface (Fu et al., 2013).

### *Cytokines and chemokines in the pregnant uterus*

So far, we have considered some of the key immune cells which are involved in the tolerance of fetally-derived cells during pregnancy. What about the chemokines responsible for the trafficking of immune cells, and cytokines which may be produced by these cells, or act on these cells? With regard to the uterus during pregnancy, there are a few cytokines, namely LIF and IL-15, which stand out as having key roles in modulating the immune environment.

The non-pregnant human endometrium of non-pregnant humans expresses several chemokine receptors (e.g. CXCR1, CXCR2, CCR5, CXCR4, CCR2, CCR3, CXCR3 and CX3CR1) and produces a number of chemokines during the implantation window (e.g., CCL2, CCL4, CCL5, CCL7, CCL11, CCL14, CCL16, CCL21, CCL22, CXCL8, CX3CL1), all of which has been extensively reviewed within the literature (Ramhorst et al., 2016, Du et al., 2014, Park and Yang, 2011, Red-Horse et al., 2004, Red-Horse et al., 2001). Many of these chemokines are involved in the trafficking of immune cells, including macrophages, Tregs, and uNK cells to the decidua. It has been suggested that chemokines and their receptors may also play other significant roles during the establishment of pregnancy, with receptors found on cells of the blastocyst and extravillous trophoblasts (Dominguez et al., 2003a, Dominguez et al., 2003b, Dimitriadis et al., 2005, Hannan and Salamonsen, 2008, Hannan and Salamonsen, 2007, Hannan et al., 2006). As will be discussed later, chemokines and their receptors have also been extensively studied for their roles in driving inflammation at the other end of the gestational period - at the point of labour.

One of the most characterised factors involved in implantation is Leukemia Inhibitory Factor (LIF), and its role during pregnancy has been extensively reviewed in the literature (Pantos et al., 2022, Li et al., 2020, Winship et al., 2015, Moberg et al., 2015). LIF is a pleiotropic anti-inflammatory cytokine which is a member of the IL-6 family. Studies using LIF-deficient mice have shown it is a highly glycosylated 40-50kDa glycoprotein that is essential for successful implantation (Stewart et al., 1992) through binding the LIF-receptor (LIFR) and inducing STAT3 activation (Suman et al., 2013, Poehlmann et al., 2005) as well as inducing both autocrine and paracrine signalling pathways in the endometrium to facilitate implantation (Cullinan et al., 1996, Dominguez et al., 2002). LIF is expressed during the mid-late phase of the menstrual cycle and early stages of pregnancy, in both the glandular and luminal epithelium (Pantos et al., 2022, Markert et al., 2011). The importance of LIF in this scenarios is demonstrated by studies showing that women diagnosed with recurrent implantation failure have significantly less LIF in their endometrial glandular epithelium than normal pregnant women (Mariee

et al., 2012). By contrast, it was found that women with recurrent implantation failure have higher levels of the cytokine IL-15 in the stroma (Mariee et al., 2012) and in the placenta (Toth et al., 2010) than in control women with normal pregnancies. IL-15 is a 14-15kDa cytokine that is a member of the IL-2 family of cytokines. IL-15 has the ability to influence both innate and adaptive arms of the immune response, by stimulating NK cells, T cells and NKT cells. IL-15 transcripts are strongly expressed during the secretory, or luteal, phase of the cycle in humans a time in which a large number of NK cells are present within the uterus (Gordon, 2021, Chegini et al., 2003, Kitaya et al., 2000). IL-15 is important for the differentiation of uNK cells within the endometrium during regular regeneration activities and during pregnancy (Strunz et al., 2021) but the placenta has low expression of IL-15 in the early development stages, but this gradually increases throughout pregnancy, with a peak in levels at the point of labour (Gordon, 2021). Furthermore, placental explant studies have shown that IL-15 production is significantly lower in pre-eclamptic placenta samples than healthy term placentas (Agarwal et al., 2001)

### **Altered Human Leukocyte Antigen expression by trophoblasts**

The placenta is an organ unique to pregnancy and crucial for its success. The process of placentation begins when the blastocyst implants into the decidua, with extravillous trophoblasts (EVT) making their way into the uterine wall. A number of pregnancy complications, such as placenta accreta and recurrent spontaneous abortions, have clear links with dysregulation of trophoblast invasion (Illsley et al., 2020, Moser et al., 2018). Given the invasive nature of this process, tight regulation is required in order to prevent attack of the trophoblasts by maternal leukocytes.

What mechanisms are in place to prevent attack of these fetally-derived, invasive cells? Interestingly, EVT cells have a unique expression of Human Leukocyte Antigen (HLA). EVTs do not express the polymorphic MHC class I molecules HLA-A and HLA-B or the class II HLA-D molecules, but do display the class I molecules HLA-C, HLA-E, HLA-F and HLA-G (Apps et al., 2009, Hackmon et al., 2017). Expression patterns are summarised in Table 2 .

HLA-C, HLA-E and HLA-F expression by EVTs provides a mechanism of protection for the fetus through modulation of activities of maternal NK cells (Papuchova et al., 2019). HLA-C can bind the NK cell inhibitory receptor KIR, thereby acting to “switch off” these cytotoxic cells which may react against fetally-derived antigens (Sharkey et al., 2008). HLA-C is thought to play a key role in early implantation through directing the activities of invasive trophoblasts (Hackmon et al., 2017), more specifically, controlling the depth of invasion of trophoblasts. In addition, maternal T cells may specifically recognize fetal HLA-C on trophoblast cells, and that this activation promotes Treg

differentiation (Tilburgs et al., 2009). The surface expression of HLA-C is known to be regulated at a transcriptional and post-transcriptional level (Papuchova et al., 2019).

HLA-E is expressed by EVT<sub>s</sub> and this has been shown to be very much restricted to first trimester (Hackmon et al., 2017). This molecule regularly forms complexes with HLA-G and together these mediate the inhibitory actions of uNK cells (King et al., 2000a). HLA-G is the most studied of the placenta-associated HLA molecules, with seven isoforms identified. HLA-G1, HLA-G2, HLA-G3, HLA-G4 being membrane bound, and HLA-G5, HLA-G6, HLA-G7 being soluble (Hviid, 2006, Hunt and Langat, 2009). The trophoblast-bound molecules have roles in binding inhibitory NK cell receptors to limit their action, and also to control the degree of trophoblast invasion into the uterine wall. The soluble forms have been associated with modulation of T cell function through impairment of expression chemokine receptors (Morandi et al., 2010). The function of HLA-F has only been more recently explored, and it has been found that it is found on the cell surface of actively migrating EVT<sub>s</sub> and this supports their specific role in early EVT invasion and interactions with uNK cells (Hackmon et al., 2017).

### **Immunomodulation by Placental Exosomes**

Exosomes are defined as membrane-bound extracellular vesicles (EVs) with a size of ~40-160nm in diameter, originating from the endosome of a cell (Kalluri and LeBleu, 2020). Interest in the immunomodulatory functions of exosomes has grown significantly in recent years, and studies into the impact of exosomes derived from the placenta has also created much interest. In fact, the identification of placental EVs was reported as far back as 1998 (Knight et al., 1998). Exosomes derived from the placenta have been associated with crucial immunomodulatory functions for the successful maintenance of pregnancy (Bai et al., 2021, Nair and Salomon, 2018, Tong et al., 2018).

Throughout pregnancy, the placenta continually sheds EVs into the mother's bloodstream, with the syncytiotrophoblast layer being the main source of these (Salomon et al., 2017, Tannetta et al., 2017, Dragovic et al., 2015). Placental EVs contribute to the modulation of the maternal immune environment for the protection of the fetus, by altering the actions of immune cells. For example, activation of the potentially cytotoxic NK cells through the NKG2D activating receptor is reduced by the binding to NKG2D ligands on placental EVs (Hedlund et al., 2009). More recently, it has been shown that placental EVs can secrete HLA-E, promoting the secretion of IFN- $\gamma$  and VEGF by decidual NK cells (Jiang et al., 2021) at implantation. Indeed, placental EVs increase significantly through the first trimester (Sarker et al., 2014, Kshirsagar et al., 2012). In addition, placental EVs can modulate the differentiation (Aldo et al., 2014), activation and subtype polarisation of decidual macrophages to favour pregnancy. One way in which this can occur is through driving the induction of the proinflammatory cytokine IL-1 $\beta$  from macrophages (Atay et al., 2011). In terms of impact on T cell

function, studies have shown that placental EVs lead to downmodulation of activity, and thereby protection of pregnancy, through inhibiting T cell proliferation and cytotoxicity, driving Treg differentiation and T cell apoptosis (Stenqvist et al., 2013).

### **The role of the maternal immune system during parturition and post-partum involution**

The initiation of labour, or parturition, in humans is complex, and the underlying mechanisms are not yet fully understood, however, many pathways have been considered such as the activation of the hypothalamic-pituitary-adrenal axis, prostaglandin production, an increase in the responsiveness to oxytocin and the functional withdrawal of progesterone (Smith, 2007).

In addition to these physiological mechanisms, the infiltration of inflammatory cells and their mediators is now considered key in driving normal labour at term. Indeed, the impact of inflammation within the uterus on labour initiation has been eluded to for some time, with infection being responsible for 30-50% of cases of preterm birth (Goldenberg and Thompson, 2003, Goldenberg et al., 2000, Romero et al., 2006). Normal labour is associated with an influx of inflammatory cells into the uterus, driven by an increase in chemokine and proinflammatory cytokine production at this site. Labour is associated with inflammation and this is characterised by an influx of macrophages, neutrophils and T cells to the myometrium and cervix (Osman et al., 2003, Thomson et al., 1999) along with an increase in the production of proinflammatory cytokines, including IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 (Osman et al., 2003, Young et al., 2002) and chemokines such as CXCL8 (IL-8), CCL2, CCL3 and CCL5 (El-Azzamy et al., 2017, Gomez-Lopez et al., 2010). Indeed, the utilisation of chemokine inhibitors to halt pre-term birth has recently been investigated (Shynlova et al., 2021, Coleman et al., 2020). Until recently, it was considered that inflammation within the myometrium was a driver of labour induction, however it is now recognised that it is more likely that inflammation is a consequence of labour induction, designed to prepare the uterus for post-partum remodelling (Singh et al., 2021, Singh et al., 2017).

Post-partum uterine repair and involution is a highly efficient process, required for the success of future pregnancies. Studies into the underlying molecular and immunological mechanisms of human post-partum repair have been slow to make it into the scientific literature, mainly due to the practical and ethical issues involved in collecting appropriate tissue samples. Much of what we do know about post-partum involution has come from other models of tissue repair (Paliulyte et al., 2017) use of mouse and rat models. Repair of the uterus requires extracellular matrix remodelling, proliferation, apoptosis and breakdown of collagen (Salamonsen, 2003, Hsu et al., 2014).

## **Consequences of pregnancy for the immune system**

### *Impact of pregnancy hormones on the immune system*

The female body significantly changes its hormonal balance for pregnancy maintenance. The sex hormones progesterone and estrogens can have many effects on the cells of the immune system (Wira et al., 2015, Menzies and Henriquez, 2009, Robinson and Klein, 2012) which can have wider implications. For example, pregnancy affects maternal autoimmune diseases and the outcome of infectious diseases (as described in detail in other areas of this book).

The number and activation status of circulating leukocytes changes in the mother during normal pregnancy. There is an increase in the total leukocyte count during pregnancy, with an increase in the number of peripheral monocytes and granulocytes (Belo et al., 2005, Luppi et al., 2002a, Luppi et al., 2002b), but a decrease in the number of lymphocytes (Castilla et al., 1989). In pregnant women, monocytes are activated, producing the proinflammatory cytokines IL-1b and IL-12 (Luppi et al., 2002a) but by comparison neutrophils appear to have reduced effector functions, with a reduction in chemotaxis and microbial killing ability (Kindzelskii et al., 2004, Crouch et al., 1995, El-Maallem and Fletcher, 1980).

While the role of T cell subsets has been studied for some time and discussed earlier within this chapter, data about the impact of pregnancy on B cells is only just emerging in the literature. While B cells constitute 5-15% of circulating lymphocytes, the number of these changes significantly in response to pregnancy. Numbers of B cells generally fall in late pregnancy and the post partum period (Lima et al., 2016). B cells are now characterised into different subsets, B1 and B2 B cells. B1 cells produce autoantibodies, which are detrimental to pregnancy, whereas B2 cells are responsible for production of asymmetric antibodies (IgG molecules with a modified Fab region), which can be protective for pregnancy (Muzzio et al., 2013, Gutierrez et al., 2005, Zenclussen et al., 2001, Barrientos et al., 2009). We previously discussed the importance of Tregs for the maintenance of pregnancy, but what about B regulatory cells (Bregs)? Much of what we know so far about Bregs has come from studies into autoimmunity, tolerance and cancer (Guzman-Genuino and Diener, 2017) and are considered to be mediators of immunosuppression, so this would suggest a key role in pregnancy protection. Bregs are a major source of the immunosuppressive cytokine IL-10, and murine studies have shown that Bregs are required for pregnancy tolerance, with IL-10 being a main mediator of this (Rolle et al., 2013, Jensen et al., 2013).

### *Impact of pregnancy on the response to infection*

It is well established that generally, women exhibit much more vigorous humoral responses than men, with higher serum levels of IgG and total IgM (Eidinger and Garrett, 1972, Giltay et al., 2000). Sex hormones play a critical role in modulating immune function, and the importance of understanding these influences is highlighted by consideration of the sex bias in the susceptibility to a number of infections. The same can be said for pregnancy, it is well known that the altered immune environment leads to pregnant women being more susceptible to some infections.

An example of this, is the fact that the pregnant women are more susceptible to the impacts of the protozoan parasite *Toxoplasma gondii*. The change in the uterine immune environment described within this chapter, that is the development of a Th2 dominant milieu, favours the transmission and replication of this parasite, which is normally controlled by a Th1 type response (Roberts et al., 1995). Transmission of the parasite leads to congenital toxoplasmosis (Gomez-Chavez et al., 2019, Singh, 2016, Hampton, 2015, Torgerson and Mastroiacovo, 2013), which can have a range of detrimental outcomes for the fetus, dependent on the stage of pregnancy at which transmission occurs.

Due to the immunological modifications which occur systemically during pregnancy, it is therefore unsurprising that pregnant women are generally more susceptible to respiratory infections (Englund and Chu, 2018), including COVID19 (Forestieri et al., 2022) and influenza (Mertz et al., 2019), leading to a higher risk of hospitalisation.

#### *Autoimmune disease during pregnancy*

As well as infections, the sex and pregnancy-associated hormones have been shown to have a significant impact on the incidence and progression of autoimmune disease. With global ageing populations, and increasing incidence of autoimmune disease, it may be necessary to explore personalised treatment options.

The significant improvement in symptoms experienced by Rheumatoid Arthritis (RA) patients during pregnancy allows us to hypothesise that treatment options based on pregnancy-associated immune modifications could be useful. Women are three times more likely to develop RA than men, however, approximately 75% of women with RA experience an improvement in their symptoms as a direct consequence of the systemic effects of pregnancy (Forger and Villiger, 2020). This effect is not long-lasting, and within 3 months post-partum, typical RA symptoms return (Adams Waldorf and Nelson, 2008). While much remains to be learned about the underlying mechanisms for the disease amelioration, recent studies have eluded to the downregulation of effector T cells, upregulation of Tregs and alterations to antibodies as potential reasons. More specifically, RA is associated with changes in the glycosylation of the IgG Fc region, however in pregnancy, it has been found that

galactosylation of these immunoglobulins is related to the symptom improvement (Bondt et al., 2013, van de Geijn et al., 2009).

Multiple Sclerosis (MS) is characterised by the immune attack of the myelin sheath surrounding nerves. Generally, women are three times more likely to develop MS as men (Disanto and Ramagopalan, 2013) with women more likely to carry the associated HLA DRB1 allele (Bove and Chitnis, 2014), however men are more likely to develop more progressive disease with poorer recovery after attacks. Similar to RA, pregnancy is associated with a reduction in the incidence of relapses, but a return of the condition in the months following delivery (Confavreux et al., 1998). Progesterone, estriol and estradiol may play an important role in the preventing relapses in sufferers of this condition (El-Etr et al., 2005, Kim et al., 1999). More recently, a nationwide cohort study has shown no links between MS and recurrent pregnancy loss (Mikkelsen et al., 2022).

Another autoimmune disease where pregnancy impacts on the disease is systemic lupus erythematosus (SLE), however unlike with RA and MS, symptoms are not improved with pregnancy, in fact in many cases symptoms worsen. Women with SLE are at a much greater risk of developing pregnancy complications and fetal loss (Moroni and Ponticelli, 2016, Foocharoen et al., 2009, Kalok et al., 2019). SLE is defined immunologically by the production of autoantibodies against nuclear antigens (Crispin et al., 2010). More specifically, 45% of SLE patients exhibit autoantibodies to the estrogen receptor, ER- $\alpha$ , which interferes with T cell homeostasis (Colasanti et al., 2012).

## **Conclusion**

As we learn more about the human immune system, we have to explore how these immune functions are modulated during pregnancy, and in turn how this impacts on the ability to deal with infections and other immune-related diseases. In this chapter, we have explored the key mechanisms involved in protection of the fetus from the maternal immune system, and eluded to how this immunomodulation can impact on other aspects of the mother's health, namely, response to infection and autoimmune disease. Much remains to be determined about how we can apply this increased knowledge of the immune adaptations to pregnancy for clinical use, to find more efficient ways of predicting, diagnosing and treating both fertility issues and pregnancy complications.

**Table 1: Studies examining detection of microorganisms within the pregnant uterus.**

Sample Type	Bacterial Species	Reference
Amniotic fluid	Proteobacteria	Collado et al., 2016
	<i>Propionibacterium</i>	Collado et al., 2016, Stinson et al., 2019
	<i>Streptococcus</i> (low abundance)	(Collado et al., 2016)
	<i>Lactobacillus</i>	Collado et al., 2016
	None detected	Lim et al., 2018
Meconium	<i>Lactobacillus</i>	Collado et al., 2016
	Proteobacteria	Collado et al., 2016
	<i>Propionibacterium</i>	Collado et al., 2016
	<i>Streptococcus</i> (low abundance)	Collado et al., 2016
	<i>Pelomonas puraquae</i>	Stinson et al., 2019
Placenta	Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, Fusobacteria	Aagaard et al., 2014
	<i>Lactobacillus crispatus</i>	Prince et al., 2016
	<i>Lactobacillus</i>	Collado et al., 2016
	Proteobacteria	Collado et al., 2016
	<i>Propionibacterium</i>	Collado et al., 2016
	<i>Streptococcus</i> (low abundance)	(Collado et al., 2016)
	None detected	Lauder et al., 2016, Leiby et al., 2018, Theis et al., 2019, de Goffau et al., 2019



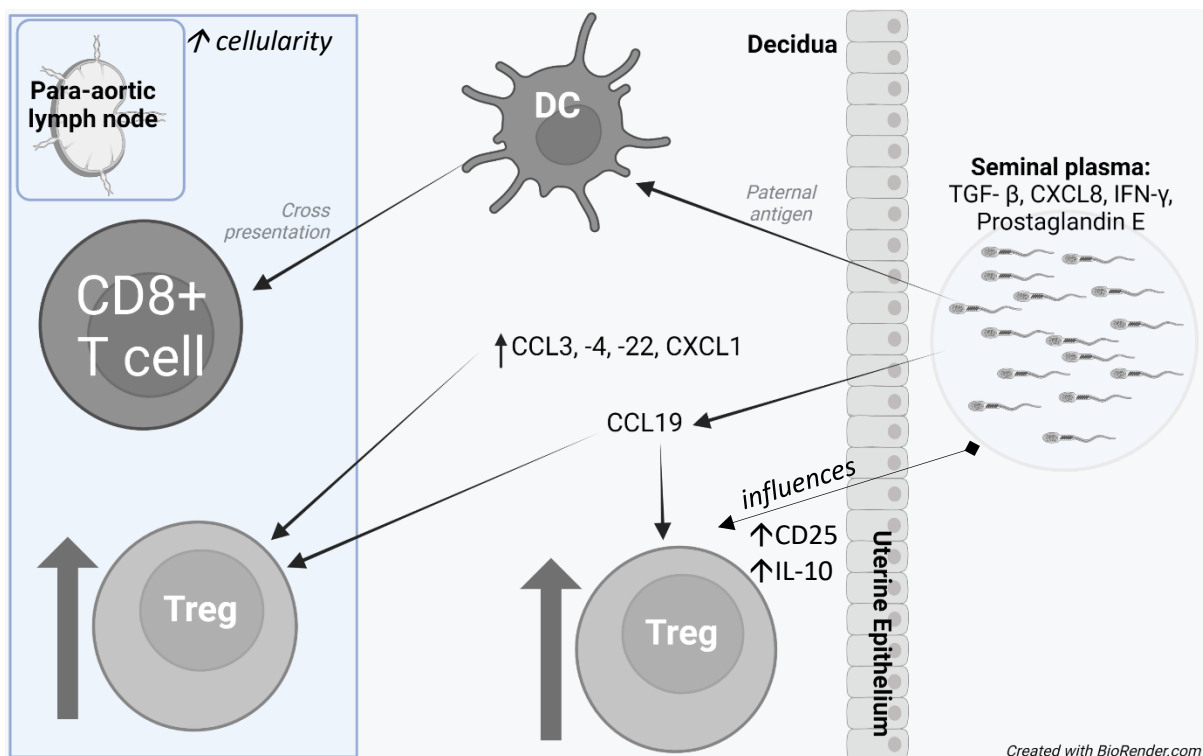
**Table 2: HLA– C, -E, -F, -G expression patterns**

<b>Molecule</b>	<b>Expression pattern</b>	<b>References</b>
<b>HLA-C</b>	Surface EVT expression	Papuchova et al., 2019, Hackmon et al., 2017, Tilburgs et al., 2017, Apps et al., 2009, Apps et al., 2008, King et al., 2000b
<b>HLA-E</b>	EVT expression, ligand for CD94/NKG2 NK cell receptor  Strong first trimester expression  Co-expressed with HLA-G on placental cells  Human umbilical cord lining epithelial cells	Hackmon et al., 2017, Cai et al., 2014, Apps et al., 2009, Ishitani et al., 2003, King et al., 2000a
<b>HLA-F</b>	Surface EVT expression  Highly expressed in cytotrophoblast and syncytiotrophoblast layers in first trimester.  EVT expression, mainly in cytoplasm during first trimester, and then surface during second and third trimester	Hackmon et al., 2017, Shobu et al., 2006, Ishitani et al., 2003
<b>HLA-G</b>	Surface EVT expression, strong levels across gestation.  Membrane bound HLA-G expressed on EVT, and sHLA-G on all placental trophoblasts.  Placental Hofbauer cells  Endothelial cells of chorionic villi  Amniotic cells  Human umbilical cord lining epithelial cells	Hackmon et al., 2017, Cai et al., 2014, Apps et al., 2009, Ishitani et al., 2003, King et al., 2000b, Blaschitz et al., 1997, Hammer et al., 1997, Yang et al., 1996

*EVT = extravillous trophoblasts; HLA = Human Leukocyte Antigen; NK = Natural Killer; sHLA = soluble Human Leukocyte Antigen*

### Figure 1: Female response to seminal plasma

The uterine epithelium responds to immunomodulatory molecules (e.g. TGF- $\beta$ , CXCL8, IFN- $\gamma$ , Prostaglandin-E) within seminal plasma by producing T regulatory-attracting chemokines. Dendritic cells cross present paternal antigens to CD8+ T cells within the para-aortic lymph nodes, which drain the uterus, and are known to increase in cellularity post-mating. These mechanisms serve to prepare the maternal immune system for the development of a semiallogeneic fetus (du Fosse et al., 2022, Guerin et al., 2011, Robertson et al., 2009a, Robertson et al., 2009b, Kallikourdis and Betz, 2007, Aluvihare et al., 2004).



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