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Review article

Transfer of maternal psychosocial stress to the fetus

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ABSTRACT

Psychosocial maternal stress experienced during different vulnerable periods throughout gestation is thought to increase the individual's risk to develop neuropsychiatric, cardiovascular and metabolic disease in later life. Cortisol has generally been identified as the major mediator of maternal stress transfer to the fetus. Its lipophilic nature allows a trans-placental passage and thus excessive maternal cortisol could persistently impair the development of the fetal hypothalamic-pituitary-adrenal axis (HPAA). However, cortisol alone cannot fully explain all effects of maternal stress especially during early to mid pregnancy before maturation of the fetal HPAA has even begun and expression of fetal glucocorticoid receptors is limited. This review focuses on mediators of maternal fetal stress transfer that in addition to cortisol have been proposed as transmitters of maternal stress: catecholamines, cytokines, serotonin/tryptophan, reactive-oxygen-species and the maternal microbiota. We propose that the effects of psychosocial maternal stress on fetal development and health and disease in later life are not a consequence of a single pathway but are mediated by multiple stress-transfer mechanisms acting together in a synergistic manner.

1. Introduction

Pregnancy is a significant time in a woman's life during which environmental influences such as maternal psychological stress not only affect the expectant mother's health but also have lifelong consequences for her developing unborn – a concept that has been termed 'fetal programming'. It is now widely recognized that antenatal exposure to maternal psychological stress is associated with an adverse pregnancy outcome and increases the individual's risk to develop neuropsychiatric, cardiovascular and metabolic disease in later life (Charil et al., 2010; Cottrell and Seckl, 2009; Glover et al., 2010; Harris and Seckl, 2011; Moisiadis and Matthews, 2014a; Weinstock, 2008). The impact of prenatal stress on the physiological and psychological outcome differs not only depending on the type and intensity of the stressor or sex of the developing offspring but also on the time of the distinct stress experience. Numerous studies of different species including humans and non-human primates have shown that the fetus is sensitive to maternal stress during different vulnerable periods of various lengths from early to late gestation (Davis and Sandman, 2010). For example, high maternal anxiety during early human pregnancy is associated with behavioural problems in 8- and 9-year-olds, whereas maternal anxiety during late pregnancy is not (Van den Bergh and Marcoen, 2004). Great effort has been directed towards elucidating the underlying mechanisms and understanding how maternal stress transfers to the unborn. In other words, to try and answer the question: How does the fetus sense that the mother is stressed? As a result, stress-induced release of maternal cortisol has been identified as the significant mediator of antenatal psychological stress. Excessive maternal cortisol (or corticosterone in rodents) can cross the placenta into the fetal compartment and induce long-lasting if not permanent changes in the postnatal activity of the fetal hypothalamic-pituitary-adrenal axis (HPAA), which is associated with behavioural and cognitive alterations in later life (Glover et al., 2010; Kapoor et al., 2008). However, cortisol alone cannot fully explain all the programming effects of psychosocial stress, especially during early gestation as amongst other reasons the maturation and vulnerable period of the fetal HPAA do not begin earlier than late pregnancy (Challis et al., 2001; Moisiadis and Matthews, 2014b) and glucocorticoid receptor (GR) expression is limited during early gestation (Meaney et al., 1985; Owen and Matthews, 2003; Slotkin et al., 2008).

In this review, in addition to cortisol, we discuss five other potential mediators of maternal-fetal stress: catecholamines, reactive oxygen species (ROS), cytokines, serotonin/tryptophan and maternal microbiota. We suggest that maternal-fetal stress transfer is a combination of numerous different transfer mechanisms that act together in a synergistic way (Fig. 1).

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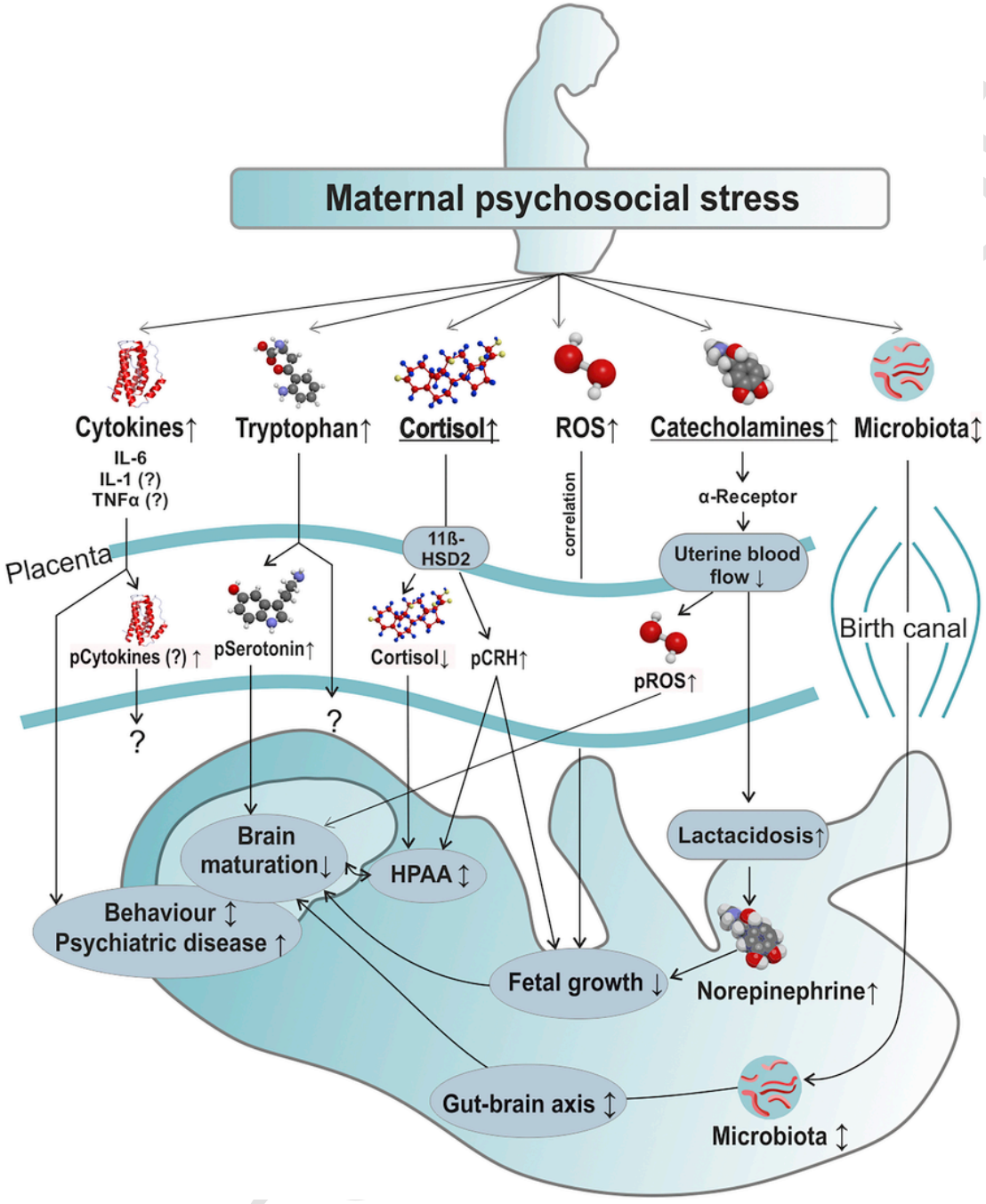

Fig. 1. Mechanisms of maternal-fetal stress transfer. Conceptual framework of mechanisms of maternal-fetal stress transfer. Current evidence is strongest for a direct effect of maternal cortisol on fetal hypothalamic-pituitary-adrenal axis (HPAA) development and, to a lesser extent, for catecholamines that exert their impact on fetal development indirectly via an impaired uterine blood flow (underlined mechanisms). Evidence for other recently proposed stress transfer mechanisms − cytokines, tryptophan/serotonin, reactive oxygen species (ROS) and the maternal microbiota - has not been fully investigated. 'p…': placental

2. Maternal cortisol and the programming of the fetal HPAA

Fetal exposure to excess concentrations of endogenous or exogenous glucocorticoids is associated with a broad spectrum of neuropsychiatric, metabolic and cardiovascular disease in later life in animal models and is inconsistent in human cohorts (Moisiadis and Matthews, 2014a,b; Van den Bergh et al., 2005). The role of the glucocorticoid ortisol (or corticosterone in rodents) as a mediator of prenatal stress has been investigated extensively over recent decades and previously reviewed in detail (Cottrell and Seckl, 2009; Glover et al., 2010; Harris and Seckl, 2011; Moisiadis and Matthews, 2014a). The following chapter will briefly summarize the cortisol-dependent mechanism of maternal-fetal stress transfer prior to discussing cortisol-independent mechanisms in more depth.

In contrast to the sympathetic-adrenal medullary system (SAMS, see below), the HPAA is thought to mediate the mid- to long-term response of an individual's stress reactions, *e.g.* by mobilization of en-

ergy depots and modulation of the sympathetically mediated stress response. In reaction to acute or chronic psychological stress, the maternal HPAA is activated by higher brain structures and, as a result, the adrenal cortex synthesizes and releases cortisol into the maternal circulation (Ulrich-Lai and Herman, 2009). Once released into the maternal circulation, highly lipophilic cortisol passes through the placental barrier and reaches the fetus.

However, the placental enzyme 11beta-hydroxysteroid dehydrogenase type 2 (11ß-HSD-2) inactivates approximately 80–90% of the maternal cortisol. In addition, the fetal HPAA is not able to produce cortisol until late gestation, indicating that the fetus is completely dependent on maternal cortisol over most of the pregnancy (Magyar et al., 1980). Consequently, fetal plasma concentrations under physiological conditions are 5–10-fold lower compared to maternal levels (Chapman et al., 2013). This mechanism is thought to protect the fetus from excessive maternal cortisol concentrations under physiological conditions. In addition to the greater exposure of the fetus to maternal cortisol released during acute maternal stress situations, the placental barrier is corrupted by psychosocial stress, thus exposing the fetus to disproportionately high fluctuations in maternal plasma cortisol. It has been demonstrated that prenatal stress itself – or maternal anxiety as a marker of prenatal stress − reduces the expression and activity of 11ß-HSD-2 in humans and animal models (Chapman et al., 2013; Jensen Pena et al., 2012; Monk et al., 2016; O'Donnell et al., 2012). Furthermore, the activity of human placental 11ß-HSD-2 decreases in uncomplicated pregnancies near term (Murphy and Clifton, 2003), suggesting a high vulnerability of the fetus to the programming potential of cortisol during late gestation.

In the fetal circulation and in particular the fetal brain, maternal cortisol can perturb the development of the fetal HPAA during vulnerable periods by resetting the set point of the HPAA's negative feedback mechanism, resulting in a long-lasting or even permanent change in HPAA activity in postnatal life (Cottrell and Seckl, 2009; Moisiadis and Matthews, 2014b). This intrauterine determination of the fetal HPAA activity in later life is thought to be one of the essential mechanisms of 'fetal programming'. The HPAA in humans and several animal species, including sheep, matures during late gestation when a physiological rise in fetal cortisol concentrations triggers tissue maturation and prepares the fetus for postnatal life (Liggins, 1994; Magyar et al., 1980; Moisiadis and Matthews, 2014b). Similar to the decrease of the activity of human placental 11ß-HSD-2, this once again suggests that the greatest vulnerability to the programming effects of maternal cortisol is during late gestation. This hypothesis is also supported by the ontogeny of the GR. Specifically, GR in central parts of the fetal HPAA that are involved in HPAA negative feedback regulation are mainly expressed from mid term onwards in several species such as rodents and sheep (Meaney et al., 1985; Owen and Matthews, 2003; Slotkin et al., 2008).

Apart from the direct transfer of cortisol to the fetus, there is limited evidence that cortisol can indirectly mediate maternal stress effects in humans by stimulating the placental release of corticotrophin-releasing hormone into the fetal and maternal circulation (Hobel et al., 1999; Sandman et al., 2006). Placental corticotrophin-releasing hormone is exclusively synthetized by the primate placenta and does not underlie negative feedback regulation. It is associated with decreased fetal growth, preterm delivery, activation of the fetal HPAA and impairment of brain maturation such as development of the fetal hippocampus and other parts of the fetal limbic system (Charil et al., 2010; Cottrell and Seckl, 2009; Sandman et al., 1999).

3. Catecholamines and reduction of utero-placental perfusion

The SAMS and its effector hormones norepinephrine (NE) and epinephrine (EPI) comprise fast-responding components of the physiological stress system. Released from the chromaffin cells of the adrenal medulla into the portal circulation and from sympathetic neurons that innervate almost all organs, NE and EPI mediate the short-term responses to various stressors from outside or inside the organism by modulating the individual's behaviour as well as the activity of the cardiovascular, metabolic, immune and central nervous systems (Kvetnansky et al., 2009; Wong et al., 2012). In contrast to the activation of the HPAA that takes tens of minutes to release its effector hormone cortisol and reach its peak serum concentration, the SAMS acts as an individual's 'first-response system' to stress and is activated within seconds after stress exposure (Ulrich-Lai and Herman, 2009). The concentration of plasma catecholamine levels largely reflects the sympathetic activity during acute stressful situations (Kvetnansky et al., 2009; McCarty, 1994).

Despite irrefutable importance of the SAMS for an individual's stress reaction, catecholamines as mediators of maternal-fetal stress have received limited attention. One reason for this lack of broad interest may be that maternal catecholamines are hydrophilic and seemingly are not able to cross the placenta in physiologically relevant concentrations. Several studies of human placental tissue and rodents have found evidence for a minor transfer of NE from mother to fetus (Morgan et al., 1972; Saarikoski, 1973; Sodha et al., 1984). However, no evidence was found for a placental passage of NE and EPI in chronically catheterized sheep when both drugs were directly infused into the maternal circulation (Jones and Robinson, 1975). Furthermore, in reaction to invasive procedures in humans, fetal and maternal NE concentration showed no correlation, suggesting that NE cannot be directly transferred from mother to fetus (Giannakoulopoulos et al., 1999).

3.1. Catecholamines and fetal development

To the best of our knowledge, there is only one published study determining the association between maternal catecholamine concentrations and pregnancy outcome in humans. In the study, a high maternal catecholamine concentration measured on three consecutive days during mid-gestation was associated with spontaneous preterm birth (Holzman et al., 2009). In animal studies, excess catecholamines can also lead to an impaired fetal development. For example, in sheep, direct fetal infusion of NE and EPI during the third trimester led to asymmetrical fetal growth retardation in the absence of hypoxaemia (Bassett and Hanson, 1998), whereas in a recent study, bilateral adrenal demedullation in growth restricted fetuses delayed fetal growth retardation (Davis et al., 2015; Macko et al., 2016). In rhesus monkeys, if infused directly into the mother, excess catecholamines induce fetal hypoxia (Adamsons et al., 1971). However, not all studies report an unfavourable consequence of elevated catecholamine concentration. In rats, chronic maternal infusion of EPI during different timeframes of pregnancy did not affect fetal and placental weight or length of pregnancy (Trend and Bruce, 1989). Other animal studies even demonstrate that catecholamines are necessary for an intact endometrium and fetal survival (Dong et al., 2016).

3.2. Catecholamine-mediated reduction of the utero-placental perfusion

Although there is some uncertainty regarding whether maternal catecholamines can affect the fetus directly, NE in particular can influence fetal metabolism indirectly by reducing the utero-placental perfusion (UPP). The monoamine NE is a potent vasoconstrictor that increases the vascular tone in a variety of organs including the uterus (Hoffman et al., 1981; Rakers et al., 2015) and the placenta (Resch et al., 2003) *via* activation of α-adrenergic receptors (Calzada and De Artinano, 2001; Dreiling et al., 2016). The uterine arteries are particularly vulnerable to excessive NE concentrations as their susceptibility to α-adrenergic vasoconstriction is higher than that of the systemic vasculature (Magness and Rosenfeld, 1986).

3.2.1. Maternal stress and UPP in human studies

During the last two decades, a number of studies have determined the correlation between prenatal psychological stress and utero-placental and fetal haemodynamics in human pregnancies using standard Doppler ultrasound techniques (Levine et al., 2016). To date, there is inconclusive evidence on the association of maternal stress and changes in maternal or fetal circulation. For example, in a recent study of 104 healthy pregnant women, maternal psychological stress measured by self-reporting questionnaires was associated with a reduced umbilical blood flow in the third trimester (Helbig et al., 2013). In line with this finding, an earlier study on 100 healthy pregnant women in their final trimester found a positive correlation between the uterine artery resistance index and maternal anxiety as a marker of prenatal stress (Teixeira et al., 1999). However, in contrast, Monk et al. were unable to demonstrate an association between depression or anxiety and a reduction in uterine or umbilical blood flow in a cohort of pregnant women with a lifetime history of mental illness (Monk et al., 2012). It should be pointed out that these ultrasound studies have two major limitations. First, they did not take acute stress situations into account. As will be discussed later, animal studies show that a stress-induced uterine blood flow decrease is transient in nature and limited to the temporary activation of the SAMS during acute stressful situations. It is therefore not surprising that the findings from human Doppler ultrasound studies based on at-rest measurements are not conclusive. Secondly, none of the studies correlated objective measures of maternal stress such as maternal catecholamines with fetal or utero-placental haemodynamics.

3.2.2. Maternal stress and UPP in animal studies

Despite the inconclusive results from the ultrasound studies in humans, the impact of acute maternal stress on the UPP and fetal homeostasis has clearly been shown in several experiments in sheep and non-human primates. In sheep, short-term physical stress induced by electric shocks or psychological stress induced by isolation immediately reduced the uterine blood flow *via* α_1-adrenergic receptors in the uterine vasculature (Dreiling et al., 2016; Rakers et al., 2015; Shnider et al., 1979). While short-term decreases of uterine blood flow of less than three minutes were not associated with changes in fetal blood gases (Shnider et al., 1979), isolation stress for two hours and a consecutive uterine blood flow decrease of approximately 20% shifted fetal metabolism towards an anaerobic metabolic condition and increased fetal catecholamine plasma concentration over the entire isolation period (Rakers et al., 2015). Interestingly, the transient uterine blood flow decrease appears to trigger a lactacidosis and a rise of stress hormones in the fetus that outlast the maternal stress reaction (Rakers et al., 2015). Fetal blood acidosis and stress-associated cardiovascular changes during maternal psychological stress appear to be multispecies effects that have also been observed in non-human primates (Myers, 1975, 1977).

3.2.3. Norepinephrine and UPP in animal studies

The inverse association between maternal NE concentrations and the UPP is well documented. Most of the studies were conducted in the 1970s and 1980s using the standard animal model for human pregnancy – the chronically instrumented, non-anaesthetized fetal sheep (Barry and Anthony, 2008). In sheep, NE directly injected into the uterine arteries (Barton et al., 1974) as well as in the maternal circulation (Gu and Jones, 1986; Ladner et al., 1970) causes an immediate vasoconstrictive response of the uterine arteries that significantly reduces uterine blood flow. The NE-induced vasoconstriction of the uterine arteries is followed by hypoxia and an anaerobic metabolic condition of the placenta (Gu and Jones, 1986). Throughout pregnancy, the α-adrenergic responsiveness of the uterine arteries is attenuated, possibly protecting the near-term fetus from a stress-induced, catecholamine-mediated decrease in the UPP (Magness and Rosenfeld, 1986).

3.2.4. Reduction of UPP and the fetus

The fetus is able to sense even small changes in the reduction of uterine blood flow and reacts to this reduction with an increase in plasma catecholamines (Gu et al., 1985; Rakers et al., 2015). In sheep, a reduction of uterine blood flow to 70–90% induced by a uterine artery occluder did not change fetal oxygenation, heart rate or blood pressure but led to a sustained increase in fetal catecholamines (Gu et al., 1985). A possible explanation for the unchanged fetal oxygenation is that a uterine blood flow decrease of one-third – as induced by maternal infusion of EPI – does not change umbilical blood flow (Gu and Jones, 1986). To date, it is unclear how the fetus senses small reductions in uterine blood flow in the absence of an altered umbilical blood flow. Fetal hypoxia in sheep is not induced until a reduction of uterine blood flow to 30–50% (Gu et al., 1985).

3.3. Stress-induced impairment of placental catecholamine metabolism

Compared to postnatal life, fetal plasma catecholamine concentration is low despite a high endogenous fetal catecholamine production (Stein et al., 1993). The reason for this is a high placental catecholamine clearance that is largely responsible for maintaining the fetal catecholamine homeostasis (Bzoskie et al., 1995). It is conceivable that a stress-induced disturbance in placental catecholamine clearance would increase fetal catecholamine concentrations that in turn affect fetal growth and development as discussed above. Recent work with sheep in our laboratory showed an increased fetal catecholamine concentration after chronic prenatal psychosocial stress during the first and second trimester (Rakers et al., under review). Indeed, there is some evidence that several placental transporters and enzymes involved in catecholamine breakdown are impaired by maternal stress or pregnancy complications. For example, in human pregnancies complicated by intrauterine growth restriction, drug abuse or fetal distress, placental NE transporter mRNA expression was lower than in uncomplicated pregnancies (Bzoskie et al., 1997). Recently, human placental monoamine oxidase A was reported to be negatively correlated to maternal depression and trait anxiety (Blakeley et al., 2013). However, although it is conceivable, a direct link between developmental effects of psychological stress and an impaired placental catecholamine clearance has not yet been shown.

4. Reactive oxygen species and oxidative stress

The life gas oxygen is one of the most important elements necessary for embryonic and fetal development (Simon and Keith, 2008). In mitochondria, oxygen is used as a substrate in the electron transport chain to generate the energy-storage molecule adenosine triphosphate. As co-products of this oxygen metabolism, it is estimated that 0.2–2% of all oxygen molecules are reduced constantly into a number of reactive oxygen species (ROS) including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical ($^{\bullet}OH$) (Shadel and Horvath, 2015). Despite their essential role for intracellular signalling, excessive ROS concentrations can induce severe cell damage by oxidation of lipids, proteins and DNA (Reczek and Chandel, 2015). For example, intracellular ROS decrease the activity of the epigenetic control mechanisms of nuclear DNA causing global DNA-hypo-methylation (Szumiel, 2015) and interfere with the control of histone methylation (Niu et al., 2015). These modifications of the fetal epigenome are thought to be one of the basic underlying mechanisms of fetal programming of the HPAA (Godfrey et al., 2007). The cell has developed an extensive defence mechanism to neutralize improper concentrations of ROS including enzymatic scavengers and antioxidant molecules (Monaghan et al., 2009). An imbalance between these enzymatic and non-enzymatic antioxidant defence mechanisms and the production of ROS is largely recognized as oxidative stress (OS), which has been proposed as playing an important role as a mechanism of fetal programming (Thompson and Al-Hasan, 2012).

During human pregnancy, a moderate increase of maternal OS is physiological (Hung et al., 2010; Little and Gladen, 1999; Yang et al., 2012). The first peak in maternal OS is observable in healthy pregnancies shortly after establishment of the maternal-fetal circulation, *i.e.* late in the first trimester when the fetal metabolism shifts from an anaerobic towards an aerobic state (Jauniaux et al., 2000; Wu et al., 2015). The second peak in maternal OS, measured by OS markers such as urinary 8-hydroxydeoxyguanosine and plasma 8-isoprostane, is observable during the third trimester (Hung et al., 2010). However, the mechanisms and biological implication for this physiological increase in maternal ROS production during pregnancy are not currently understood (Avila et al., 2015).

4.1. Oxidative stress and fetal development

There is growing evidence that excessive OS during different phases of human pregnancy is associated with adverse pregnancy outcomes such as spontaneous abortion (Gupta et al., 2007), intrauterine growth restriction (Turpin et al., 2015; Weber et al., 2014), preterm delivery (Ferguson et al., 2015; Joshi et al., 2008), gestational diabetes (Zhu et al., 2015) or preeclampsia (Sanchez-Aranguren et al., 2014), which are in turn believed to contribute to fetal programming of health and disease in later life (Jansson and Powell, 2007). However, evidence for a direct correlation between prenatal OS and disease in later life is scarce. In a longitudinal study of primarily uncomplicated pregnancies, high maternal levels of urinary OS markers in the first and second trimester correlated with the risk for small-for-gestational-age fetuses (Potdar et al., 2009). In agreement with that study, normal-weight children that were born small-for-gestational-age were found to have increased levels of OS and signs of insulin resistance (Chiavaroli et al., 2009). Although well-designed human studies are lacking at present, there are several studies conducted in rats that have used maternal application of potent antioxidants to investigate the programming capabilities of OS. For example, prenatal maternal stress induced by restrained stress impaired cognitive function, neurogenesis and hippocampal GR expression in the offspring of rats. However, when the pregnant rats were fed with the antioxidant hydroxytyrosol, these effects were prevented (Zheng et al., 2015). Similar results were also achieved with other antioxidants (Feng et al., 2010; Feng et al., 2012). However, whether and at what concentration these antioxidants are able to be transferred to the fetus remains unclear. An indirect effect of antioxidants on the feto-placental unit has been described by Thakor et al. (Thakor et al., 2010). Herein, maternal intravenous treatment of pregnant sheep with melatonin or vitamin C increased the umbilical blood flow by increasing the bioavailability of the potent vasodilator nitric oxide. Oxidative stress may be particularly involved in the programming of cardiovascular and metabolic disease characterized by endothelial irregularities. Experimental studies using prenatally diet-restricted rats that consecutively develop hypertension have revealed that the underlying mechanism − an impaired endothelial dysfunction − is caused by increased levels of OS (Franco Mdo et al., 2002). However, the importance of these findings for human pregnancies is unclear.

4.2. Induction of oxidative stress by psychosocial stress

Several exogenous (*e.g.* food consumption, air pollutants, medical drugs, radiation, psychological stress) and endogenous (*e.g.* physical exercise, inflammation, ischaemia/reperfusion) OS-eliciting factors have been identified (Moller et al., 1996), amongst which psychosocial stress is of special interest for the purpose of this review.

The association between psychosocial stress and OS has been demonstrated in several human and animal studies. In a group of university students on the day of examination, single-strand breaks of DNA in lymphocytes and oxidation of lipoproteins were increased and plasma antioxidant activity significantly reduced compared to a non-examination period (Sivonova et al., 2004). In a young and healthy population, self-reported stress load at work or at home was associated with a strong decrease in blood antiradical resistance in a cross-sectional study (Lesgards et al., 2002). In agreement with this, in a cohort of healthy blue-collar workers, 8-hydroxydeoxyguanosine (a marker of oxidative DNA damage) was positively correlated to the perceived workload and psychological stress particularly in females (Irie et al., 2001). Similarly, in rodents, oxidative status was significantly increased in central neuronal tissue as well as in peripheral blood cells, heart, liver and spleen following acute restraint stress (Chen et al., 2014; Spiers et al., 2013; Spiers et al., 2016; Wang et al., 2007). In contrast, acute psychological stress decreased production of ROS measured by chemiluminescence in phagocytic cells in a small study of 13 healthy subjects (Atanackovic et al., 2002). Consequently, larger clinical studies are required to verify the effects of acute and chronic stress on oxidative status in humans. Moreover, it is currently unknown whether psychological stress has an effect on or alters the effects of OS during pregnancy.

4.3. Transfer of oxidative stress to the fetus

There is preliminary evidence supporting a positive correlation between OS markers in the mother and the fetus, suggesting a direct or indirect interaction between maternal and fetal oxidative systems. Argülles et al. found that the oxidative state of the mother defined by serum concentrations of lipid peroxides, carbonyl groups, and total antioxidant capacity strongly correlated with the fetal oxidative state during labour (Arguelles et al., 2006). In agreement with this, a positive correlation between maternal and neonatal oxidative status was found for small-for-gestational-age newborns (Saker et al., 2008). In mice, acute restraint stress caused OS in the uterus along with abnor-

mal embryo implantation (Liu et al., 2014). The detailed mechanism of the demonstrated interaction between maternal and fetal oxidative systems is unknown. In contrast to maternal stress hormones like cortisol, a direct maternal-fetal transfer of ROS induced by psychological stress is not feasible due to the short half-life of highly reactive ROS (Reth, 2002). However, maternal psychosocial stress may induce OS in the fetus *via* indirect mechanisms such as a stress-induced reduction of placental perfusion or in response to maternal cortisol. Although as discussed above, evidence showing that acute maternal stress in humans reduces uterine perfusion is currently lacking, recent studies in pregnant sheep − the standard model for human pregnancy − have shown a stress-induced intermittent reduction of UPP (Dreiling et al., 2016; Rakers et al., 2015). It is well established that the placenta in humans and animals reacts to recurrent periods of hypoxia and reoxygenation with the generation of high levels of ROS (Burton and Hung, 2003). For example, a recent study demonstrated that rat placenta responded *in vitro* to a hypoxia-reoxygenation challenge with the secretion of several factors that induced ROS in neurons of the embryonic rat cerebral cortex (Curtis et al., 2014). These ROS-inducing factors further decreased the dendritic lengths, branching complexity, spine density and synaptic activity of the fetal cortical neurons *in vitro*. Furthermore, glucocorticoids are known to increase OS in different tissues, with the greatest effects observed in the brain (for summary of meta-analysis see (Costantini et al., 2011)).

5. Cytokines and maternal immune response

Prenatal psychosocial stress during critical phases of pregnancy can increase the risk for developing neuropsychiatric disorders in later life that have also been associated with prenatal maternal infection. Examples of these disorders are schizophrenia, non-affective psychosis, mood disorders, autism spectrum disorders and epilepsy (Blomstrom et al., 2015; Fine et al., 2014; Khandaker et al., 2013; Simanek and Meier, 2015; Sun et al., 2008; Weinstock, 2008; Zerbo et al., 2015). This suggests that both stressors, *i.e.* psychological stress and maternal infections induce similar biological pathways that can transfer maternal stress to the fetus. It has been specifically proposed that maternal release of immunomodulation cytokines plays a significant role in transferring psychological stress to the fetus (Entringer et al., 2010b; Ratnayake et al., 2013).

Cytokines are an inhomogeneous group of soluble polypeptides that mainly act as mediators of cell-to-cell signaling, are involved in immunomodulation and have endocrine effects (Deverman and Patterson, 2009). These proteins stimulate or suppress inflammation through several mechanisms including modification of T-cell differentiation, vascular permeability or release of acute-phase proteins (O'Shea et al., 2002). Excess cytokines may alter fetal brain development by direct interaction with fetal glial cells (Ratnayake et al., 2013) and are closely linked to maternal-fetal stress transfer by cortisol and ROS. Specific cytokines such as TNF-α, IL-1ß and IFN-γ promote the production of ROS (Liu et al., 2000; Weaver et al., 2012) and have also been shown to increase intracellular levels of OS. In addition, pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 can activate the HPAA and stimulate glucocorticoid release (Silverman and Sternberg, 2012).

Some researchers have proposed a slight elevation in circulating maternal cytokines during normal human pregnancy (Christian, 2012). However, the available data are conflicting and longitudinal studies on cytokine concentrations during uncomplicated human pregnancies report inhomogeneous results. For example, in a large cohort of 1274 Danish women, Curry et al. found that IL-12, IL-6 and IFN-γ slightly increased from early to mid pregnancy, while IL-2 and TNF-α remained stable (Curry et al., 2008). In contrast, two smaller studies found a decrease of IL-2 and IFN-γ (Marzi et al., 1996) or reported stable concentrations of IL-6 and IFN-γ during pregnancy (Makhseed et al., 2000).

5.1. Cytokines and fetal development

Despite the various epidemiological studies linking maternal immune-activating prenatal infections with neuropsychiatric, metabolic or immunological disease in later life, evidence for the programming potential of maternal cytokines remains vague and is mainly based on animal studies using pro-inflammatory substances to provoke a maternal immune reaction (Mandal et al., 2013; Meyer et al., 2008; Straley et al., 2016). To date, three smaller human birth cohorts have been used to investigate the association between maternal cytokine concentrations during pregnancy and the risk for schizophrenic spectrum disorders in the offspring. In all three studies, the majority of the pro-inflammatory maternal cytokines that were analysed were not associated with the risk for psychosis in the offspring. Furthermore, when positive associations between specific maternal pro-inflammatory cytokines, *e.g.* TNF-α or IL-8, and the risk for neuropsychiatric disease in the offspring were detected, these could not be reproduced in the other studies (Allswede et al., 2016; Brown et al., 2004; Buka et al., 2001). However, one of the studies reported a protective effect of anti-inflammatory Th2 cytokines (IL-4/5/13) for developing psychosis (Allswede et al., 2016). Due to the nature of these clinical studies, a causal link between maternal cytokine concentration and fetal outcome is not possible.

There are only a few experimental studies investigating the role of stress-induced maternal inflammation or direct maternal cytokine application in fetal programming. In a mouse model of early prenatal stress, maternal stress induced an upregulation of pro-inflammatory placental genes including IL-1ß and IL-6 and resulted in a hyperactive phenotype in male offspring. This gene upregulation and hyperactive phenotype could be prevented by maternal application of non-steroidal anti-inflammatory drugs (Bronson and Bale, 2014). In studies using pregnant rats, application of IL-6 resulted in structural changes in the hippocampus of offspring and decreased learning potential (Samuelsson et al., 2006), increased body weight and decreased insulin sensitivity (Dahlgren et al., 2001), as well as arterial hypertension and hyperactivity of the adult HPAA (Samuelsson et al., 2004). Prenatal maternal immune activation with a viral mimic in wild-type mice resulted in schizophrenia-like behavioural changes in their offspring that were not present in the offspring of IL-6-knockout mice (Smith et al., 2007). In addition, when an IL-6 antibody was added to the viral mimic, maternal immune activation-related changes in gene expression in brains of adult offspring could be prevented (Smith et al., 2007). These studies suggest a prominent role of maternal IL-6 in the programming of behavioural and cardiovascular disease. However, results attained from studies of human cohorts do not fully support this observation, which may be a consequence of small numbers of study patients and significantly different designs and outcome assessments.

5.2. Release of cytokines by psychosocial stress

It is well established that in non-pregnant women and rodents, psychosocial stress elicits a sustained increase in circulating inflammatory cytokines (LeMay et al., 1990; Steptoe et al., 2007). Since maternal cardiovascular and neuroendocrine stress sensitivity as well as the general immune responsiveness are attenuated during human pregnancy (Christian, 2012; Entringer et al., 2010a; Weetman, 2010),

observations from non-pregnant women cannot be extrapolated to cytokine release in pregnant women. Yet, there is preliminary evidence that acute or chronic stress can also trigger cytokine release during pregnancy. In a study of 24 pregnant women, chronic psychosocial stress and a low level of social support were associated with higher plasma concentrations of pro-inflammatory IL-6 and TNF-α as well as low levels of anti-inflammatory IL-10 (Coussons-Read et al., 2005). Another study recently showed that acute mental stress in pregnant women provoked a sustained and prolonged increase in the pro-inflammatory circulating IL-6 concentration (Christian et al., 2013).

5.3. Transfer of cytokines to the fetus

Knowledge about the transfer of maternal cytokines to the human fetus is limited, although animal studies suggest that maternal cytokines can pass through the placenta and enter fetal circulation (Andersson et al., 2016; Dahlgren et al., 2001; Zaretsky et al., 2004). A very recent study of 43 pregnant women examined the association between stress perception during the second trimester and cytokines in the umbilical cord blood of newborn infants (Andersson et al., 2016). In that study, increased maternal stress measured by five different questionnaires during the second trimester was associated with increased levels of IL-1ß, IL-4, IL-5, IL-6 and IL-8 in the umbilical cord blood of newborn infants. However, due to the nature of the study design, a causal link between maternal and fetal cytokines could not be demonstrated and it remains unclear whether fetal cytokines were of endogenous or maternal origin. *Ex vivo* perfusion studies in healthy term human placentas provide contradictory results regarding the ability of cytokines to pass through the placental barrier. While Aaltonen et al. could not demonstrate a placental transfer of the maternal cytokines IL-1, IL-6 and TNF-α to the fetus (Aaltonen et al., 2005), Zaretsky et al. reported a predominantly bidirectional transfer of these cytokines from mother to fetus and vice versa (Zaretsky et al., 2004). In another perfusion study, IL-8 was not able to cross the human placenta in either direction (Reisenberger et al., 1996). In contrast to these ambiguous results from human perfusion studies, rodent studies suggest maternal-fetal transfer for at least some cytokines, such as IL-6. In rats, maternal-fetal transfer of IL-6 was found to be more distinct in mid than in late gestation (Dahlgren et al., 2006), whereas in mice, IL-4 and IL-13 were not seen to cross the placenta (Lim and Kobzik, 2009). Apart from a transfer of maternal cytokines to the fetus, it is also conceivable that the placenta itself is a source of cytokines that are secreted into the fetal circulation in response to maternal stress. Interestingly, it has been shown that maternal immune activation and consecutive cytokine release trigger placental production of IL-6 and other pro-inflammatory cytokines (Hsiao and Patterson, 2011). However, whether maternal stress can induce placental cytokine production remains unclear.

6. Serotonin and tryptophan

The monoamine serotonin (5-hydroxytryptamine, 5-HT) functions as a neurotransmitter in the central, peripheral and enteric nervous systems of animals and humans. 5-HT is synthesized from the essential amino acid tryptophan *via* the enzyme tryptophan hydroxylase and is involved in the pathophysiology of several neuropsychiatric diseases including depression, psychosis and cognitive disorders (for review see (Naughton et al., 2000)). Recently, it has been proposed that 5-HT and its precursor tryptophan are involved in maternal-fetal stress transfer and fetal programming (Bonnin and Levitt, 2011; Goeden et al., 2013; St-Pierre et al., 2015). However, evidence, especially from humans, is limited at present.

6.1. Serotonin and fetal development

5-HT, detectable at as early as seven weeks of human fetal development (Kinney et al., 2007), is crucial for placentation and embryonic, fetal and postnatal brain and cardiovascular development in humans and animals (Bonnin and Levitt, 2011; St-Pierre et al., 2015). Thus, it is plausible that prenatal disturbances in the fetal serotonergic homeostasis may have long-lasting psychological and physical consequences for later life. For example, knockout mice lacking central parts of the serotonergic system are vulnerable to developing anxiety disorders, aggression and drug abuse in adulthood (Gingrich and Hen, 2001). Experimentally induced maternal depletion of 5-HT levels during pregnancy was found to reduce serotonin receptor expression in the developing rat forebrain (Chen et al., 2012) and to induce dilated cardiomyopathy in the offspring, with the severity being negatively correlated to the maternal plasma 5-HT concentration during pregnancy (Fligny et al., 2008). However, the impact of excessive maternal serotonin concentrations on fetal development is less clear. Feeding of a tryptophan-enriched diet to pregnant rats resulted in hyperserotonaemia (Castrogiovanni et al., 2014; Musumeci et al., 2014), low growth hormone concentration (Musumeci et al., 2014), changes in the expression of 5-HT-regulating genes (Blažević and Hranilović, 2013) and a delayed maturation of the central serotonergic system (Huether et al., 1992) in the developing offspring. Repeated maternal injections of tryptophan administered to pregnant rats resulted in an increased brain serotonin synthesis (Hernandez-Rodriguez and Chagoya, 1986) and reduced anxiety-like behaviour in the offspring (Blazevic et al., 2012). In contrast, pups of pregnant rats given injections of 5-HT during mid to late gestation exhibited an increased anxiety-like behaviour (Blažević et al., 2011), suggesting that the effects of tryptophan injections on the fetus are not or not entirely mediated by serotonin.

6.2. Release of serotonin and tryptophan by psychosocial stress

Though experimental alterations in maternal serotonin or tryptophan homeostasis during pregnancy influence fetal development, it is currently not well understood if psychosocial stress can elicit similar effects. Preliminary evidence derived from rodents suggests that psychosocial stress during pregnancy increases maternal tryptophan plasma concentrations that are associated with an increase in tryptophan and 5-HT levels in the fetal brain (Peters, 1990). It has been reported that stress induced by electric foot shocks, restraint, dipping in cold water or prolonged water immersion restraint increases plasma tryptophan and 5-HT concentrations (Malyszko et al., 1994; Weil-Fugazza and Godefroy, 2014), whereas these parameters decrease after a short water immersion restraint stress (Takada et al., 1996). These results demonstrate the potential impact of stress on serotonin metabolism that appears to depend on the type, intensity and duration of the stressor. However, whether acute or chronic stress in humans can elicit similar alterations and the influence of pregnancy on these potential alterations remains to be clarified.

6.3. Transfer of serotonin and tryptophan to the fetus

Maternal 5-HT appears to be essential for normal fetal development in rodents and it has been suggested that maternal 5-HT can be transferred directly to the fetus (Cote et al., 2007). However, using an *ex vivo*, perfused and live murine placenta, it has been demonstrated

that less than 0.5% of free maternal plasma 5-HT is able to overcome the placental barrier (Bonnin et al., 2011), thus making a direct impact of maternal 5-HT on fetal development less likely. In contrast, the positive correlation between a stress-induced increase of maternal plasma tryptophan concentration and fetal brain tryptophan concentration in rodents reported by Peters (Peters, 1990) suggests a greater likelihood that stress-induced maternal tryptophan is able to cross the placenta into the fetal circulation. Indeed, active transport of amino acids, including tryptophan, across the placenta is essential for human and animal fetal growth and development and, moreover, the transport mechanisms are well characterized (for review see (Cleal and Lewis, 2008)). In addition, an indirect effect of maternal stress-induced increase of tryptophan on the fetus has recently been proposed (Bonnin et al., 2011; Goeden et al., 2013). Tryptophan injected into the uterine arteries of a perfused mouse placenta leads to an increase in 5-HT in the fetal placental circulation (Bonnin et al., 2011). Similarly, maternal stress-induced increases in tryptophan concentrations could act as a substrate for placental 5-HT synthesis. Indeed, during early pregnancy, the placenta is an exogenous source of 5-HT necessary for the developing fetal forebrain (Bonnin et al., 2011). Disturbance of the serotonergic signaling in mice *in vivo* leads, for example, to pathological thalamocortical axon trajectories (Bonnin et al., 2007). The tryptophan-induced placental synthesis of serotonin could help explain the programming effects of maternal stress on behaviour and neuropsychiatric disease, especially during early pregnancy when fetal HPAA is not mature and GR are not widely expressed.

7. Maternal microbiota and programming of the gut-brain axis

All stress-transfer mechanisms reviewed thus far can exert their direct or indirect influence during different timeframes from early till late pregnancy when neural plasticity and relative brain growth is at its greatest. An additional stress-transfer mechanism – the maternal-fetal transmission of an impaired maternal microbiota and programming of the developing 'gut-brain axis' – differs in that it exerts its effect on the fetus only during parturition or shortly thereafter. Since evidence for this relatively new hypothesis has only recently been extensively reviewed (Jašarević et al., 2015; O'Mahony et al., 2017), we only briefly discuss the background and principle idea of this indirect stress-transfer mechanism.

The healthy human gut is colonized by diverse microbial communities consisting essentially of bacteria and to a lesser degree of archea, viruses, fungi and protozoa (Sommer and Backhed, 2013). These diverse microbial communities are collectively referred to as the gut microbiota. Its physiological role has long been regarded solely as being a supplement for the hosts' metabolism and digestion.Tremaroli and Backhed, 2012). However, it is now thought that the gut microbiota is essential for early development and modulation of the regulation of hosts' physiology, immune response, central nervous function, neurocognition, behavior and the neuroendocrine system including the HPAA (O'Mahony et al., 2015; Sherman et al., 2015; Sommer and Backhed, 2013). The gut microbiota communicates with the central nervous system and the immune system *via* an integrated, bidirectional communication pathway that amongst others involves inflammatory cytokines, neuromodulators and neurotransmitters (Mayer, 2011; O'Mahony et al., 2015; Petra et al., 2015; Sommer and Backhed, 2013; Tremaroli and Backhed, 2012). Consequently, disturbances in this communication system – the so called 'gut-brain' axis – have been associated with a number of neurological and psychiatric diseases such as depression, anxiety disorders, attention deficit hyperactivity disorder and autoimmunological disease such as multiple sclerosis (Foster and McVey Neufeld, 2013; Petra et al., 2015).

The initial development of the 'gut-brain' axis is thought to begin mainly during parturition when the fetus passes the birth channel and ingests parts of the vaginal microbiota that colonizes the so far sterile fetal gut (Cilieborg et al., 2012). The vaginal microbiota itself is known to be quite sensitive to chronic maternal stress that in addition to the pregnancy per se also suppresses maternal immune function (see Chapter 5). For example, chronic maternal stress increases the risk for bacterial (Culhane et al., 2001; Nansel et al., 2006) and fungal (Ehrstrom et al., 2005) vaginosis potentially altering the vaginal microbiota. It has been hypothesized that stress-induced unfavorable changes in the vaginal microbiota are transferred to the fetus during parturition, affect initial gut colonization and thus, change the enteric synthesis of neuroinflammatory cytokines, neuromodulators and neurotransmitters involved in the newborns' neurodevelopment (Jašarević et al., 2015). This modulated function of the 'gut-brain' axis and a different trajectory of neurodevelopment may lead to a greater susceptibility for neuropsychiatric disease in later life (Jašarević et al., 2015).

First data supporting this new hypothesis have lately been published. For example, a large case-control study reported an association between urovaginal infections during pregnancy and autism spectrum disorders in the offspring (Zerbo et al., 2015) even though it is unknown whether these infections are linked to maternal stress. Maternal stress, however, was associated with intestinal microbiota of human infants determined by a phylogenetic microarray (Zijlmans et al., 2015). In the study, especially the gut microbiota of infants of highly stressed mothers was colonized with pathogenic proteobacterial groups. Yet, due to the study design, a causal relationship between maternal stress and the infants' gut microbiota could not been substantiated. It could recently be demonstrated in mice that prenatal stress altered the mothers' vaginal microbiome that was associated with the offspring' microbiota composition and changes in metabolic pathways of the 'gut-brain' axis relevant for physiological neurodevelopment (Jasarevic et al., 2015). Interventional therapies are already under discussion and, most notably, maternal application of probiotic micro-organisms has received greater attention (Dinan and Cryan, 2012). However, as yet, the impact of probiotic therapy on infants' gut microbiota and neurocognitive development especially under consideration of prenatal stress is unclear.

Even though some promising results already exist, it is currently unclear if a stress-induced alteration in maternal microbiota and its vertical transmission to the fetus or newborn is a relevant stress-transfer mechanism. However, the importance of the maternal microbiota for offspring development and the modulation of the maternal microbiota by psychological stress is currently a highly dynamic research field and new insights can be expected in the near future.

8. Conclusion

Cortisol is a well-established and well-characterized mediator of maternal psychosocial stress to the fetus. The ability of cortisol to pass through the placenta, to modify the maturation and function of several organ systems and to induce long-lasting changes in the fetal HPAA's activity is a fundamental mechanism of fetal programming of health and disease. The maturation of the fetal HPAA and the peak of GR expression during late gestation suggest that the programming effects of maternal cortisol on the fetus are particularly relevant in advanced pregnancy. In addition to cortisol, there is emerging evidence that several other substances such as catecholamines, ROS, cytokines and serotonin that are released during acute or chronic mater-

nal stress have direct or indirect stress-transfer capabilities. Maternal catecholamines released during an acute stressful situation may play a greater role in maternal-fetal stress transfer than previously assumed. Even though catecholamines are not able to pass through the placental barrier in physiologically relevant concentrations, they are capable of reducing the UPP *via* α_1-adrenergic vasoconstriction of the uterine arteries, as has been shown in sheep and non-human primates. The consecutive shift of the fetal metabolism towards an anaerobic metabolic state and the induction of endogenous fetal catecholamine secretion may contribute to an adverse fetal development. Similar to maternal cortisol and catecholamines, maternal OS has also been associated with an adverse pregnancy outcome and impaired fetal development. In addition, OS can interfere with epigenetic control mechanisms including histone methylation. However, although psychosocial stress can promote OS formation in the mother and maternal and fetal OS statuses are closely related, the mechanism of OS transfer from mother to fetus and thus the role of OS as a mediator of prenatal maternal stress are not well understood. Maternal ROS cannot be transferred directly to the fetus due to their short half-life. Yet, in response to repetitive hypoxia-reoxygenation, the placenta generates large amounts of OS that can affect fetal neuron development *in vitro*. Further studies are required to determine whether psychosocial stress also leads to repetitive hypoxia-reoxygenation conditions in the placenta that induce ROS and consecutively affect fetal development *in vivo*. Several maternal cytokines including pro-inflammatory IL-6 are released during acute or chronic psychosocial stress. Animal studies show that cytokines are able to pass through the placenta and reach the fetus. This makes them potential candidates for transmitting maternal psychological stress to the fetus with potentially negative effects for the offspring. For example, maternal IL-6 appears to increase the risk for behavioural disorders and cardiovascular diseases in later life in the offspring. However, concerning human studies, only small cohorts have been analyzed and have generated ambivalent results regarding maternal-fetal cytokine transfer in the primate placenta. Amongst the mediators of maternal stress to the fetus, serotonin and its precursor tryptophan have recently attracted particular attention. Serotonin and tryptophan are released during psychological and physical stress. While maternal serotonin cannot pass through the placental barrier, it has recently been discovered that maternal tryptophan is converted into serotonin by the placenta during early, but not late, pregnancy and released into the fetal circulation. Since there is preliminary evidence derived from rodents that excess maternal serotonin levels during pregnancy are associated with behavioural problems in the offspring, placental conversion of maternal tryptophan into serotonin may contribute to the vulnerability of the fetus during early pregnancy to develop neuropsychiatric disorders after exposure to maternal stress. At this stage of fetal development, it is not very likely that increased maternal-fetal cortisol transfer solely mediates the programming effects of maternal stress because fetal GR are not yet expressed in relevant numbers and the fetal HPAA is silent. However, evidence for maternal-fetal stress transfer *via* tryptophan is currently based on rodent studies and verification of this stress-transfer mechanism in other species including humans is pending. The same is true for the newly hypothesized role of a stress-induced alteration in the maternal microbiota and its transmission to the fetus or newborn. Even though some promising results derived from rodents exist, the importance of this indirect stress transfer mechanism has to be determined and the translation into human population has yet to take place.

To summarize, direct maternal transfer of stress to the fetus by cortisol which crosses the placenta is supplemented by numerous other mediators, including catecholamines, ROS, cytokines and serotonin/tryptophan, which transfer maternal stress to the fetus directly or indirectly. However, we are only just beginning to understand the specific roles of the individual mediators, the vulnerable time-windows of the fetus to these mediators and the interactions amongst the mediators. In this highly dynamic field of research, even new stress transfer mechanisms such as the maternal microbiota have been proposed. For a better understanding, further investigations are required, especially in large animal models of human pregnancy and human cohorts.

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Declaration of interest

All authors report no conflict of interest.

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