Eur Child Adolesc Psychiatry (2014) 23:943–956
DOI 10.1007/s00787-014-0566-3

REVIEW

Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis

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Received: 8 March 2014 / Accepted: 19 May 2014 / Published online: 30 May 2014

Abstract Accumulating evidence from preclinical and clinical studies indicates that maternal psychosocial stress and anxiety during pregnancy adversely affect child outcomes. However, knowledge on the possible mechanisms underlying these relations is limited. In the present paper, we review the most often proposed mechanism, namely that involving the HPA axis and cortisol, as well as other less well-studied but possibly relevant and complementary mechanisms. We present evidence for a role of the following mechanisms: compromised placental functioning, including the 11β-HSD2 enzyme, increased catecholamines, compromised maternal immune system and intestinal microbiota, and altered health behaviors including eating, sleep, and exercise. The roles of (epi)genetics, the postnatal environment and the fetus are also discussed. We conclude that maternal prenatal psychosocial stress is a complex phenomenon that affects maternal emotions, behavior and physiology in many ways, and may influence the physiology and functioning of the fetus through a network of different pathways. The review concludes with recommendations for future research that helps our understanding of the mechanisms by which maternal prenatal stress exerts its effect on the fetus.

Keywords Prenatal stress · Anxiety · Child outcomes · Mechanisms · HPA axis

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Introduction

Research on both animals and humans is providing accumulating evidence that maternal psychosocial stress during pregnancy can have long-term effects on offspring development. This process is often referred to as fetal programming [1–3], because the effects are profound, long-term, and seem to be transmitted from the offspring to the next (grandchild) generation [4, 5]. Many reviews have described the role of prenatal stress in various outcomes (see below for details [6–11]). Less clear, however, is which mechanisms underlie the link between prenatal stress and negative child outcomes. The aim of this review is to provide a systematic overview of the possible mechanisms. We scrutinized the existing literature for all sorts of mechanisms that may explain the association between prenatal stress and adverse child outcomes. We start by describing the role of the HPA axis, and continue by discussing less well-known but potentially equally relevant pathways. These mechanisms are not necessarily proposed as alternatives to the HPA axis, but as additional mechanisms that may act in conjunction with, or as moderators or mediators of, the effects produced by the HPA axis (see Fig. 1). It is important to increase our understanding of the mechanisms involved because this will facilitate the study of possible adverse outcomes and contribute to developing strategies to prevent these outcomes.

Maternal prenatal psychosocial stress has been conceptualized as comprised of stressful situations (or just

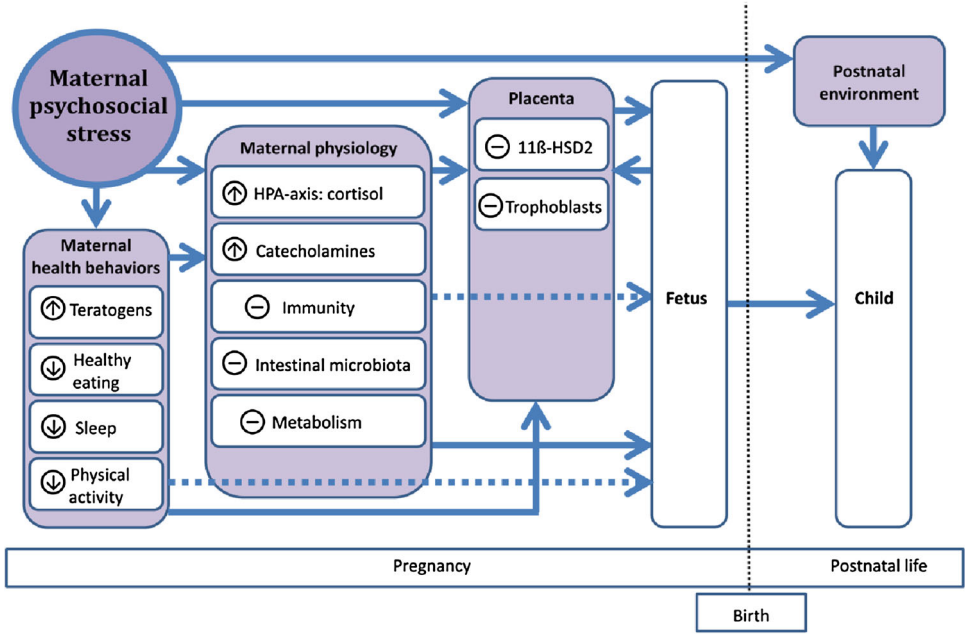

Fig. 1 An overview of the proposed mechanisms underlying maternal prenatal stress and child outcomes

stressors), perceptions or evaluations of these stressors (appraisals), and stress responses such as subjective experienced and expressed emotions [12, 13]. Research within this context has found links between child outcomes and maternal stress conceptualized at each of these levels, such as maternal stress after being exposed to a threatening and stressful situation during pregnancy (e.g., an ice storm or 9/11), or maternal stress based on self-reported measures of anxiety [14]. Another more specific component of prenatal psychosocial stress comprises emotional responses to the stressfulness of pregnancy itself, also referred to as pregnancy-specific stress [15]. Examples of pregnancy-specific stress are concerns about the health of the child and fear of giving birth. Although pregnancy-specific stress tends to co-occur with general pregnancy stress, it is often found to be a more powerful predictor of pregnancy and child outcomes [14, 16].

Throughout the review, we will use the term 'psychosocial stress' to refer to maternal general and pregnancy-specific stress and anxiety, mostly measured with self-reports of symptoms. Research carried out in populations with clinical mental disorders, including anxiety disorders, depression and post-traumatic stress disorders, has received less attention [17], and will be beyond the scope of this review. This review will also not discuss the mechanisms involved in the effects of prenatal depression on offspring outcome. Although there is co-morbidity between anxiety and depression and symptoms may overlap, the effects of prenatal depression on fetal development are to some extent different from those of prenatal stress and anxiety (see for a review [17]). Moreover, the underlying mechanisms linking prenatal depression to infant outcomes may also be different. For example, a role of low maternal serotonin levels is proposed in prenatal depression research [18].

Firm estimates for the incidence of prenatal psychosocial stress do not exist, but past studies suggest that a significant proportion of mothers experience stress during pregnancy [17]. Furthermore, taking into account that almost all the studies on prenatal psychosocial stress have been carried out in relatively highly stable Western countries with high economic resources, the incidence of prenatal psychosocial stress may be underestimated on a worldwide basis.

Prenatal psychosocial stress and offspring development

Animal models have provided ample evidence that stress in the pregnant female leads to a range of long-term effects in the offspring such as cognitive impairments, including decreased learning capacities and reduced attention, behavioral problems, including increased anxiety and depressed-like behavior, and immune and metabolic alterations (for reviews see 1 [19–21]). Furthermore, animal studies have made clear that maternal prenatal stress is related to changes in offspring brain structure and functioning, and that the effects may be transmitted from one generation to the next [3, 22]. Apparently, exposure to prenatal stress results in a general susceptibility to psychopathology, rather than exerting a direct effect on a specific form of psychopathology [15].

Many studies in humans have also found links between maternal prenatal stress, and perinatal and postnatal offspring outcomes. As many reviews have extensively described the effects of prenatal stress and offspring development, we only shortly summarize the findings here. The most commonly

studied infant outcomes as a possible consequence of prenatal psychosocial stress are preterm birth and low birth weight. Psychosocial stress and anxiety in pregnancy are found to be related to shorter gestations and lower birth weights [17]. Pregnancy-specific anxiety appeared to be an especially potent risk factor for low birth weight. Similar conclusions were reached by Shapiro and colleagues [23] showing that most studies found moderate effect sizes for preterm birth and that subjective stress and pregnancy-specific anxiety appeared to be the factors most closely associated with preterm birth.

Other physical infant outcomes related to prenatal psychosocial stress include a decrease in gray matter density in the brain [24] and possible effects on orbitofrontal cortex functioning [25]. In addition, severe psychological stress during pregnancy has been related to obesity and metabolic dysfunction in the offspring (for a review, see [26]).

Behavioral outcomes in the offspring of prenatally stressed mothers include emotional or cognitive problems for the child with the effects persisting at least into adolescence [11, 27]. Behavioral outcomes in the form of Attention Deficit Hyperactivity Disorder (ADHD)-related behavior and increased anxiety have been observed [28, 29]. A recent meta-analysis concludes that there is a modest association between maternal prenatal psychosocial stress and cognitive outcomes [30]. Severe adversity during pregnancy may increase the risk to psychotic and depressive disorders in the offspring [31, 32].

Mechanisms

Maternal HPA axis and cortisol

The most important mechanism to explain the relations between maternal prenatal psychosocial stress and child outcomes is the hypothalamic–pituitary–adrenal axis (HPA axis), with its end product cortisol. When the mother is exposed to stress, the HPA axis is activated, resulting in the release of multiple hormones, including cortisol [16]. Fetuses need cortisol for various aspects of brain development and late gestational lung maturation [22, 33]. Nevertheless, exposure to high cortisol concentrations in utero is thought to compromise fetal behavioral, immunological and brain development [34]. Specifically, the prefrontal cortex, hippocampus and amygdala seem to be affected by cortisol. These are in particular the brain areas associated with executive functioning, emotion regulation, attention, memory and fear [35], and these brain areas also regulate the HPA axis. Problems associated with these brain areas and with the regulation of the HPA axis are among the adverse offspring outcomes that can be expected as a result of prenatal psychosocial stress [36].

There are multiple ways through which heightened cortisol levels in the mother can result in heightened cortisol levels in the fetus. For instance, increased maternal cortisol concentrations may be directly transported across the placenta and enter the fetal circulation. It has been found that maternal cortisol accounts for about 40 % of the variance in fetal cortisol concentrations [37]. Also, increased maternal cortisol concentrations may lead to an increased production of placental CRH [38]. Placental CRH concentrations have been related to decreased fetal growth and size at birth [39]. The placenta synthesizes and releases CRH in large amounts into the maternal and fetal circulations. Placental CRH stimulates the fetal HPA axis, resulting in increased levels of fetal cortisol [38].

The hypothesis that prenatal psychosocial stress programs the offspring via heightened cortisol concentrations is supported by animal research. For example, administering dexamethasone (synthetic glucocorticoids) to pregnant rats in the last week of pregnancy reduced birth weight by 10 % and potentiated glucose responses to exogenous corticosterone [40]. In pregnant sheep that were infused intravenously with saline, dexamethasone, or corticosterone for 2 days from 26 to 28 days of gestation, corticosterone, but not dexamethasone, treatment caused fasting hyperglycemia in adult male offspring [41]. Next to offspring growth and glucose tolerance [40, 41], the HPA axis also appeared to be affected. When nonhuman primates (African vervets) were given oral doses of dexamethasone from mid-term, offspring of mothers that received the highest dose of dexamethasone showed an exaggerated corticosterone response to mild stress [42]. Together, these studies show that administration of exogenous dexamethasone or corticosterone to pregnant animal mothers is related to diminished growth, increased HPA axis reactivity and glucose intolerance in the offspring. Markers of maternal HPA axis functioning, including the cortisol circadian rhythm, have also been related to human offspring outcomes. For example, in our own studies, we found that the maternal prenatal cortisol awakening response (CAR) during the third trimester predicted cortisol and behavioral responses to a repeated stressor in 9-month-old infants [43]. In addition, a flattened diurnal cortisol rhythm and higher evening cortisol during pregnancy were related to more respiratory illnesses and skin illnesses, respectively, in infants during their first year of life [44].

We now know that adverse fetal programming may occur as a result of exposing the mother to psychosocial stress not only late in pregnancy, but also very early in pregnancy, before the brain or neuroendocrine systems have developed [45, 46]. Although cortisol could affect the migration of brain cells, exposure to heightened cortisol concentrations in utero is not likely to be directly responsible for the programming effects on the fetal brain and

neuroendocrine systems in early pregnancy [47]. Moreover, human fetuses are relatively protected from higher maternal cortisol concentrations. During pregnancy, the HPA axis of women responds less to stress compared that during non-pregnancy, affording the fetus some protection from elevated maternal glucocorticoids [48, 49]. In addition, fetuses are also protected from higher maternal cortisol concentrations by the placental enzyme 11β-hydroxysteroid dehydrogenase-type 2 (11β-HSD2). This leaves the question how the programming effects of psychosocial stress early in pregnancy can be explained, as well as how increased maternal cortisol concentrations can reach the fetus. The answer to these questions may be that exposure to prenatal psychosocial stress impacts placental functioning, including the 11β-HSD2 enzyme [47].

The placenta and the 11β-HSD2 enzyme

The placenta is a mammalian adaptation to facilitate in vivo gestation and it has diverse functions ranging from nutrient and oxygen transport to complex neuroendocrine signaling. There is a general sense that the placenta is understudied, while it could be an important window for understanding the mechanisms underlying fetal programming [50]. One placental function of critical importance is the protection of the developing fetus from maternal environmental insults. The placental 11-β hydroxysteroid dehydrogenase-type 2 (11β-HSD2) enzyme, for example, prevents the majority of maternal cortisol from crossing the placenta by converting cortisol to the inactive cortisone. Hereby the fetus is protected from heightened maternal cortisol concentrations [33, 51].

Animal models show that maternal prenatal stress can affect placental functioning, including 11β-HSD2 enzyme expression and activity [22, 52]. A study in rats found that chronic maternal restraint stress inhibits the capacity to up-regulate 11β-HSD2 activity in the face of an acute stressor [53]. While immediate up-regulation of 11β-HSD2 enzyme activity may protect the fetus against high levels of maternal glucocorticoids, exposure to chronic stress apparently diminishes this protection. A recent human study also suggests that maternal prenatal anxiety may increase the permeability of the placenta to cortisol by causing a down-regulation of the 11β-HSD2 enzyme, allowing more cortisol to cross from the maternal to fetal blood [54]. However, this human study was limited by a relatively small sample size, and the mothers were recruited the day before delivery by elective cesarean section, increasing the urge for replication and further investigation of the 11β-HSD2 enzyme in humans.

In case the activity of the 11β-HSD2 enzyme is compromised by maternal psychosocial stress early in gestation, the reduced activity of the enzyme may continue throughout pregnancy. This may explain how, even in the absence of maternal stress for the rest of the pregnancy, the down-regulation of the 11β-HSD2 enzyme allows for more cortisol to cross from the maternal to fetal blood later in gestation, hence affecting the developing fetal brain and HPA axis [47].

So far we have discussed that prenatal psychosocial stress might be related to heightened maternal cortisol levels or down-regulation of the 11β-HSD2 enzyme, resulting in increased fetal cortisol concentrations. In turn, heightened cortisol concentrations of fetuses are thought to affect their later behavioral, immunological and brain development [34]. In addition, prenatal heightened cortisol concentrations might also impact other placental functions, such as the regulation of placental glucose transporters. Altered placental glucose transport from the maternal to fetal compartment, as a possible result of heightened maternal cortisol concentrations, has been related to fetal growth retardation and adult diabetes [33, 55].

Despite the clearly important role of cortisol in fetal programming, there are multiple indications that the associations between maternal prenatal psychosocial stress and offspring outcome may be explained or complemented by other mechanisms than cortisol physiology. For example, the number of empirical studies that found significant associations between prenatal maternal cortisol and child outcomes is small [56]. Of the 27 reviewed studies, 76 % of all the statistical analyses performed in these studies did not find a significant association between prenatal maternal cortisol and child outcomes (including health, cognitive, behavioral and cortisol outcomes). Moreover, maternal reports of psychosocial stress tend to be only weakly related, or even unrelated, to heightened maternal cortisol or a flattened cortisol rhythm, and prenatal psychosocial stress often independently predicts infant outcomes irrespective of maternal cortisol markers [44]. These findings raise the possibility that other mechanisms explain or complement the cortisol explanations underlying the link between maternal prenatal psychosocial stress and infant outcomes.

Catecholamines

Next to the HPA axis, the sympatho-adrenomedullary (SAM) system is important for maintaining or reinstating homeostasis during stress. Activation of the SAM system represents the classic ‘fight or flight’ response and is also known as the sympatho-adrenal response. When confronted with stress, secretion of catecholamines is activated, including adrenaline (epinephrine) and to a lesser extent noradrenaline (norepinephrine). Adrenaline is often associated with an acute stress response and reactivity, whereas noradrenaline is released to balance or down-regulate the stress response [57].

In humans, only few studies assessed the relation between maternal catecholamine concentrations during pregnancy and infant outcomes. One study, for example, found that higher levels of maternal adrenaline concentrations during late pregnancy were associated with lower infant soothability, whereas higher levels of maternal noradrenaline were related to higher infant soothability and lower distress to novelty [58].

At the same time, no correlation was found between maternal prenatal catecholamine concentrations and maternal reports of prenatal stress, anxiety, or life events. Similarly, Petraglia and colleagues [59] found no relation between psychosocial stress and catecholamine levels in pregnant women at 28 weeks gestation. In addition, pregnancy does not seem to alter noradrenaline concentrations in response to thermal stress, while the adrenaline concentrations increased the most in pregnant women who felt discomfort during or after the exposure [60]. As there are only a few studies available, it might be too early to conclude whether maternal prenatal catecholamine concentrations are related to psychosocial stress. Moreover, the findings to date warrant carrying out future research on the relationship between prenatal catecholamine concentrations and offspring outcomes [58].

Catecholamines may influence both placental and fetal units. Increased concentrations of catecholamines in maternal blood lead to constriction of placental blood vessels, decreasing fetal supply of nutrients and oxygen, and activating fetal catecholamine release [61]. Most of the catecholamines in the placenta are metabolized by the enzymes monoamine oxidase and catechol-*O*-methyltransferase [62]. Nevertheless, several studies report that small amounts of unmetabolized catecholamines are transferred from the maternal to the fetal side of the human and guinea pig placentas, subsequently altering the fetal development ([63–65], for a review see also [66]). Offspring exposed to high catecholamine concentrations may be programmed in utero to become highly reactive to stimuli in their postnatal environment, altering their reactivity to stressful and novel events [58]. Indeed, animal models of sympathetic stimulation via hormone injection have provided evidence that catecholamines affect fetal development and offspring outcomes as suggested [58]. On the contrary, another human study suggests that noradrenaline does not cross the placenta. When fetal and maternal plasma noradrenaline responses to invasive procedures were measured in pregnancy, no correlation was found between maternal and fetal noradrenaline levels [67].

Maternal immune system and health

Another mechanism by which prenatal psychosocial stress could have effects on child development is by affecting the maternal immune system and health. Chronic stress is related to a less well-functioning immune system, higher susceptibility for infections, and generally lower quality of physical health (e.g., [68–70]). Psychosocial stress has also been related to unbalances in the intestinal microbiota, and related gastrointestinal conditions, such as irritable bowel syndrome [71, 72]. Abnormalities in both maternal immunity and maternal intestinal microbiota may affect fetal and neonatal development.

Maternal immunity

Stress has complex effects upon immunity that depend on time and severity of the stressors [73]. In general, temporary stressors of a mild to moderate nature enhance immunity, while later phases of the stress response have immunosuppressive effects, returning immune function to baseline. If the stress becomes chronic, immunosuppression can be severe enough to compromise defenses against infectious agents. Contrarily, if the immunosuppression of the later phases of the stress response fails to take place, this can increase the risk for immune overactivity or autoimmune diseases.

Chronic prenatal stress may therefore affect the maternal immune status, leading to increased vulnerability to infections. Intrauterine inflammation as a consequence of a bacterial infection is one of the most important causes of premature delivery (approximately 25–40 % of all preterm births [74]). Also, maternal prenatal infections with Toxoplasma gondii, influenza or herpes simplex viruses have been related to severe neuropsychiatric and neurodevelopmental disorders in the offspring, such as schizophrenia, autism, and psychosis [33]. These effects are thought to be mediated through increased maternal levels of pro-inflammatory cytokines which may act on the placenta or directly cross the placenta into the fetal compartment. And indeed, psychosocial stress has been found to alter cytokine production across pregnancy. Studies have found elevated stress scores to be positively related with higher levels of the pro-inflammatory cytokines IL-6 and with low levels of the anti-inflammatory cytokine IL-10 [75]. These relations were evident both early and late in pregnancy [75, 76].

Little is known over how pro-inflammatory cytokines may affect the developing human fetal brain, but data from rodent studies suggest a very negative impact [77]. In theory, both glucocorticoids and cytokines during sensitive developmental windows may have a programming impact on the structure and function of the brain, as well as those of peripheral organs and tissues related to body composition, energy balance homeostasis and metabolic function [26].

Maternal prenatal stress may also have an impact on the transfer of passive immunity to the offspring [66]. In

rodents and primates, IgG antibodies are transferred to the fetus through the placenta, and evidence has been found in animal models that this transfer is affected, sometimes in a sex-specific manner, in fetuses of prenatally stressed mothers. However, maternal stress only appears to play a role if the stress period covers the end of gestation, which corresponds with the period of active transplacental transfer of maternal IgG [78].

Finally, chronic or long-lasting maternal prenatal stress may also produce immune alterations in the offspring. For example, one study compared the cytokine production between healthy young women whose mothers experienced major negative life events during their pregnancy ($N = 34$) and a female comparison group ($N = 28$). A bias for T-helper 2 (Th2) cytokine production due to an overproduction of IL-4 relative to IFN-gamma was observed in the women from prenatally stressed mothers. In addition, IL-6 and IL-10 were also significantly elevated [79]. According to Merlot [66], there are several potential mechanisms through which maternal prenatal stress can produce immune alterations in the offspring. These would include direct effects, e.g., by affecting the ontogeny of immune cells, or more indirect effects, such as those produced by a deregulated fetal HPA axis. An altered HPA functioning could affect the offspring's neuroimmune communication, and could accelerate the fetal gut maturation which in turn may lead to an impaired immunoglobulin acquisition after birth. Finally, an altered fetal HPA functioning is thought to compromise fetal behavioral, immunological and brain development (see Sect. 2.1).

Maternal intestinal microbiota

Maternal prenatal stress may affect the child by means of a more indirect mechanism, namely through effects on the neonate's colonization of the gut by microbiota. Infants are born with virtually sterile intestines, and within hours the colonization by bacteria begins [80]. A rapid, diverse, and balanced colonization of the neonate's intestines is important for establishing a rich intestinal ecosystem that will perform vital functions in the child's future development, with effects reaching far into adulthood [81]. Importantly, the intestinal microbiota plays a pivotal role in the development of the child's immune system, and hence in the child's early and future health [82]. Also, it has recently become clear that the intestinal microbiota, by means of the gut–brain axis, influences brain development and behavior [83, 84]. In mice, for example, chronic treatment with a lactic acid bacteria *Lactobacillus rhamnosus* induced region-dependent alterations in the brain in GABA receptor expression with increases in cortical regions and reductions in the hippocampus and amygdala. Moreover, treatment with Lactobacillus rhamnosus also reduced anxiety- and depression-related behavior in the mice [85].

But how could maternal prenatal stress affect the infant's intestinal colonization by microbiota? The explanation is that the mother is the main source of microbiota for an infant. Already in the prenatal phase, maternal intestinal bacteria may travel through the blood stream to the amniotic fluid. This fluid is regularly swallowed by the fetus, hence possibly providing the fetal intestines with the first bacteria [80, 81]. However, evidence for this proposed transfer of intestinal bacteria from the mother to the fetus is as yet scarce or originates from animal models [86, 87], and in any case, a neonate's meconium displays relatively low diversity in bacterial species [88]. In children delivered vaginally, the first major source of microbiota is encountered during the delivery, when the infant comes into contact with maternal vaginal and fecal microbiota. Indeed, a strong mother–infant association has been observed in fecal microbiota in the first 6 months after delivery [89].

Therefore, the quality of the maternal vaginal and intestinal microbiota will be of utmost importance in the initial phase of colonization and possibly even have long-term consequences for the infant's development and health [90]. As mentioned above, psychosocial stress is related to immune deficiencies and to unbalances in intestinal microbiota. It follows that pregnant women suffering from high levels of prenatal stress may have unbalances or (subclinical) infections in their vaginal or intestinal microbiota. During delivery (and perhaps already during pregnancy), mothers will transfer these microbiota to their infants, providing them with a non-optimal basis for intestinal colonization [80].

To date these ideas are highly speculative as there is as yet no evidence in humans for relations between maternal prenatal stress, and maternal and infant intestinal microbiota. However, the results of a study by Bailey and colleagues [91] in rhesus monkeys are in line with this proposed mechanism, as they found negative effects of prenatal maternal stress on the offspring's intestinal microbiota (especially if the stress was in late pregnancy). Moreover, lower diversity and stability of infant microbiota during the first weeks of life, as well as specific bacterial signatures, have been related to excessive crying or colic [88, 92]. To date, increasing importance is allocated to the role of intestinal microbiota in the development of health and behavior [83, 84]. The fact that the links between maternal prenatal stress and infant microbiota have yet to be determined in humans, should not deter future researchers from investigating this promising area. The maternal intestinal microbiota may very well turn out to be one of the major factors mediating the observed relations between maternal stress during pregnancy and the offspring's health, behavior, and development.

Lifestyle and health behaviors

Pregnant women who are highly stressed may have adverse lifestyle habits or health behaviors that can adversely affect their offspring. For instance, psychosocial stress during pregnancy has been related to changes in prenatal maternal behaviors, including smoking, alcohol and other substance use [93, 94]. Often, prenatal stress research takes cigarettes, alcohol and other substance use into account, as these factors could confound the relationship under study. Pregnant mothers might be excluded from participation, or the study statistically controls for smoking, alcohol and other substance use [26]. Nevertheless, if psychosocial stress indeed leads to substance use during pregnancy, subsequently resulting in adverse child outcomes, the role of prenatal psychosocial stress might be underestimated by controlling for these adverse health behaviors. Mediation or path analyses could help to shed light on not only the direct effects, but also indirect effects, of prenatal psychosocial stress on infant outcomes. For example, Lobel et al. [94] found that pregnancy-specific stress contributed directly to preterm delivery and indirectly to low birth weight through its association with smoking. Other health behaviors that are often associated with psychosocial stress, including (emotional) eating, sleep and physical activity, are often less well controlled for and might also account for the impact of prenatal psychosocial stress on child outcomes.

Eating

Psychosocial stress contributes to unhealthy eating [95], also during pregnancy [96]. For example, pregnant women who reported higher levels of psychosocial stress ate more food overall and consumed less folate, possibly due to decreased fruit intake [96]. Another study found that pregnancy-specific stress was associated with unhealthy eating, and inversely associated with healthy eating and vitamin use [94]. Many nutrients are known to have prenatal effects of the fetus, for example on the developing brain (for a review, see [97]). Unhealthy eating and a lack of proper nutrients needed in pregnancy might therefore be related to adverse child outcomes. Next to the possibility that prenatal psychosocial stress is related to unhealthy eating, some nutrients also play a role in stress responses and/or their metabolism may be altered by stress (for a review, see [98]). For example, psychosocial stress promotes protein breakdown which has an impact on the nutrient status of the mother, and consequently of the fetus [98]. Taken together, stress-induced maternal unhealthy eating and stress-induced changes in the metabolism of nutrients during pregnancy can have effects on fetal development. Nevertheless, hardly any studies have simultaneously studied maternal eating behavior and psychosocial stress during pregnancy [98].

Sleep

Sleep disturbances are a common complaint of pregnant women [99] and the literature is acknowledging the role of disturbed sleep in adverse outcomes more and more, including in preeclampsia, labor duration, preterm birth and impaired glucose metabolism [100, 101]. Sleep disturbances during pregnancy are also associated with perceived stress. For example, early in gestation, women who are sleep deficient report more perceived stress than those who are not sleep deficient [101, 102]. Disturbed sleep affects several biological pathways, including neuroendocrine, metabolic, and inflammatory systems. As proposed by Okun et al. [103], inflammatory activation, as a result of sleep disturbances, could account for adverse pregnancy outcomes. One mechanism by which inflammation may increase adverse pregnancy outcomes is by interfering with normal trophoblast invasion [103]. Trophoblasts are specialized cells of the placenta, formed early in gestation, that play an important role in embryo implantation and provide nutrients to the embryo. Despite the necessity of a dominant pro-inflammatory profile for early pregnancy success [104], heightened inflammatory activation would interfere with normal trophoblast invasion [103]. This was shown by in vitro experiments in which cytokines were observed to inhibit trophoblast invasion [105, 106].

Other pathways linking sleep disturbances to offspring outcomes can also be hypothesized. For example, one night of restricted sleep was found to reduce morning cortisol concentrations, elevate afternoon/evening cortisol area under the curve concentrations, and decrease the diurnal decline in cortisol concentrations in non-pregnant young women [107]. If similar neuroendocrine processes take place in pregnant women, disturbed sleep might be related to altered cortisol physiology resulting in adverse child outcomes (see Sect. 2.1). The role of sleep during pregnancy, its associated biological mechanisms, and the impact on child outcomes are just beginning to be understood. Maternal sleep during pregnancy and its relation to maternal psychosocial stress, definitively merit more research efforts in the future.

Physical activity

Physical exercise, ranging from aerobics to yoga, can have effects on both maternal and fetal health (for a review, see [108]). It seems that moderate exercise increases functioning of the placenta and birth weight, but only if exercise is decreased in late pregnancy. Nevertheless, Field [108] warrants that more research and controlled trials are

needed before recommendations can be made about the amount, type and intensity of physical exercise during pregnancy. Interestingly, Lobel et al. [94] found that pregnancy-specific stress was associated with less physical activity and exercise. The most frequently suggested mechanism for the hypothesized positive effects of prenatal exercise is the opioid theory (for a review, see [109]), suggesting that exercise increases endorphin levels. It is also suggested that exercise decreases cortisol concentrations and enhances the production of serotonin, leading to less maternal sleep disturbances [110] and reduced maternal depression [111]. Indeed, positive effects of physical exercise on psychological wellbeing have been shown in pregnant obese women [112].

In sum, changes in health behaviors, including eating, sleep and physical activity, as a result of prenatal psychosocial stress can contribute to pregnancy complications, poor offspring health outcomes and/or alterations in offspring development [113–117]. This provides a basis for proposing that these health behaviors could at least partly account for the relations found between maternal prenatal psychosocial stress and child health outcomes.

Genetic transmission and epigenetics

In the human prenatal stress research, most studies are not genetically informed. It is therefore not possible to exclude the possibility that at least some of the child outcomes considered are in fact the result of shared underlying genes. Mothers and their infants share 50 % of their genome, and maternal reports of high levels of prenatal stress and anxiety may be indicative of certain genetic predispositions that are linked to the behavioral outcomes observed in the offspring. This mechanism is called gene–environment correlation. It could lead to erroneous conclusions as to the effects of prenatal stress on child outcome, since the driving force might be the transmission of risk genes from the mother to her child rather than the effect of prenatal stress per se. For example, genetic variations in serotonin signaling genes are closely linked to the regulation of emotions, and more specifically to anxiety and depression (e.g., [118, 119]), and may therefore at least partly explain links between maternal prenatal stress and child internalizing behavioral problems. The results of a recent study using a genetically informed design are illuminating. This 'prenatal cross-fostering' design included both pregnant mothers who were related or unrelated to their child as a result of in vitro fertilization (IVF). As such, this allowed to disentangle maternally inherited from environmental influences. Prenatal stress appeared to have similar associations with offspring birth weight, gestational age and antisocial behavior in both related and unrelated mother–offspring pairs, indicating these being environmental links. In contrast, prenatal stress was linked to offspring attention deficit hyperactivity disorder only in related mother–offspring pairs, reflecting the transmission of risk genes. Finally, the effect of prenatal stress on offspring anxiety appeared to be due to postnatal maternal anxiety and depression rather than prenatal stress [120]. Another way of distinguishing prenatal environmental versus genetic influences on offspring, is by comparing children of discordant identical (monozygotic) or fraternal (dizygotic) female twins [36]. In sum, child outcomes in studies of maternal prenatal stress can be attributed both to inherited genetic factors and to stress in the prenatal environment, and there are study designs that help distinguish between both. It is beyond the scope of this review to go further into the subject of genetic transmission, but it is important that researchers take the role of genes into account when looking into the mechanisms by which maternal prenatal stress may affect the offspring.

The molecular basis for the mechanisms described in Sect. 2, as possible mediating links between maternal prenatal psychosocial stress and offspring outcome, would involve changes in the activity of the DNA. Functional changes in DNA expression that do not involve changes in the nucleotide sequence of the genome are called epigenetic changes. These epigenetic changes consist of alterations in the physical structure and chemical properties of the DNA, and hence gene expression [121]. Examples of epigenetic effects on the DNA are histone acetylation and DNA methylation. The first is related to greater levels of gene transcription, and the second to silencing of the gene expression [122]. Studies in animals and humans have found evidence that maternal prenatal stress influences the activity and gene expression of the 11β-HSD2 enzyme through epigenetic changes ([22, 123], see also Sect. 2.2). In animals, maternal prenatal stress has been related to epigenetic changes in the offspring brain [22, 124]. Very probably, most of the offspring outcomes that are attributed to fetal programming by maternal psychosocial stress would be the result of epigenetic cellular mechanisms.

Postnatal environment

The effects of the environment on the development of the offspring do not stop at delivery. The early postnatal environment will naturally also play an essential role in child development, and the effects of prenatal and postnatal factors are often difficult to disentangle in human studies. For example, it is plausible that in many cases prenatal psychosocial stress foreshadows the quality of the postnatal environment [125, 126]. Women that are highly stressed or anxious during pregnancy are more likely to be so also

during the postpartum period, possibly compromising family functioning or parenting quality [36, 127]. On the other hand, positive (psychosocial) factors in the postpartum environment may exert effects on offspring development that modify those of the prenatal environment. For example, in animal studies, enrichment of the rearing environment can have compensatory effects on the effects of maternal prenatal stress [128, 129].

The relevance of controlling for postpartum stress and anxiety becomes clear when studies report their findings before and after controlling for maternal postpartum symptoms. For example, the Generation R study recently showed that antenatal maternal anxiety and depression were no longer associated with child attention problems, when adjusting for maternal symptoms after giving birth [130]. Further, as already described above, the effect of prenatal stress on offspring anxiety was explained by postnatal maternal anxiety and depression rather than prenatal stress [120]. Nowadays, many human studies on maternal prenatal stress and anxiety statistically control for postpartum symptoms, and the findings for maternal prenatal stress are often found to be independent of a diversity of perinatal and postnatal potential confounding factors [44, 126]. Nevertheless, there is no clear guidance for what to control for when conducting prenatal stress research. Moreover, the role of prenatal psychosocial stress might be underestimated by controlling for diverse perinatal and postnatal factors (see also Sect. 2.5).

Until recently, the predominant view held that prenatal stress impairs child development. From an evolutionary perspective, however, it has been suggested that the fetal programming effects seen as a result of prenatal stress constitute adaptations to the postpartum environment that will be most likely encountered [131]. Only in the case of a mismatch, when the prenatal environment does not adequately reflect the postnatal environment (i.e., prenatal environment with stress and a postnatal environment without stress or vice versa), more child health and behavioral problems are expected. Otherwise, prenatal stress might equip the child with a cognitive, behavioral and immunological repertoire to best handle a stressful postnatal environment.

Role of the fetus

In the mechanisms described before, we have left out the hypothetical role of the fetus in his/her own programming. There are indications that the fetus can play an active role in programming mechanisms. For example, by playing a role in the timing of birth, the fetus may be limiting the time and extent to which the maternal and placental compartments can directly program the fetus. According to Pike [132], the fetus will receive maternal cues signaling a stressful internal environment. For example, when maternal stress is induced by means of the Stroop color–word task or an arithmetic task, both mothers and their fetuses respond to the manipulation with increased heart rate levels [133, 134]. In cases where the fetus is chronically receiving signals of a stressful environment, the fetus may then initiate a number of compensatory responses that may include accelerated organ maturation and decreased growth. Although these measures will increase survival chances in a resource-limited intrauterine environment in the short-term, they may often be accompanied by long-term costs to health. In extreme cases in which the responses are unsuccessful and the environment remains insufficient, the fetus may initiate an endocrine cascade leading to parturition, hence permitting early expulsion from the stressful environment. Pike [132] argues that although the costs of preterm birth are potentially high for both mother and fetus, the timing of parturition will always represent a compromise between maternal and fetal strategies and conditions.

Complicating matters more, the fetal adaptations to stress in the prenatal environment would vary according to fetal sex. According to Clifton [135] the placenta functions in a sex-specific manner. When glucocorticoid levels rise in the mother, the functional adaptations in genes, proteins and steroid metabolism will depend on the sex of the fetus. These differences in strategies for coping with environmental adversity would result in continued growth but with greater susceptibility to later stress in male fetuses and a decrease in growth with greater probability of survival in female fetuses. These sexually dimorphic mechanisms could be programming sexually specific patterns of stress responses very early in fetal development [136]. Moreover, they may also help explain why maternal prenatal stress appears to program males differently than females, for example by affecting their central HPA axis control mechanisms more [47]. For an evolutionary explanation on why these differences in male–female prenatal programming may confer adaptive advantages to the sexes see Glover and Hill [137].

In sum, fetal programming events will likely involve complex interactions between the maternal physiology, the placenta, and the developing fetus, as well as exacerbating factors such as fetal sex and gestational stage of development [33]. The notion of sex-specific prenatal programming should be incorporated to all future research on the subject.

Conclusions

Research has come a long way in describing relations between maternal prenatal psychosocial stress and child

outcomes. Nonetheless, the main conclusion to be drawn from the present review is that there still is a long way ahead in determining the mechanisms through which the maternal environment would exert programming effects on the fetus. Even for the mechanism that is most often brought forward as underlying empirical findings, the hormone cortisol and the HPA axis, it is clear that many questions remain.

The fact that maternal self-reports of psychosocial stress are often weakly related or even unrelated to maternal cortisol markers of psychosocial stress, raises two possible explanations. First, the validity of both the self-report measures and the cortisol markers can be questioned. Self-report measures are subject to problems of recall and social desirability. Future research might therefore consider other ways, or complementary ways, to assess maternal psychosocial stress. Possibilities include making use of partner reports of maternal stress symptoms, carrying out observations of maternal stress-related behavior during challenge tests, and using indirect or implicit psychological measures to determine maternal stress and anxiety. In addition, cortisol markers are often based on one or a few samples and may not accurately reflect the dynamics of cortisol physiology. Longitudinally sampling over the course of pregnancy, and obtaining sufficient cortisol samples over multiple days, will help provide better measures. We also recommend the exploration of the use of experience sampling methodology in prenatal stress research. Ambulatory assessment of daily stressors and subjective variables, including stress and anxiety, followed by saliva cortisol samples taken approximately 20–30 min after the subjective assessments, might provide more insight in the relation between stress and HPA axis functioning during pregnancy. In this context, it is important to note that one of the problems associated with pregnant women's ambulatory cortisol sampling is that of compliance. Lack of compliance in the timing and methods of saliva collection may profoundly influence the outcomes of studies, and when possible measures should be taken to improve compliance [138].

Second, the explanation for the lack of a strong relation between self-report and cortisol measures might be that elevations in basal cortisol are not the only or the most important physiological manifestation of maternal stress during pregnancy. By focusing almost exclusively on cortisol, we may be trying to over-simplify a network of physiological processes into simple correlations. During the non-pregnant state, the functioning of the stress system is already complex, with physiological processes intertwined with many other bodily systems such as the immune system and the gut–brain axis. During pregnancy, physiological stress systems and endocrine control mechanisms are modified [4]. Also, the placenta, which can be seen as a transient neuroendocrine system, plays an essential role during pregnancy and is regulated by both the mother and the fetus [4]. Pregnancy might thus complicate the functioning of the stress system even further and prenatal maternal stress and anxiety will therefore be translated into physiological changes that may be different from those of the non-pregnant state. Furthermore, prenatal stress might affect maternal behavior (e.g., substance use and sleeping problems) in ways that may produce other physiological changes and programming effects on the fetus without there being a strong correlation between maternal reports of stress and cortisol. Finally, different types of maternal psychosocial stress, such as general stress versus pregnancy-specific stress, might lead to the involvement of different underlying mechanisms, and in turn, to different outcomes. Combinations of psychosocial stressors during pregnancy have also received little attention to date, but may of course have different effects [17].

In this paper, several possible mechanisms were reviewed that may act in conjunction with the maternal HPA axis. We propose that these mechanisms influence each other, for instance by provoking chain reactions, and also that these mechanisms can have independent effects on the fetus. For example, in the case of malnutrition, the activity of the HPA axis of the mother will increase and over time this will have a negative effect on maternal immunity. The effects of maternal malnutrition on the fetus will then be double: through fetal malnutrition as well as through a lower passage of passive immunity from the mother to the fetus [139].

Looking at alternative, possibly complementary mechanisms, by which maternal prenatal stress may program the fetus is essential for bringing the field of fetal programming a step further. Up till now, we mostly focused on the HPA axis, which albeit its importance, may perhaps be better approached in a more adequate manner by investigating it in combination with the additional possible mechanisms proposed in this review. This approach may require larger study populations (e.g., combined efforts of different research groups) and more sophisticated statistical analyses, but could open the door to a richer knowledge and new insights. As argued by Entringer [26], to systematically study the programming effects of prenatal stress and its underlying mechanisms, a multilevel approach is necessary that includes molecular and cellular studies, animal model studies, and well-designed human studies. One direction for these human studies would be the investigation of (epi)genetic processes responsible for the fetal programming effects seen by collecting genotypes of mother and child.

As stated before, the incidence of prenatal psychosocial stress may be greatly underestimated on a worldwide basis. An improved understanding of the mechanisms by which

maternal prenatal stress programs the fetus will provide essential information for the development of effective, individually and culturally tailored interventions. In turn, these interventions may provide substantial health, well-being and economic benefits for generations to come.

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