Introduction

Birth is often viewed as the moment where a child becomes aware of the world and people often think that experiences before birth have no influence on later life development. However, accumulating research has shown that this is not the case: experiences during the first nine months of our life can shape later life health and wellness. Researchers found that there are persisting changes in the body structure and function of the fetus that are caused by environmental stimuli, such as maternal nutrients, toxins and hormones. They referred to this process as ‘fetal programming’. More and more research finds evidence for fetal programming, both in animal and human research.

A good example of fetal programming is the Dutch Hungerwinter of 1944, a period during World War II of severe famine. Pregnant women had to survive on about 400-800 calories a day for a couple of months. Adults that were conceived during the famine now show an increased risk for all kinds of diseases, such as coronary heart disease, diabetes, obesity, but also depression, addiction and schizophrenia (e.g., Franzek et al 2008, Kahn et al 2009). The detrimental effects of the famine are most profound when the exposure to nutrient restriction took place in the first trimester of pregnancy.

Nowadays, it is common knowledge that drinking (alcohol) and smoking during pregnancy are bad for the unborn child. Most mothers also know that they should avoid some specific foods and should eat more of other certain foods. However, less is known about the influence of environmental pollutants and maternal psychological wellbeing on the child.

In this module, the following questions will be answered:

1. How can maternal behavior, wellbeing, and environment during pregnancy influence child development?
2. What is the influence of prenatal exposure to maternal diet on child development?
3. What is the influence of prenatal exposure to alcohol consumption and smoking on child development?
4. What is the influence of prenatal exposure to environmental pollutants on child development?
5. What is the influence of prenatal exposure to maternal psychological state on child development?
6. What are the implications of these studies for the care for pregnant women?

Mechanisms of fetal programming

For nine months, mother and fetus share a body. During these nine months, the fetus is exposed to everything the mother eats, drinks and experiences. How
From the Womb into the World: an Introduction to Fetal Programming

these maternal nutrients, toxins, and hormones exactly ‘program’ the fetus and cause cognitive and mental health issues later in life, is still not completely understood by scientists. Most likely it is an interaction of several mechanisms acting together in a complex way. Here, we discuss three of the most prominent and often-proposed mechanisms from animal and human science: the hypothalamic-pituitary-adrenal (HPA-)axis, the placenta, and epigenetics.

**HPA-axis.** The most often proposed mechanism is the involvement of the hypothalamic-pituitary-adrenal (HPA-)axis and its end product cortisol – the so-called “stress hormone”. When a pregnant women gets stressed, for instance due to poverty, mental issues, and/or violence, the hypothalamic-pituitary-adrenal (HPA-)axis gets activated, resulting in the release of multiple hormones, including cortisol. But not only mental health issues and psychological stress can increase cortisol levels, also physical ‘stress’ on the body, such as not having enough food or living with an abusive partner, can increase stress hormone levels. One study showed women with a history of childhood sexual abuse had elevated cortisol levels during pregnancy (Bublitz et al 2014).

The HPA-axis first responds with producing corticotropin releasing hormone (CRH) in the hypothalamus in the brain. The pituitary glands respond by secreting andrenocorticotropin hormone (ACTH), which in turn activates the adrenal cortex to produce cortisol and secrete it into the blood stream. Research has shown that cortisol crosses the placental barrier and that maternal and fetal cortisol levels are strongly correlated (Sarkar et al 2007). Although exposure to some levels of cortisol is essential for normal development of the fetus, excessive levels of cortisol in the fetal circulation may alter fetal brain functioning with long lasting effects on later life outcomes. So, when a mother is exposed to extreme stressors (e.g., war, natural disaster, major negative life event) or to chronic emotional stress (e.g., marital conflict, depression/anxiety) the fetus can be overexposed to maternal cortisol.

Prenatal exposure to high levels of maternal cortisol is likely to affect fetal brain development. Several studies have found associations between prenatal exposure to maternal cortisol or stress and alterations in brain structure and function (e.g., Buss et al 2012, van den Heuvel et al 2015a). These brain alterations may cause social, emotional, and cognitive problems later in life.

**Altered placental function.** Perturbations in the maternal environment must be transmitted across the placenta in order to affect the fetus (Jansson & Powell
The placenta maintains fetal homoeostasis by performing a wide range of physiological functions, which after birth are carried out by the kidney, gastrointestinal tract, lungs and endocrine glands of the neonate. The placenta has several ways to protect the fetus from harmful exposures. For example, there is a special placental enzyme (11β-HSD2) that protects the fetus from maternal cortisol by converting cortisol to the inactive cortisone (Wyrwoll et al 2011). When the placental function is weakened or placental malformations occur, fetal development is at stake. Research has shown that maternal psychological stress can decrease the function of the 11β-HSD2, causing extra cortisol to cross the placenta (O'Donnell et al 2012). In addition, maternal smoking, alcohol consumption, and exposure to environmental pollutants have all shown to increase the risk for placenta-associated complications, such as placenta praevia, accreta, and preeclampsia (Michikawa et al 2016, Niu et al 2015).

**Epigenetics.** Recently, insights from the field of epigenetics gave rise to another possible mechanism: epigenetic modifications, which are molecular mechanisms that alter gene activity without changing their DNA sequence (Monk et al 2012). These modifications can cause altered gene expression in multiple tissues, including the brain, with consequences for the functioning and connectivity of neural circuits. Therefore, they may underlie alterations in neurodevelopment seen in offspring exposure to maternal smoking, alcohol consumption, stress, and environmental toxins. Recent research has found epigenetic changes in the DNA of children prenatally exposed to maternal depression and anxiety (Hompes et al 2013, Monk et al 2012), famine (Heijmans et al 2008), and maternal smoking (Joubert et al 2016). Researchers also found epigenetic changes in the DNA of infants born from women who were exposed to the extreme violence during pregnancy in the Dominican Republic of Congo. These epigenetic changes were, in turn, linked to lower birth weight in these infants (Mulligan et al 2012).

Other proposed mechanisms, not discussed in this module, include reduced blood flow to the fetus, compromised maternal immune functioning, increased catecholamines (i.e., adrenalin and noradrenalin), altered intestinal microbiota, and changed maternal health behaviors (for a recent review, see Beijers et al 2014).

**Maternal diet during pregnancy**

A poor diet during pregnancy can have negative effects on child development. The unavailability of nutrients itself poses a serious threat to the developing fetal brain (Ramel & Georgieff 2014). Two different studies performed in persons prenatally exposed to the Dutch famine in 1944-1945, have shown reduced brain size and other brain abnormalities (de Rooij et al 2016, Hulshoff Pol et al 2000). These effects seem to last a lifetime, as the participants in these studies were already in their 60's (de Rooij et al., 2016). Besides global undernutrition during
pregnancy, long-term effects of specific nutrient shortages during pregnancy have also been shown and many of these effects are related to cognitive function. Important effects have been shown for long chain polyunsaturated fatty acids, protein, zinc, iron, choline and folate. For example, one study found that a higher concentration of Omega-3 fatty acid in the blood of pregnant women decreased the risk for emotional problems in their children at age 5-6 years (Loomans et al 2014). For a review on the effects of nutrients during pregnancy on child development see Monk et al (2013).

**Prenatal exposure to maternal alcohol intake and smoking**

The effects of prenatal alcohol intake and smoke exposure are heavily investigated and clearly show detrimental effects of both, including emotional and behavioral problems, physical health issues, and cognitive deficits. Drinking and smoking during pregnancy have also been associated with alterations in brain function and structure in the offspring (Gil-Mohapel et al 2014, Haghighi et al 2013).

The deleterious effects exerted by prenatal alcohol exposure are often referred to as fetal alcohol spectrum disorders (FASD). Probably one of the most well-known and severe consequences of heavy drinking during pregnancy is Fetal Alcohol Syndrome (FAS) – the most severe form of FASD. The long-term outcomes of children affected with FAS are very poor, with a high percentage of children with mental retardation, emotional disorders, sleep disorders, and abnormal habits (Steinhausen & Spohr 1998). As adults, they are far more likely to be unemployed, have psychiatric disorders, and received special education (Rangmar et al 2015). Because prenatal exposure to maternal alcohol intake also increases the risk for the child to get addicted to alcohol, with a life time prevalence of 35% (Streissguth et al 2004), the family gets stuck in a vicious cycle of alcohol abuse. The chance of escaping these adverse life outcomes are increased 2 - to 4-fold by receiving the diagnosis of FAS or FASD at an earlier age and by being reared in good stable environments (Streissguth et al 2004).

Infants born with FAS often have specific facial characteristics:
Prenatal exposure to environmental pollutants

Accumulating research has shown that prenatal exposure to environmental pollutants has effects on fetal development that can last a lifetime. Research on traffic-related air pollution, such as ambient nitrogen dioxide (NO₂) and benzene, is relatively novel. Recent studies have shown that prenatal exposure to these pollutants may cause preterm birth (Estarlich et al 2016), child asthma, eczema and allergies (Deng et al 2016), and even child behavioral problems related to attention and delinquent or aggressive behavior at age 8 years (Yorifuji et al).

Heavy metals, such as mercury, lead, and cadmium can severely affect fetal health and subsequent child development. Mercury, lead, and cadmium can all cross the placenta and accumulate in fetal tissues. To make story worse, fetal exposure to these metals can even occur if the mother was exposed in the past, even if the current environment is clean. For example, lead can be stored in maternal bones at the time of lead exposure. Mobilization of maternal bone lead stores during pregnancy has been clearly identified as a major source of fetal lead exposure. Lead exposure during pregnancy has been associated with decreased cognitive abilities, such as lower intelligence (Schnaas et al 2006) and child behavioral problems at age 3 years (Wasserman et al 1998).

Maternal stress during pregnancy

Pregnancy is often viewed as a period of happiness and joy. Mothers are expected to be ‘glowing’ and grateful for the opportunity to bring new life into the world. For a vast amount of women, however, this is not the case. Loomans et al (2013), for instance, investigated maternal psychosocial stress during pregnancy in a large multi-ethnic community-based cohort study in the Netherlands and reported that about 30% of pregnant women experience some form of stress during pregnancy (i.e., anxiety, depression, job strain). Another
study focusing on pregnant Latinas living in the U.S. and Mexico found that 32.4% of the pregnant Latinas and 36.8% of the Mexicans showed symptoms of depression. About 15.7% of the Latinas and 23.9% of the Mexicans suffered from clinical depression during pregnancy (Lara et al 2008). Especially the rates for the Mexican women are shockingly high. Importantly, studies demonstrate that teenage women are at particular risk for developing depression during pregnancy compared to adult women (Figueiredo et al 2007). Receiving social support from the teenager’s mother or the infant's father is associated with lower rates of depression during pregnancy, while conflict with the child’s father is strongly associated with increased rates of depressive symptoms in teenagers (Barnet et al 1996).

Although those rates already seem extremely high, they are likely to be an underestimation caused by the tendency to ignore or suppress negative feelings, worries and anxiety during pregnancy or to regard them as ‘just being hormonal’. Research seems to confirm this notion as it has been found that the majority of pregnant women meeting the criteria for psychiatric disorders were undiagnosed and untreated (Andersson et al 2003, Glover 2014). In one study, a strikingly low percentage of only 5.5% of women at need for treatment actually received it (Andersson et al 2003). Care for the emotional well-being of pregnant women clearly seems to be a neglected part of obstetric medicine (Glover 2014).

Besides causing an emotional burden on pregnant women, accumulating research has shown that maternal anxiety during pregnancy can also affect the unborn child (Graignic-Philippe et al 2014).

Maternal stress during pregnancy has been associated with numerous negative child outcomes. Researchers have found strong links between maternal stress during pregnancy and difficult temperament in infancy (Henrichs et al 2009, van den Heuvel et al 2015a). Infants with more difficult temperament cry more often and longer and are more sensitive to their surrounding (noises, smells, etc.). When children prenatally exposed to maternal stress grow older, they are also more at risk to develop emotional and behavioral issues. Multiple studies have found associations between maternal stress during pregnancy and child mental health problems, such as ADHD (Van den Bergh & Marcoen 2004), autism (Rijlaarsdam et al 2016, Walder et al 2014), and anxiety and depression (Van den Bergh & Marcoen 2004). In addition, children prenatally exposed to maternal stress also seem to have more cognitive problems, such as lower
intelligence (Bergh et al 2005).

**Clinical implications of prenatal programming**

A large body of research clearly shows that the intrauterine environment is important for later life functioning and that the nine months before birth should not be disregarded. Midwives, obstetricians, and general practitioners should therefore inform (future) pregnant women that the development of a child does not start at birth but at conception (or even better: before conception). Besides information about alcohol intake, smoking and diet during pregnancy, more attention should be paid to the emotional wellbeing of pregnant women. Because many pregnant women do not seek help from mental health services, midwives have a crucial role in the identification, support, and referral of women experiencing mental health problems. A recent investigation of student midwives in the UK revealed that they often under-estimated the risk of women with existing mental health problems, felt ill-prepared, and lacked confidence in caring for them (Jarrett 2015). These results emphasize the need for better informing and training midwives.

A short screening tool could be incorporated in routine prenatal care to target women in need for intervention. One study showed that the risk for depressive symptoms in Latinas living in the U.S. and Mexico increases if: it is not the first pregnancy, the women has a history of suicidal thoughts, the women has a higher education, the women is living with a partner but are not formally married (Lara et al 2008). Besides including a screening tool that measures depressive symptoms, health care providers could also screen for these risk factors.

Also, effective interventions should become available for them. Some studies showed beneficial effects of mindfulness for both mother and child (Braeken et al 2016, van den Heuvel et al 2015b) and thus suggest mindfulness as an effective component of stress-reduction interventions for pregnant women experiencing anxiety and worries. Such interventions may provide pregnant women diagnosed with anxiety disorders with an alternative to pharmacological interventions. In addition, research has shown that higher partner support during pregnancy predicts less maternal and infant distress (Stapleton et al 2012). Health practitioners could actively involve the partner in pregnancy and explain the beneficial effects of partner support.

Alternatives for psychopharmacological treatment during pregnancy are highly desired, since these treatments have been associated with detrimental effects for the fetus, such as higher risk for premature birth and low birth weight (Huang et al 2014) and reduced fetal head growth (El Marroun et al 2012). Moreover, stressing the beneficial effect of being mindful and partner support during pregnancy provides a more positive and possibly more effective message to pregnant women than stressing the potential dangers of being anxious.
Recommended reading


References


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