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# Maternal stress, nutrition and physical activity: Impact on immune function, CNS development and psychopathology

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ABSTRACT

Evidence suggests that maternal and fetal immune dysfunction may impact fetal brain development and could play a role in neurodevelopmental disorders, although the definitive pathophysiological mechanisms are still not completely understood. Stress, malnutrition and physical inactivity are three maternal behavioral lifestyle factors that can influence immune and central nervous system (CNS) functions in both the mother and fetus, and may therefore, increase risk for neurodevelopmental/psychiatric disorders. First, we will briefly review some aspects of maternal-fetal immune system interactions and development of immune tolerance. Second, we will discuss the bidirectional communication between the immune system and CNS and the pathways by which immune dysfunction could contribute to neurodevelopmental disorders. Third, we will discuss the effects of prenatal stress and malnutrition (over and undernutrition) on perinatal programming of the CNS and immune system, and how this might influence neurodevelopment. Finally, we will discuss the beneficial impact of physical fitness during pregnancy on the maternal-fetal unit and infant and how regular physical activity and exercise can be an effective buffer against stress- and inflammatory-related disorders. Although regular physical activity has been shown to promote neuroplasticity and an anti-inflammatory state in the adult, there is a paucity of studies evaluating its impact on CNS and immune function during pregnancy. Implementing stress reduction, proper nutrition and ample physical activity during pregnancy and the childbearing period may be an efficient strategy to counteract the impact of maternal stress and malnutrition/obesity on the developing fetus. Such behavioral interventions could have an impact on early development of the CNS and immune system and contribute to the prevention of neurodevelopmental and

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psychiatric disorders. Further research is needed to elucidate this relationship and the underlying mechanisms of protection.

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## 1. Introduction

The maternal and fetal immune systems communicate in a bi-directional manner and their interconnection is critical for maintaining a healthy pregnancy, maternal immunocompetence and proper development of the fetal immune system (Szekeres-Bartho, 2002; Mold and McCune, 2012; Erlebacher, 2013). The maternal immune system develops an active immunologic tolerance against fetal–placenta antigens (recognition and activation). Following recognition of these antigens, the maternal immune system reacts with a wide range of protective immunoregulatory mechanisms (Saito et al., 2010; Jiang et al., 2014; Szekeres-Bartho, 2002; Mold and McCune, 2012; Erlebacher, 2013; Schumacher and Zenclussen, 2014). Well-controlled maternal immune responses play a positive physiological role in fetal immune and central nervous system (CNS) development. The immune system and CNS also communicate with each other in a bidirectional manner, through both neural and hormonal pathways (Marques-Deak et al., 2005; Sternberg, 2006; Silverman and Sternberg, 2008; Dantzer, 2009; Marques et al., 2009; Thayer, 2009; Dantzer et al., 2011; Raison and Miller, 2011). During the prenatal period, the blood–brain barrier (BBB) is not fully developed and larger molecules (e.g., antibodies, cytokines) may have greater access to the brain (Diamond et al., 2009). Accordingly, the presence of maternal pathogenic autoantibodies, maternal immune activation (MIA), increased levels of proinflammatory cytokines, and reduced $CD4^+$ T cells (number/function) (Filiano et al., 2014) are potential pathways by which early immune dysfunction could impact brain development and contribute to an increased risk of neurodevelopmental disorders in the offspring, as well as psychiatric disorders, autoimmune diseases and allergies later in life (Brown et al., 2004; Bresnahan et al., 2005; Ellman and Susser, 2009; Bilbo et al., 2012) (Deverman and Patterson, 2009; Dhabhar, 2009; Lee et al., 2009; Derecki et al., 2010; Yirmiya and Goshen, 2011; Baruch and Schwartz, 2013; Meyer, 2013; Rattazzi et al., 2013). In addition, the microbiota-gut-brain axis has been shown to play a role in normal brain and immune function and development, whereby one mechanism of the microbiota-gut-brain crosstalk may be mediated by immune regulation (Rook et al., 2014).

The timing of immune dysregulation is important, as distinct immune and neurodevelopmental programs are affected differently depending on the fetal stage of its occurrence. This creates a sensitive window of vulnerability (Dietert and Dietert, 2008). The fetal CNS and immune systems are particularly vulnerable to disruptions caused by environmental factors that might impact maternal physiological systems, such as malnutrition, toxins and stress. We will discuss the effects of prenatal stress and malnutrition (over and undernutrition) on perinatal programming of the neuroendocrine stress response (hypothalamic–pituitary–adrenal [HPA] axis), stress-sensitive brain regions and the immune system and how this might influence neurodevelopment (Jansson and Powell, 2007; Lupien et al., 2009; Palmer, 2011; PrabhuDas et al., 2011; Breton, 2013; O'Connor et al., 2013; Reynold, 2013; Lin and Wang, 2014; Rook et al., 2014). We will also discuss the main maternal health benefits of regular physical activity during pregnancy (Pivarnik et al., 1993; Genest et al., 2012; Prather et al., 2012; Robledo-Colonia et al., 2012; Ruchat et al., 2012), as well as its impact on the fetus and infant (e.g., reduced fat mass and short-term neurodevelopment benefits) (Brenner et al., 1993; Clapp, 1996; Clapp et al., 1998; Clapp et al., 2000; San Juan Dertkigil et al., 2007; May et al., 2012; Prather et al., 2012). Although regular physical activity/exercise has been shown to promote neuroplasticity (Dishman et al., 2006; Cotman et al., 2007; Knaepen et al., 2010; Hayes et al., 2013) and an anti-inflammatory state (Gleeson et al., 2011; Hamer et al., 2012; Hayes, Hayes et al. 2013) in the adult, there is a paucity of studies evaluating its impact on the CNS and immune system during pregnancy. Overall, encouraging and implementing stress reduction, proper nutrition, and ample physical activity during pregnancy and the childbearing period may be an efficient strategy to counteract the impact of maternal stress and malnutrition/obesity on the developing fetus. Such behavioral interventions could have an impact on early development of the immune system and CNS and contribute to the prevention of neurodevelopmental and psychiatric disorders.

## 2. Maternal–fetal immune system interactions: Immune tolerance

Maternal–fetal immune system interactions are characterized by bi-directional communications that rely upon the maternal immune system's recognition of antigens (derived from fetal, placental and paternal genomes) at the maternal-fetal interface, as well as a bi-directional transplacental trafficking of fetal and maternal cells throughout pregnancy (Taglauer Waldorf et al., 2010; Mold and McCune, 2012). Fetal antigens are recognized by maternal immune cells leading to an active suppression of alloreactive maternal immune responses and induction of fetal tolerance. Maternal immune tolerance against fetal–placental antigens depends on cell–cell interactions that take place between maternal immune cells in the decidua (natural killer cells and macrophages) and trophoblast antigens, as well as on immunoregulatory mechanisms (e.g., cytokines) that are critical for the maintenance of a healthy pregnancy, development of the fetal immune system and maternal immunocompetence (Mold and McCune, 2012).