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The role of Th17 cells in the pathophysiology of pregnancy and perinatal mood and anxiety disorders

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Abstract

T cells play a key role in adaptive immune responses, and shifts among T cell classes occur in normal pregnancy. There is evidence for the role of T_H17 cells and dysregulation of the T_H17:T_{reg} cell balance in morbidities and autoimmune diseases during pregnancy. Because T_H17 responses may play a role in depression and anxiety outside of pregnancy, we hypothesize that T_H17 responses and the balance of T_H17:T_{reg} activity may also contribute to the development of depression and anxiety during pregnancy. To explore this hypothesis, this review has three main aims: 1) to evaluate systematically the role of T_H17 cells and cytokines during pregnancy; 2) to compare changes in the ratio of T_H17:T_{reg} cells during pregnancy morbidities with the changes that occur in depression and anxiety outside of pregnancy; and 3) to provide a basis for further research on T_H17 cells in perinatal mood and anxiety disorders, with an eye toward the development of novel therapeutics. We also review the limited literature concerning perinatal mood and anxiety disorders, and hypothesize about the potential role of T_H17 cells in these illnesses. Understanding the pathophysiology of perinatal mood and anxiety disorders will aid development of novel therapeutics that address immunological mechanisms, in addition to the serotonin system, which are targetable molecules in treating depression and anxiety during pregnancy.

Keywords

pregnancy; perinatal; anxiety; depression; T_H17; T_{reg}

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1.1 Introduction

Early research into immune functioning during pregnancy focused on pregnancy as a time of immune suppression, with maternal immune responses hypothesized to be down-regulated to avoid rejection of the fetus (Chen et al., 2012). The improvement of some autoimmune diseases, such as multiple sclerosis, in pregnancy was thought to be evidence of immune suppression, but more nuanced assessment of immune responses during pregnancy led to the conclusion that, rather than blanket suppression, there were shifts among different classes of immune cells, including T cells, during normal pregnancy (Larocca et al., 2008). Initial research pointed to a shift away from helper T cell type 1 (T_H1 ; pro-inflammatory) and toward helper T cell type 2 (T_H2 ; anti-inflammatory) cells. This simplistic paradigm has also proved insufficient, as inflammation appears to change throughout pregnancy, and as our knowledge of other immune responses and cells has increased, there has been a paradigm shift away from simplistic assumptions about immunological changes during pregnancy and toward greater analysis and consideration of the kinetics of immune cells and responses during pregnancy (Kraus et al., 2012). One such cell population is T_H17 cells, which can be both pro-inflammatory and anti-inflammatory in diverse tissue sites, including within the placenta and reproductive tract during pregnancy.

T_H17 cells promote inflammation, help to amplify neutrophilic responses, promote B-cell class switching, activate barrier epithelial cells, and produce antimicrobial peptides (Murphy, 2017). Naïve T cells are prompted to differentiate into T_H17 cells in response to IL-6 and transforming growth factor (TGF)- β , secreted primarily by innate immune cells. T_H17 cells develop in the presence of IL-23 and mature T_H17 cells produce IL-17(A-F) and IL-22, with IL-17 stimulating innate immune cells to enhance the production of IL-6. When TGF- β is present in the absence of IL-6, T_{reg} cells will develop instead of T_H17 . Certain damage-associated molecular pattern molecules (DAMPs), including especially the alarmin high-mobility group box 1 (HMGB1), also stimulate T_H17 responses (Li et al., 2014).

T_H17 cells generally induce inflammation and are involved in the pathogenesis of some autoimmune conditions, including multiple sclerosis; in contrast, T_{reg} cells induce tolerance by inhibiting the production and proliferation of cytokines, natural killer (NK) cells, dendritic cells (DCs), and immunoglobulins (Saito et al., 2010). The balance between these two types of CD4+ T cells – one promoting inflammation, the other controlling adaptive immune responses – is tightly regulated by the presence or absence of IL-6, and an enhanced T_H17 response (thus throwing the T_H17/T_{reg} ratio out of balance) is increasingly thought to be associated with inflammatory morbidities of pregnancy, as well as with symptoms of depression and anxiety outside of pregnancy (Beurel and Lowell, 2017; Saito et al., 2010).

IL-6 is a pleiotropic cytokine produced by many cell types (Tanaka and Kishimoto, 2014) and is a marker of both acute and chronic inflammation. IL-6 has been implicated in a number of pregnancy morbidities that affect outcomes for both mother and fetus, including preeclampsia and preterm birth (Wei et al., 2010), as well as in depression and anxiety outside of pregnancy (Dowlati et al., 2010). The role of T_H17 cells in both pregnancy morbidities and mood and anxiety symptoms raises the question of whether the actions of T_H17 cells may be a mechanism through which IL-6 is exerting its deleterious effects – and

whether we should consider the role of T_H17 cells and cytokines in the pathophysiology of perinatal mood and anxiety disorders.

T_H17 cells were first identified in 2005, and have since been linked to many inflammatory diseases, including rheumatic diseases (e.g., psoriasis, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, and undifferentiated spondyloarthritis), non-rheumatic autoimmune diseases (e.g., multiple sclerosis, autoimmune myocarditis, and endometriosis), pulmonary diseases (e.g., allergies and asthma), atopic dermatitis, inflammatory bowel disease, and periodontal disease (Tesmer et al., 2008). T_H17 cells and cytokines also play a role in immune responses to cancer, infection, and transplantation, though the exact nature of this role is still unclear (Knochelmann et al., 2018; Tahmasebinia and Pourgholamnejad, 2017). There is substantial evidence of the involvement of T_H17 cells in numerous pregnancy morbidities (e.g., preeclampsia, recurrent spontaneous abortion, cholestasis of pregnancy, and others) and in symptoms of mental illness, especially depression. The presence of increased T_H17 cells and their cytokines in the central nervous system leads to inflammation and microglial activation, which can in turn lead to mood and anxiety symptoms in at least two ways – by direct neuronal damage and by induction of indoleamine 2,3, dioxygenase, the enzyme that shunts the metabolism of tryptophan away from serotonin (thus depleting the brain's supply) and toward the neurotoxic kynurenic acid (see Figure 1) (Anderson et al., 2012).

Because antenatal depression and anxiety are frequently co-morbid with other pregnancy morbidities that have now been closely associated with T_H17 cells (Bansil et al., 2010; Osborne and Monk, 2013), we hypothesize that immunological changes in T_H17 cells and cytokines during pregnancy may play a role in perinatal mood and anxiety disorders. The goals of this review are three-fold: 1) to evaluate systematically the role of T_H17 cells and cytokines during pregnancy; 2) to compare changes in the ratio of T_H17:T_{reg} cells during pregnancy morbidities with the changes that occur in depression and anxiety outside of pregnancy; and 3) to provide a basis for further research on T_H17 cells in perinatal mood and anxiety disorders, with an eye toward the development of novel therapeutics. Human literature on all of these topics is as yet limited, and we have elected throughout to make reference to animal literature as well – though animal models are not always reflective of human pathology.

2.1 Healthy Pregnancy

In order to understand the role of enhanced T_H17 activity and dysregulation of the T_H17:T_{reg} balance during perinatal morbidities, it is important first to understand how these cell types behave throughout healthy pregnancy. Early in pregnancy, to help the blastocyst break through and damage uterine tissue in order to implant (and then repair it), a strong pro-inflammatory environment is required. During the second trimester, fetal growth is prioritized and an anti-inflammatory environment may prevail; whereas in late pregnancy, inflammation is again necessary to induce parturition (Mor et al., 2011). Over the course of pregnancy, paternal allo-antigens challenge the immune system and promote dominance of T_{regs} over T_H17 in order to prevent fetal rejection (Figueiredo and Schumacher, 2016; Saito et al., 2011). But it does not, therefore, follow that T_H17 cells are necessarily reduced; some

studies show higher levels of circulating cells in pregnant women than in their non-pregnant counterparts in early pregnancy (Wu et al., 2014), while others show that levels of circulating T_H17 cells do not actually change across the course of pregnancy (Nakashima et al., 2010), despite the fact that the uterine environment as a whole likely changes from pro to anti-inflammatory and back again. At the maternal-fetal interface, animal studies indicate that adequate frequencies of T_{regs} are essential for immunological tolerance at implantation (Saito et al., 2010), but this dominance may be a relative increase only (Mjosberg et al., 2009), as T_H17 cells are higher in the decidua than they are in the periphery (Saito et al., 2010; Wu et al., 2014) and are perhaps necessary for immunological defense against infection at the maternal-fetal interface, with frequencies that may be increased in pregnancy compared to the non-pregnant state. It may be that the type of T_H17 cells at the maternal-fetal interface is different from that found in the periphery, with more gamma-delta T ($\gamma\delta$ T) cells of a type that produces higher amounts of IL-17. These data suggest a pregnancy-specific recruitment or expansion of IL-17-producing cells at the maternal-fetal interface, with even higher levels in allogeneic as opposed to syngeneic pregnancies (Pinget et al., 2016). T_H17 products (e.g., IL-17) in the human placenta (both term and those from spontaneous abortions) play a role in angiogenesis and immune regulation, which is not exhibited in mouse placentae (Pongcharoen et al., 2007). Thus, IL-17 may play a key role in placental development, and current mouse models may not be useful in describing this role.

Whether and how T_H17 cells at the maternal-fetal interface are active in pregnancy (and at what times in pregnancy) depends not only on the presence of these cells and their regulatory counterparts, but also on the actions of hormones and signaling pathways that change across pregnancy. Animal studies illustrate that progesterone (P4) inhibits the expression of IL-17 in a dose-dependent fashion (Maeda et al., 2013). Progesterone also reduces the expression of IL-6 throughout normal pregnancy, with a sharp burst in expression at parturition (Telleria et al., 1998). Reduced IL-6 will in turn reduce the progression of naïve T cells to T_H17 cells, and numerous studies have shown that optimal IL-6 regulation, with levels neither up or down, may be crucial to the avoidance of pregnancy morbidities and to carrying successful pregnancies to term (Markert et al., 2011). Leptin and ghrelin are also important. T cells express receptors for both, with pro-inflammatory leptin increased in early pregnancy and anti-inflammatory ghrelin increased in later pregnancy. The combined effect of the two is to enhance the presence of T_{regs} in early pregnancy and promote the presence of IL-17A in later pregnancy (Orlova and Shirshiev, 2014).

Co-stimulatory pathways that are activated within T_H17 and T_{reg} cells may also play fundamental roles in the outcome of pregnancy. One such pathway is that of PD-1-PDL-1. PDL-1 is an immune regulatory molecule expressed on a variety of immune cells, and especially on macrophages. It is induced by IFN- γ and by T_H1 cells. PDL-1 blockade has been associated with an increase in embryo resorption, a decrease in T_{reg} cells, and an increase in T_H17 cells, with resulting deleterious effects on fetomaternal tolerance; moreover, the increase in T_H17 arises from cells newly differentiated from naïve T cells (rather than those converted from T_{reg}). In one study, neutralizing IL-17 reversed the effect on fetal survival (D'Addio et al., 2011).

While our understanding of the role of T_H17 and T_{reg} in healthy pregnancy is still evolving, the balance between defense and tolerance is crucial to sustaining a healthy pregnancy, and that balance changes across pregnancy, with T_{reg} higher in early pregnancy to promote fetal tolerance and lower in late gestation to promote the initiation of parturition by pro-inflammatory forces (Figueiredo and Schumacher, 2016). When this balance goes awry, pregnancy morbidities ensue – and it will be the argument of this paper that those morbidities likely include perinatal anxiety and depression.

2.2 Pregnancy Morbidities

2.2.1 Recurrent spontaneous abortion (RSA)

Recurrent spontaneous abortion (RSA) is a relatively common, multifactorial problem affecting 1–2% of reproductive women; in women with untreated antenatal depression, that rate is increased, leading to speculation about common etiologies (Field et al., 2006). Over half of women with RSA have an autoimmune condition, with antiphospholipid syndrome being the most common. Studies into other causes have focused on NK cells and T_H1 cells, and, more recently, on T_H17 and T_{reg} cells. Findings have included higher proportions of T_H17 cells and the cytokines they produce, including IL-17 and IL-23, in both peripheral blood and decidual tissue; gene polymorphisms; and increases in T_H17 and decreases in T_{reg} (either peripheral or decidual) during early pregnancy in subjects with RSA compared to normal pregnancy. In addition, fetal loss has been induced by exogenously administered IL-17 in healthy mouse models, and improved pregnancy outcomes have been achieved in RSA subjects treated with intravenous immunoglobulin to address a $T_H17:T_{reg}$ imbalance. These findings and others have been thoroughly reviewed elsewhere (Fu et al., 2014; Lee et al., 2012; Liu et al., 2017). Together, these findings make a strong argument for a role for enhanced T_H17 activity in early pregnancy in women with RSA, and the literature supporting a decrease in fetal loss when IL-17 is blocked makes a strong case for this dysregulation as at least in part a causative mechanism. This is plausible, as T_{reg} cells are known to regulate the maternal response to the fetus in normal pregnancy, and a dearth of them could therefore lead to an overactive immune response (from T_H17 cells as well as other immune actors) that would result in pregnancy loss. Other literature points to upregulated activity of the HMGB1 gene in women with recurrent pregnancy loss (though the timing during pregnancy is unspecified), further indirect evidence of enhanced T_H17 activity as this alarmin increases T_H17 activity (Jin et al., 2015).

2.2.2 Preeclampsia.

Preeclampsia, a condition characterized by high blood pressure and proteinuria, usually after the 20th week of pregnancy, affects up to 7% of pregnancies worldwide and is a substantial cause of morbidity; some (but not all) literature shows an elevated risk in women with antenatal depression (Osborne and Monk, 2013), which may indicate shared pathophysiology. The exact cause is unknown, though research has implicated pre-existing maternal pathology (e.g., hypertension) and abnormal placentation, along with immunologic factors (Jido and Yakasai, 2013). Possible mechanisms include rejection of the fetus by an overactive immune response causing inflammation that affects placentation, angiogenesis, and endothelial dysfunction; the fact that women who have not been exposed to paternal

immune priming (i.e., donor embryos) and those with a weaker exposure (e.g., first-time mothers, those with new partners, those with a longer break between children) have higher rates of preeclampsia lends credence to this theory. Numerous studies have found increased T_H17 cells or an increase in the T_H17/T_{reg} ratio in preeclamptic women compared to normotensive and/or non-pregnant subjects, when measured either in peripheral blood, decidual tissue, or umbilical cord blood, while others have found correlations between IL-17 and increased blood pressure or intrauterine growth restriction; a substantial literature also supports a role for elevated IL-6 (a key player in the differentiation of T_H17 cells) in preeclampsia. These and other findings have been extensively reviewed elsewhere (Cornelius and Lamarca, 2014; Fu et al., 2014; Lau et al., 2013; Saito, 2010). Other studies have found elevated levels of HMGB1, a marker for increased T_H17 activity, at times in conjunction with increased levels of IL-17; most of these studies examined either late pregnancy or the postpartum period, but some also confirmed results in those with early onset (first trimester) preeclampsia (Brien et al., 2018; Chen et al., 2016; Li et al., 2018; Shao et al., 2016; Xu et al., 2018; Zhu et al., 2015).

2.2.3 Other pregnancy morbidities.

Although the amount of research on RSA and preeclampsia far outweighs that available for other pregnancy morbidities, there is some limited evidence for involvement of a T_H17 bias in preterm birth, chorioamnionitis, cholestasis of pregnancy, and gestational diabetes, and these findings have not been reviewed elsewhere. For preterm birth a considerable amount of research links increased local IL-6 in the cervix (Wei et al., 2010), but evidence of T_H17 involvement on a systemic basis is limited and conflicting. T_H17 cells have been found to be decreased, and T_{regs} increased, in the mouse spleen just prior to preterm birth (Arenas-Hernandez et al., 2016), and IL-17 has been found to be lower in serum just before delivery (Hee et al., 2011) and higher in amniotic fluid at delivery (Ito et al., 2010) when subjects with preterm birth (at gestational week 24 and above) were compared to those with normal term pregnancies. HMGB1 has also been found to be elevated at birth in cases of preterm birth (Buhimschi et al., 2009; Romero et al., 2011). For chorioamnionitis, levels of both IL-17 (Ito et al., 2010) and IL-6 (Yoon et al., 1995) have been found to be elevated at birth in amniotic fluid, and several studies point to a role for elevated HMGB1 (Qiu et al., 2017; Romero et al., 2012). In intrahepatic cholestasis of pregnancy (ICP), a common condition in which the normal flow of bile is affected by pregnancy hormones, resulting in a buildup of bile salts, intense itching for the mother, and higher rates of fetal distress, preterm birth, and stillbirth, IL-17 has been shown to be elevated in the third trimester in both serum and placenta of women with ICP compared to normal pregnant controls (Kirbas et al., 2016; Kong et al., 2017). In gestational diabetes, there has been little research to date on T_H17 cells or the cytokines they produce directly, but some evidence concerning IL-6 – that higher serum IL-6 in early pregnancy predicted the later development of gestational diabetes in a group of women at high risk (Abell et al., 2017), and that women with early onset gestational diabetes had higher serum levels of IL-6, and those with late-onset gestational diabetes higher levels of sIL-6R, when compared with normal pregnant women (Kuzmicki et al., 2014). One study found that serum HMGB1 was related to hyperglycemia and also independently to diagnoses of gestational diabetes in the third trimester (Giacobbe et al., 2016). Taken together, the literature on these other pregnancy morbidities is too limited to

make any kind of judgment about the role of T_H17 cells, even in areas such as gestational diabetes, preterm birth, and chorioamnionitis that are known to have an inflammatory component and have also been associated with antenatal depression (Osborne and Monk, 2013) – but there are enough positive signals (some increases in IL-17, some in IL-6 or HMGB1) to make further study in each of these warranted.

2.3. Asthma and Autoimmune Disease in Pregnancy.

Both asthma and autoimmune disease have increased prevalence in individuals with depression and anxiety (Andersson et al., 2015; Gao et al., 2015), though they have been explored little in antenatal depression and anxiety (and one recent review found that asthma was not associated with perinatal mental illness (Brown et al., 2018). The behavior of these diseases in pregnancy, however, indicates that this is an area ripe for future research. Certain autoimmune diseases (e.g., rheumatoid arthritis [RA] and multiple sclerosis [MS]) go into relative remission in pregnancy but flare in the postpartum, while others (e.g., systemic lupus erythematosus [SLE]) can flare during pregnancy; asthma and atopic diseases are variable (Fischer-Betz and Specker, 2017; Grosso et al., 2018; Voskuhl and Momtazee, 2017). A limited literature points to the role of T_H17 in these patterns of inflammatory disease remissions and flares during pregnancy. Subjects with multiple sclerosis have been found to have no difference from healthy controls in the proportion of T_H17 or in the pattern of change in T_{reg} cells across pregnancy and postpartum (Neuteboom et al., 2010). Those with inflammatory bowel disease have a marked reduction in IL-17A from pre-conception to the second trimester (Seow et al., 2015). Subjects with SLE, on the other hand, have been found to have increased secretion of IL-17, IL-6 and TNF- α at various pregnancy timepoints (as well as outside of pregnancy) when compared to healthy controls (Su et al., 2001; Torricelli et al., 2011). Women with autoimmune antithyroid antibodies have been shown to have increased IL-17 (Turhan Iyidir et al., 2015) and IL-6 (Oztas et al., 2015) in early pregnancy when compared to healthy controls. Finally, several groups have looked at asthma in pregnancy, with one finding that pregnant asthmatics (>18 weeks gestation) have an enhanced IL-17 response compared to healthy pregnant controls (Vanders et al., 2013) and another finding that all asthmatic women (pregnant and not) had elevated prevalence of T_H17 cells and pregnant asthmatic (weeks 20–35) women had blunting of T_{regs} when compared to healthy nonpregnant women; this resulted in an increased T_H17/T_{reg} ratio for asthmatic pregnant women when compared to healthy pregnant women (Toldi et al., 2011). Taken together, these data on autoimmune disease may indicate that T_H17 activity is increased (and/or T_{reg} activity decreased) when autoimmune or atopic disease flares in pregnancy, opening up a theoretically plausible reason for the comorbidity of these diseases with antenatal depression and anxiety. While there is currently no literature on HMGB1 and asthma/autoimmune disease in pregnancy, there are consistent findings of elevations of HMGB1 in these conditions outside of pregnancy (as reviewed in (Imbalzano et al., 2017; Zhu et al., 2018)), suggesting an area ripe for new research.

An increase in T_H17 cells and cytokines and/or an imbalance in the T_H17/T_{reg} ratio is thus an integral characteristic of numerous pregnancy morbidities, with the greatest amount of evidence concerning recurrent spontaneous abortion and preeclampsia. Given the comorbidity of these conditions with antenatal depression and anxiety, it is a logical next

step to examine how these cells behave in pregnant women with depression and anxiety, who are now thought by some to represent an inflammatory subtype of depression (Osborne and Monk, 2013). Because the evidence in the perinatal literature is sparse, we must begin by looking at psychiatric illness beyond pregnancy and extrapolating from these examples.

2.4 Depression and Anxiety Outside of Pregnancy

2.4.1 Depression.

The animal and human literature linking depression to elevation of pro-inflammatory markers is substantial (Miller and Raison, 2016). Inflammation has been noted to increase depressive symptoms, both when inflammatory agents are given directly (e.g., in the treatment of Hepatitis C virus infection with interferons (Machado et al., 2017)) and when inflammation is noted in people who are depressed. Numerous studies exist of elevated proinflammatory cytokines in depression, and the cytokines most frequently implicated include IL-6, IL-1 β , and TNF- α (Dowlati et al., 2010). The fact that each of these cytokines is involved in the differentiation of T_H17 cells has led researchers to investigate the involvement of T_H17 in depression. There are several reviews of the role of T_H17 and/or their cytokines in depression (Beurel and Lowell, 2017; Slyepchenko et al., 2016; Waisman et al., 2015), the most comprehensive of which posit theoretical mechanisms for the involvement of T_H17 cells in depression. Although it is not yet known how closely measures of T_H17 function in the periphery are mirrored in the central nervous system (CNS), it is clear that peripheral immune cells can access the CNS through lymphatic vessels, leaky areas of the blood-brain barrier, and possibly the choroid plexus; they are also extremely plastic and can differentiate from other T cell populations once in place (Baruch et al., 2016). T_H17 cells and/or IL-17A are present in the CNS in other related disorders, including multiple sclerosis, autism spectrum disorders, epilepsy, and dementia (Tahmasebinia and Pourgholaminejad, 2017). Once present in the brain, there are numerous mechanisms by which T_H17 cells and IL-17A may instigate depression, including activating astrocytes and microglia and stimulating the production of other pro-inflammatory cytokines (Beurel and Lowell, 2017). Those pro-inflammatory cytokines may in turn affect serotonin production by enhancing the actions of indoleamine 2,3 dioxygenase (IDO), the enzyme that preferentially shunts the metabolism of tryptophan away from serotonin and down the kynurenine pathway (Roomruangwong et al., 2018).

Transfer of T_H17 cells to male mice results in characteristic of depression, including learned helplessness. Those mice that were deficient in ROR γ T (i.e., the transcription factor that regulates T_H17 cell differentiation), as well as wild-type mice given an inhibitor of ROR γ T along with the T_H17 cells, had reduced levels of learned helplessness when compared with mice that were administered undifferentiated CD4⁺ T cells or vehicle (Beurel et al., 2013). In a mouse model of psoriatic inflammation, increased levels of IL-17A correlated with increased depressive-like symptoms, which were reduced when an IL-17A inhibitor was administered; administering IL-17A alone to wild-type mice led to the same depressive-like symptoms (Nadeem et al., 2017). (In contrast, examinations of the spleen have turned up contradictory findings, including decreased T_H17 splenic lymphocytes and *increased* splenic T_{reg} cells (and TGF- β) in a mouse model of chronic unpredictable mild stress-induced

depression (Hong et al., 2013), possibly indicating that results in the periphery ought not to be compared to those in lymphoid tissue). In human literature, subjects with major depressive disorder have been found to have a significant increase in circulating T_H17 cells and a significant decrease in T_{reg} cells (and thus an increased ratio) when measured by flow cytometry; increased levels of ROR γ T; and higher levels of circulating IL-17 when compared to healthy controls (Chen et al., 2011); and increases in both IL-17 and the stimulating cytokine TGF- β compared to age-matched controls (Davami et al., 2016). Mouse models have indicated that elevated HMGB1 is associated with increased depressive-like symptoms as well (Franklin et al., 2018; Wang et al., 2018; Wu et al., 2015).

Not all studies have found a positive association between T_H17 and depression, however. One study found a decrease in the number of T_H17 cells in depressed subjects compared to age and gender-matched healthy controls, but also found a decrease in the number of T_{reg} cells from depressed subjects when the sample was restricted to those over 28 years of age (Grosse et al., 2016). Others have found no differences in plasma levels of IL-17A between a group with late-life depression and a group of healthy matched controls (Saraykar et al., 2017), or a decreased level of IL-17A in patients with recurrent depressive disorder (Rybka, 2013). This seemingly contradictory literature, in both animals and humans, may perhaps be explained by differences between acute depressive symptoms and those of chronic depression, which some have posited represent two different states of immune regulation, with activation at the time of acute symptoms and suppression in the face of chronic symptoms (Hong et al., 2013).

There also are many examples of studies highlighting the role of IL-6 in depression and depressive symptoms, in both human and animal literature. The vast majority of these studies, as reviewed in (Hodes et al., 2016), find a positive correlation between elevated IL-6 and symptoms of depression, or between lack of IL-6 and resistance to depressive-like symptoms. Elevated IL-6 in depression may also be directly related to level of traumatic experiences (Bob et al., 2010). Gimeno and colleagues measured IL-6 and cognitive symptoms of depression in a group of British civil servants at baseline and approximately 12 years later, and found that inflammatory markers at baseline predicted depressive symptoms at follow-up, but not vice versa (Gimeno et al., 2009). A few other studies find no relationship or opposite findings (i.e., decreased IL-6 in depressed populations (Carpenter et al., 2004; Podlipný et al., 2010). The Kern group found that decreased IL-6 predicted future depression, but that increased IL-6 was associated with concurrent depression in a population of older women (Kern et al., 2013, 2014).

Finally, the normalization of IL-6 in depressed subjects after treatment, as well as resistance to the antidepressant effects of medication in the presence of centrally administered IL-6, lends further support to the notion that IL-6 and the cells and cytokines induced by it may play a role in symptoms of depression (Sukoff Rizzo et al., 2012b). Mechanisms used to reduce both IL-6 and depressive symptoms include exercise (Lavebratt et al., 2017), antidepressants (Hiles et al., 2012), anti-inflammatory agents (Abbasi et al., 2012), and electroconvulsive therapy (ECT) (Järventausta et al., 2017). In addition, IL-6 has been found to be a marker of antidepressant response to ketamine, raising the possibility that at least one

mechanism to explain ketamine's efficacy may lie in its ability to reduce inflammation (Yang et al., 2015).

If IL-6 and consequent dysregulation of the T_H17/T_{reg} ratio plays a role in antenatal depression, then any evidence on sex differences in IL-6 in depression would be informative. Transgenic mice with an overproduction of IL-6 in the CNS exhibited an increase in depression-like behaviors (Sukoff Rizzo et al., 2012a); the increase was stronger in male mice, whereas female mice had a stronger increase in anxiety-like behaviors. Tsuboi and colleagues found a positive correlation between IL-6 and depressive symptoms in women alone (Tsuboi et al., 2014). And Jha and colleagues recently found that increased IL-17 correlated with increased anhedonia in men only, with no relationship found for women (Jha et al., 2018)

In summary, there is a small number of studies directly examining the relationship between depression and T_H17 cells and the cytokines they produce. While this literature is yet sparse, most studies do show an increase in T_H17 and/or the T_H17/T_{reg} ratio in depression – though the one study that accounted for sex differences found that effect to be driven by men only. The literature linking IL-6 to depression, on the other hand, is vast, and almost uniformly shows a positive correlation between levels of IL-6 and depression outside the perinatal period, as well as a normalization with antidepressant treatment; studies that account for sex differences are too few to draw any conclusions.

2.4.2 Anxiety.

There is a vast literature concerning the role of the hypothalamic pituitary adrenal (HPA) axis and the stress response system in anxiety, but surprisingly few attempts to investigate immune functioning in anxious individuals. In the perinatal period, it is vital that we begin to expand our investigations of the biological causes of anxiety, as anxious symptoms may be at least as common as depressive symptoms in the perinatal period, and anxiety disorders are frequently comorbid with depression (Goodman et al., 2014). The literature linking anxiety outside of pregnancy to a T_H17 cell imbalance so far is limited. When compared to cells of healthy controls, *in vitro* cell culture from individuals with generalized anxiety disorder shows an increased proportion of T_H17 cells (Vieira et al., 2010), and a dominant T_H17 phenotype in cells from individuals with GAD but not controls was enhanced by the administration of dopamine (Ferreira et al., 2011) and of Substance P (Barros et al., 2011). Several groups have reported on the role of IL-6, with one group finding that greater anxious attachment was significantly associated with higher levels of IL-6 following coronary artery bypass surgery (Kidd et al., 2014) and another group finding that IL-6 expression increased with increasing anxiety scores on the Hospital Anxiety and Depression Scale, and that IL-6 expression in anxious individuals was also strongly correlated with DNA methylation of important epigenetic regulatory enzymes *DNMT1* and *EZH2* (Murphy et al., 2015). O'Donovan and colleagues, in the only study to address sex differences, found that IL-6 was elevated in individuals with clinically significant anxiety regardless of sex, age, or depressive symptoms (O'Donovan et al., 2010). Studies in anxiety thus are extremely limited, but those that exist support a possible role in anxiety for T_H17 cells and IL-6.

2.5 Perinatal Depression and Anxiety

The literature cited above may convince the reader of the theoretical plausibility of the involvement of T_H17 in perinatal depression and anxiety, but is there any direct evidence? Yes, but it is limited, confined mostly to evidence about IL-6 rather than about T_H17 directly, and conflicting. The only study to look directly at a marker of T_H17 activity (IL-17C), in the context of a study on 92 inflammatory markers at gestational weeks 35–39 in women with antenatal depressive symptoms (as defined by EPDS ≥ 13), women on SSRIs, and healthy controls, found that IL-17C was significantly *lower* in the women with antenatal depressive symptoms and the women on SSRIs when compared to the healthy controls, and found no relationship between IL-6 and depressive symptoms. This finding stands in contrast to the literature (undifferentiated by sex) for depression outside of pregnancy, and may indicate that this relationship differs by sex as well as by stage of pregnancy (Edvinsson et al., 2017). All other studies have considered IL-6 only. Walsh and colleagues found that interaction with early life adversity explained lower IL-6 levels in depressed pregnant adolescents at the second trimester (Walsh et al., 2016). One group found that elevated IL-6 at delivery predicted the later development of PPD (Liu et al., 2016), while another group found that it did not (Skalkidou et al., 2009). Increases in IL-6 at single-time measurements in pregnant (various time points) or early postpartum women with self-reported depressive symptoms compared to healthy controls (Azar and Mercer, 2013; Boufidou et al., 2009; Cassidy-Bushrow et al., 2012; Christian et al., 2009; Haeri et al., 2013; Maes et al., 2000) are also consistently reported. Osborne and colleagues recently examined IL-6 (and other pro-inflammatory cytokines) across pregnancy and up to 6 months postpartum, comparing women with higher depressive symptoms (as measured by the Beck Depression Inventory) to those with lower symptoms, and found significant differences in the slope of change across time as well as significant increases in IL-6 levels at the third trimester for more depressed women (Osborne et al., 2018a). Another recent study examined women with major depressive disorder (defined by DSM criteria) in the third trimester of pregnancy, and found elevated levels of IL-6 for the depressed women compared to healthy controls (Osborne et al., 2018b), while another found that IL-6 did not correlate with concurrent depressive symptoms in the third trimester of pregnancy but was a significant predictor of postpartum scores on the Edinburgh Postnatal Depression Scale (EPDS) (Simpson et al., 2016). Corwin and colleagues found no relationship between IL-6 and depressive symptoms when measured in the third trimester or early postpartum, but found that cortisol AUC increased with increasing levels of IL-6 for women with depressive symptoms but not for those without at 14 days postpartum (Corwin et al., 2015). Other studies have found no relationship at gestational week 24 (Karlsson et al., 2017) or at week 18 or 32 (Blackmore et al., 2011). The majority of the literature thus finds a correlation between increased depressive symptoms and increased IL-6, but not all studies support this.

Very few studies have tackled anxiety in the peripartum, with none looking directly at IL-17 or other markers of T_H17 activity. Maes and colleagues found that higher IL-6 was correlated with higher STAI scores at 1 day postpartum (Maes et al., 2000). In a published poster abstract only, Fishe and colleagues found higher IL-6 levels in those with pregnancy-specific anxiety in the second trimester (Fishe et al., 2013). Osborne and colleagues found

elevated levels of IL-6 among subjects with higher anxiety during late pregnancy and early postpartum (Osborne et al., 2018a). A study of infertile couples trying to conceive found that anxiety was correlated with stress, and stress with increased cervicovaginal IL-6 and decreased serum TGF- β 1, and with a higher likelihood of IVF failure (Haimovici et al., 2018). As with depression, the results are not uniform, however. No relationship was found between IL-6 and either general or pregnancy-specific anxiety at gestational week 24 (though relationships were found with other cytokines not related to T_H17) (Karlsson et al., 2017). IL-6 did not differ between African American women with high vs. low anxiety when measured on average at gestational week 20 (Catov et al., 2015), nor was it related to anxiety in a study of diverse women at high psychosocial risk when measured at gestational weeks 18 and 32 (Blackmore et al., 2011). These mixed findings, and the lack of any studies directly measuring IL-17 or other direct markers, make it impossible to draw any consistent conclusions about T_H17 cells and anxious pregnancy.

3.1 Discussion.

There is substantial evidence of a role for T_H17 dysregulation in numerous pregnancy morbidities, as well as more limited but growing evidence of a role for T_H17 dysregulation in depression and anxiety outside of pregnancy and inconsistent evidence of IL-6 dysregulation (which may in turn lead to T_H17 dysregulation) for depression and anxiety in pregnancy. The T_H17 cells and cytokines produced in both the decidua and periphery in pregnancy morbidities, such as preeclampsia and recurrent spontaneous abortion, can easily cross into the CNS, promote disruption of the blood brain barrier (Kebir et al., 2007), and are found in higher numbers in the cerebrospinal fluid of individuals with other neuroinflammatory conditions such as multiple sclerosis (Matusevicius et al., 1999). While some of these data come from animal literature – which makes them inherently limited in informing our understanding of human physiology – there is a growing amount of data from human studies as well.

Could T_H17 dysregulation be the missing link that connects pregnancy morbidities to antenatal depression and anxiety? Substantial (though not uniformly positive) literature links preeclampsia, preterm birth, and gestational diabetes to antenatal depression (as reviewed in (Osborne and Monk, 2013)), as well as to immune dysregulation – but the evidence is scattered and inconclusive on how or whether immune dysregulation is directly related to antenatal depression and anxiety. Perhaps this is because we are not asking the right questions. Most studies thus far are cross-sectional and are limited to examinations of a single or a few cytokines in the peripheral blood. If any consideration is given to T cell dysregulation, it is on the lines of the old T_H1/T_H2 paradigm. If the immune dysregulation that characterizes antenatal depression and anxiety is associated with shifts in immune cell populations, we are not using the right tools or the right lens to examine this question. Future studies should examine broader groups of cytokines, across time; immune cell phenotypes, both peripherally and centrally; and what happens to those immune cells when stimulated by a stressor. Moreover, studies must distinguish between the role of immune cells measured directly and that of cytokines, many of which are notoriously pleiotropic and may indicate the presence of more than one type of immune response. (IL-17, for example, the quintessential T_H17 cytokine, is also associated with innate lymphoid cells – so studies

that look only at IL-17 and not directly at cells may in fact be measuring innate lymphoid rather than T-cell pathology.) Only when we use the appropriate tools will we be able to answer our questions about what role the immune system may play in the mood and anxiety symptoms that plague up to 39% of pregnant women (as reviewed in (Goodman et al., 2014)) and affect their health and that of the generations to come. Symptoms of depression and anxiety have been linked to adverse pregnancy outcomes (such as preterm birth and growth restriction) as well as adverse outcomes in children, including increased rates of internalizing disorders, attention disorders, and conduct disorders (Capron et al., 2015; Field, 2011; O'Donnell et al., 2017).

Developing this knowledge will not only help us to understand mechanism; it may also help us to develop novel therapeutics. The target in nearly all antidepressant drugs remains serotonin – but the success of some anti-inflammatory treatments as adjunctive antidepressants (Faridhosseini et al., 2014); the recent though short-lived successes of ketamine (IL-6 has been found to be elevated in ketamine responders) (Yang et al., 2015); and the FDA breakthrough status given to a synthetic version of allopregnanolone (a progesterone metabolite, which may also act through inhibiting pro-inflammatory cytokines including IL-17 and IL-6) (Kanes et al., 2017), the first drug to be proposed to the FDA for postpartum depression specifically, indicate that drugs that affect immune dysregulation may be an exciting new target for antidepressant (and anti-anxiety) action in the perinatal period.

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Highlights

- Immune dysregulation in pregnancy is known to be related to pregnancy morbidities, and recent literature supports a role for shifts among T cell classes
- There is also evidence for the role of T_H17 cells and dysregulation of the T_H17:T_{reg} cell balance in depression and anxiety outside of pregnancy
- This paper combines the evidence about pregnancy morbidities and that concerning depression and anxiety to hypothesize about the role of T_H17:T_{reg} imbalance in antenatal depression and anxiety
- Understanding the relationship between immune dysregulation and perinatal mood and anxiety disorders can help develop novel targets for treatment

Fig. 1.

Illustration of our hypothesized model, showing that environmental or genetic triggers may act directly to affect TH17/Treg balance in the brain, the periphery, and the placenta. In the placenta, this imbalance is connected to pregnancy morbidities (such as preeclampsia) and to endocrine dysregulation; in the periphery, to autoimmune disease; and in the brain (crossing in from the periphery across the blood-brain barrier), to depression and anxiety.