

1. Introduction

Different lines of research provide empirical evidence that pre-, peri- and postnatal development phases are crucial in association with the development of mental and somatic health in children and adolescents (Lupien et al., Seckl & Holmes, 2009; Cottrell and Seckl, 2009; O'Regan et al., 2008; Van den Berg et al., 2007; Ward et al., 2010). Periods of important development steps such as high cell mitosis activity and brain development during the prenatal phase are sensitive to endogenous and exogenous influences of adverse life conditions (Barker, 2002; Lupien et al., 2009; Newman & Newman, 2009; O'Regan et al., 2008). Adverse life conditions such as prenatal stress are considered to be a predictor of lower gestational week, lower birth weight and size as well as hypertension, cardiovascular morbidity and mortality in adulthood (Barker, 2002; Braveman & Barclay, 2009; Cottrell & Seckl, 2009; Seckl & Homes, 2007; Ward et al., 2010). Moreover, prenatal stress seems to be also associated with long-term cognitive, psychological, social and behavioral diseases in children and adolescents (Andersen & Teicher, 2008; Lupien et al., 2009; Seckl and Holmes, 2007; Van den Berg et al., 2005; Ward et al., 2004). Lower gestational week, lower birth weight and size are correlated with heightened risk of neonatal and infant morbidity and mortality (Braveman & Barclay, 2009; Forssas et al., 1999; Pedersen et al., 2007; Seckl & Holmes, 2007) as well as with long-term influences on adult blood pressure and the incidence of cardiovascular morbidity and mortality (Barker et al., 2006; Ericsson et al., 2002; Kajantie et al., 2005; Nuyt et al., 2009; O'Regan et al., 2008; Woods & Weeks, 2006). There is also clinical evidence of associations between perinatal adverse birth outcomes and psychological diseases such as depression (Abe et al., 2007; Nomura et al., 2007). Furthermore, animal and human research showed that the postnatal period is also very important for development, and there are also sensitive phases for the influence of negative environmental effects due to the

further maturation process of different brain structures such as the prefrontal cortex or amygdale (McEwen, 2008; Newman & Newman, 2009; Petermann et al., 2004; Vasconcelos et al., 2007). There is empirical evidence that early life events are strongly associated with numerous psychological and physiological disorders (Heim et al, 1998; Heim et al., 2000; Heim et al., 2001; Maniglio, 2009; Zielinski, 2010). Furthermore, empirical research also gives rise to the hypothesis that beyond pre- and perinatal as well as adverse early life conditions, there might be further life events correlated with negative health outcomes in children and adolescents. These are low socioeconomic status (Braveman, 2009; Gilman et al., 2003; Latinen et al., 2001; Lawlor et al., 2002; Lidtfeldt et al., 2007; Waylen & Stuart-Brown, 2009; Zielinski, 2009), parental divorce (Cartwright, 2006; Herland et al., 2002; O'Conner et al., 1999), psychiatric disorder of the mother and/or of the father (Waylen&Stuart-Brown, 2009), as well as birth of sibling, child psychiatric and/or somatic disorder, environmental disasters and transitional events. Life events seem to have an influence on the onset of depressive disorder as well as an impact on higher rates of depression in older age (Comjis et al., 2007; Horsch et al., 2008), somatic symptoms (Furniss et al. 2009; Liakopoulou-Kairis, 2002; Robinson et al, 1989) such as higher rates of abdominal pain in children (Hodges et al., 1984; Liakopoulou-Kairis, 2002; Robinson et al., 1990) and headache (Rhee, 2001) as well as generally on mental well-being (Bouma et al., 2008; Fruniss et al., 2009).

Quite often, numerous life events have a positive and a negative side. Challenging life conditions are required for a regular development. Stress, for example, is also considered to have positive effects. Dalziel et al. (2005), for instance, found no negative effect of prenatal stress in 31-year-old subjects. In school-aged children treated prenatally with glucocorticoids, Hirvikoski et al. (2008) showed no negative effects compared to the control group. The

different findings might reflect the various effects of pre-, peri-, and postnatal adverse conditions depending on multiple bio-psycho-social factors.

We planned to explore the impact of adverse life conditions during pre-, peri-, and postnatal periods on psychological and somatic health. We aimed to investigate the single impact of prenatal stress. Furthermore, we wished to examine the combined effect of interactions between pre-, peri- and postnatal adverse life conditions on psychosomatic health in children.

This thesis is subdivided into three main parts: the theoretical background, including the methodological procedures, the empirical investigation and the general discussion. The first part introduces developmental and sensitive phases, as well as health as a basis for the development of mental and somatic health. Both serve as basis for the chapter on adverse life conditions, with the essential developments of the stress concept, prenatal stress, perinatal adverse conditions and postnatal critical life events. These constructs are summarized under the macro-category of life adversities and depict the basic principles of general influences of adverse pre-, peri- and postnatal conditions. The theoretical background is followed by the presentation of the study idea, the hypothesis and general methodological procedures. Part II presents the findings of the empirical research, followed by a general discussion in part III.

Part I – Theoretical Background

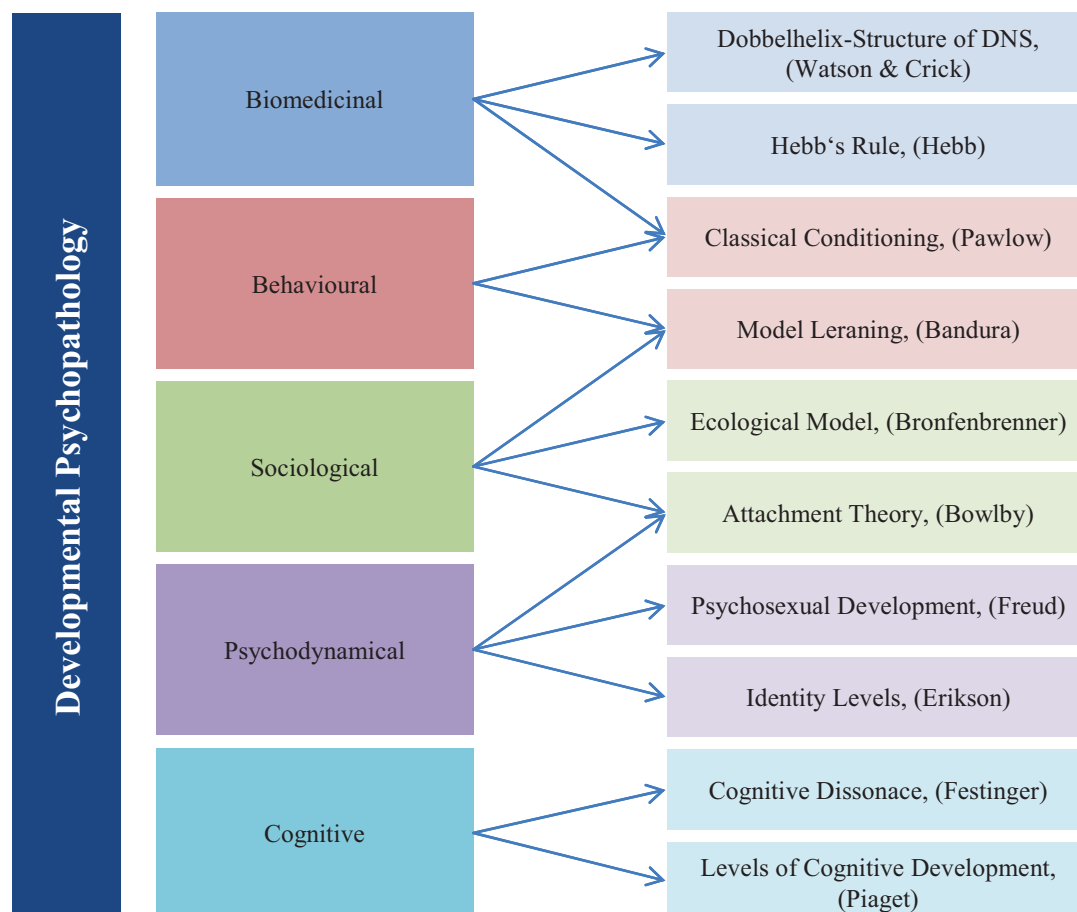
2. Pre-, Peri- and Postnatal Developmental and Sensitivity Phases for Adverse Life Conditions

Pre-, peri- and postnatal developmental phases are defined through natural developmentally given factors such as pregnancy, birth or puberty period as well as through social norms, e.g. school age or maturity (Keverne, 2004; Newman & Newman 2009; Petermann et al., 2004). Human development for its part is influenced through genetic, physical and social environmental factors as well as structural and personal factors. Hence, depending on timing, intensity and frequency, there are sensitive periods that might interact with possible influences through numerous adverse life conditions (Newman & Newman 2009; Petermann et al., 2004). Adverse life conditions can be generally classified into exposure to damaging substances (e.g. toxins, drugs, nicotine), natural or man-made disasters or exposure to violence, maltreatment or psychological stress. Empirical animal and human studies show negative health consequences based on complex multifactorial interactions, which can lead to health-threatening long-term mental and physical influences (Cottrell & Seckl, 2009; Newman & Newman 2009; Petermann et al., 2004). These complex interactions are investigated and integrated in the so-called developmental sciences, which are briefly described in the following.

Development science has only existed as an autonomous, interdisciplinary scientific method for three decades (Bronstein & Lamb; 2005; Petermann et al., 2004). The roots of developmental science can be found in “Developmental Psychobiology”, which dates back to 1888 from the term Psychobiology coined by Clarence Luther Herrick (1858-1904).

Development science is a specific approach that includes multiple levels of developmental analyses such as Psychology, Endocrinology, Neurophysiology, Embryology, Zoology,Cultural Anthropology and Psychiatry, for investigating, understanding and explaining human behavior (Gilbert, 2002; in Petermann et al., 2004). Therefore, a definition of the term development is not easily accessible, because there are several theories among numerous research disciplines (Lerner et al.; in Bornstein & Lamb, 2005). In 1990, Achenbach presented his broad interdisciplinary approach of Developmental Psychopathology (Figure 1).

Figure 1. Developmental Psychopathology – an interdisciplinary approach (adapted from Achenbach, 1990; in Petermann et al., 2004)

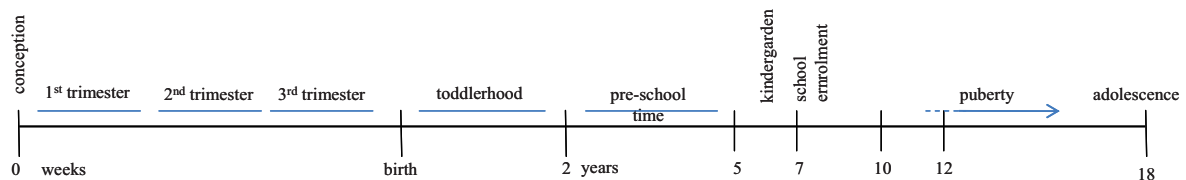


Each of the presented theories has its own theory-specific definition of Development as well as theory-specific research methods. The high variability of developmental theories and the disciplines on which they rely, are a good indicator of the broad field of Development (Cicchetti & Cohen, 1995; Petermann et al., 2004). In contemporary developmental science, the basic process of development shows multifactoral relations between different levels of organization, ranging from biology through individual and social functioning to physiological, cultural, ecological and historical contexts of development of a human being. The developmental hypothesis includes direct effects of unique exogenous or endogenous adaptive or maladaptive circumstances as well as interactional effects, including genetic, environmental and individual characteristics (Lerner et al.; Bornstein & Lamb, 2005). It is a convergence of all three development models: dispositional, environmental and interactional (Petermann et al., 2004).

Based on considerations of different research lines, the term development can be defined as a multidisciplinary, multifactoral as well as life-stage and life-long research discipline. First, the approaches stem from different research areas such as Genetics, Microbiology, Obstetrics, Medicine, Endocrinology, Pediatrics, Psychiatry and Developmental Psychology. Second, it includes numerous factors of relevance for development, such as biological, emotional, behavioral, social and microbiological factors. Finally, it contains the time factor from the beginning of a life – conception – until the end of a human life – death (Bernstein & Lamb, 2005; Newman & Newman, 2009; Petermann et al., 2004). In the following, we will focus especially on the prenatal period, the pregnancy and the perinatal period, and also on childhood until puberty because of their importance for this thesis. The considerations will be two-poled, taking a developmental and sensitivity perspective for negative health effects. Figure 2 provides an overview of important developmental phases of these periods. Each of

them might have also sensitive windows for negative influences of adverse pre-, peri- and postnatal conditions.

Figure 2. Developmental stages and potential sensitive phases for adverse pre-, peri- and postnatal conditions



2.1 Pregnancy – Prenatal Development

For most women, pregnancy and birth are an extraordinary experience. In addition to distinctive physiological modifications, such as hormonal and anatomic changes, there are psychological adjustment processes required, such as coping with the challenges of the physical changes and the role and responsibility as mother (Bühling & Friedmann, 2004; Ehlert et al., 2003; Petersen et al., 2009). During a pregnancy, there are bidirectional influences of the fetus and the pregnant woman within her social and cultural environments (Bühling & Friedmann, 2004; Newman & Newman, 2009; Stauber & Weyerstahl, 2005). Such interactions are also important in terms of the mother's experiences of stressful situations and can consequently have influences on the fetal development (Davis et al., 2007; Schneider, 2000; Wadhwa et al., 1997; Wadhwa et al., 2004). Important stress-reactive systems such as the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic and parasympathetic nervous system are explained in section 4.1.2.

2.1.1 Developmental and Sensitive Phases of Pregnancy

A pregnancy is defined as the time after conception and before the childbirth. The pregnancy can be divided into three equivalent time periods.

First trimester – Gestational Weeks (GW) 1 to 13

Second trimester – GW 14 to 26

Third trimester – up to the 27th gestational week until birth (40th GW)

In humans, birth commonly occurs at a gestational age of about 40 weeks. A normal birth range is from 37 to 42 GW. Childbirth before fulfilling the 37th week of gestation is described as preterm (premature), whereas birth after 42 GW is considered postterm (too late) (The American Congress of Obstetricians and Gynecologists, ACOG, 2002; Petermann et al., 2004). Premature birth and its consequences will be described in the pregnancy complications in section 2.1.3.1.

In the following, the most important fetal developmental steps and fetal sensitive phases for endogenous and exogenous adverse conditions are described (Figure 4).

Fetal development during the first trimester – GW 1 to 13

In the first 10-13 days after the conception, rapid cell mitosis leads to the initiation of the embryogenesis, including basic neurodevelopmental building of the ecto-, endo- and mesodermal-layer and the first part of the central nervous system, the neural plate. From the neural plate, the neural groove is generated, and in the next step the neural tube. On the 24th day after conception, through high mitotic cell activity, three vesicles are built from the neural tube: the basal forebrain (prosencephalon), the midbrain (mesencephalon) and the hindbrain (rhombencephalon). From the prosencephalon, the hypothalamus is developed, an important organ of the hypothalamus-pituitary-adrenal (HPA) axis. The HPA is crucial in all human reactions associated with adverse life conditions (e.g. physical or psychological stress) and for maintaining homeostasis in the organism (Cannon, 1929a, b; Cannon, 1939; Goldstein & Kopin, 2007; McEwen & Wingfield, 2009; Petermann et al., 2004). Based on these three

anatomic structures, there is a further growth and cell differentiation for all parts of the central as well as the vegetative nervous system – which is ongoing until adolescence, e.g. frontal cortex and amygdale (Lupien et al., 2009; Newman & Newman, 2009; Petermann et al., 2004). At the end of the first trimester, all organs are established, the blood building cells in the bone marrow begin to build blood, and in the brain stem, the first electrical signals can be detected (Newman & Newman, 2009; Petermann et al., 2004).

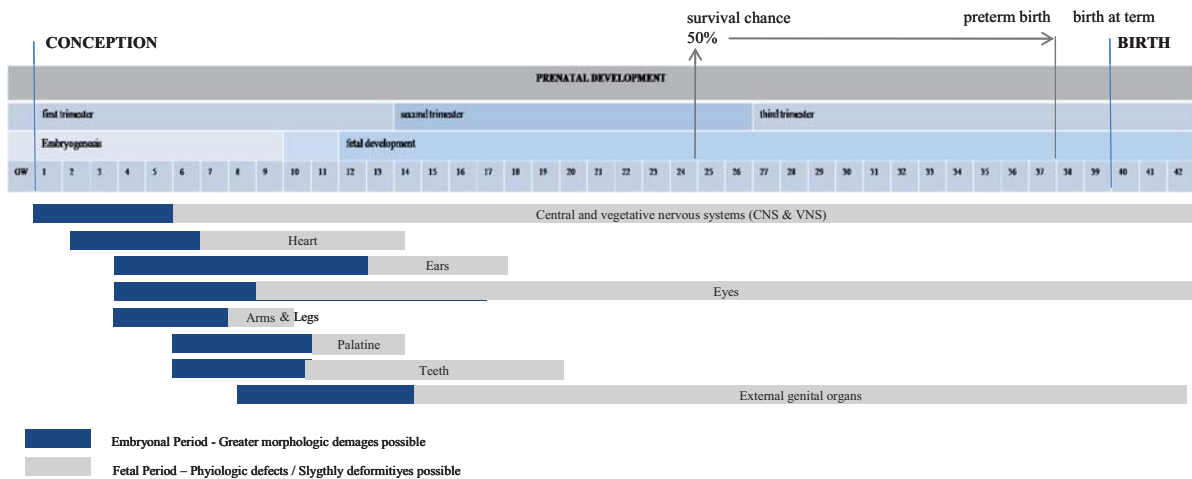
Fetal development during the second trimester – GW 14 to 26

During this time, genitals, bones and joints are formed and the disjunction of the two halves of the brain is visible. Numerous reflexes are present, including sucking and swallowing reflex. Up to the 24th GW, the fetus is in the fore and has a survival chance of 50% (Newman & Newman, 2009; Petermann et al., 2004).

Fetal development during the third trimester – up to the 27th GW until birth (40th GW)

In this pregnancy period, the fetus lung begins to build surfactant, which is an important substance (surface active agent) to protect the lungs from a collapse, and by the end of the 7th month of gestation, breathing is possible. The development of the central nervous system (CNS) is advanced and the fetus gains weight and is ready for the birth process and the beginning of a life in the environment. In the course of all of these periods of a pregnancy, adverse intrauterine and environmental conditions can lead to damages of different levels depending on timing, frequency and duration of these negative conditions (Lupien et al., 2009; Newman & Newman, 2009; Petermann et al., 2004).

Figure 3. Prenatal development and sensitive stages for environmental influences (adapted from Bühling & Friedmann, 2004; Petermann et al., 2004; Newman & Newman, 2009)



Sensitive phases for possible negative influences during pregnancy

Sensitive phases can be defined as time periods in which a human being is more sensitive to certain impulses and through the human being's own behavioral reactivity, there can be an increased vulnerability to exogenous stimuli (de Kloet et al., 2005; Petermann et al., 2004). The embryo / fetus is especially sensitive during pregnancy, with the highest vulnerability in the embryonic period (Figure 3). Depending on the time of pregnancy, the nature of the influencing substance, and finally the duration and intensity of the harmful exposure, greater fetal damages can result (Bühling & Freidmann, 2004; Schwab, 2007; Welberg & Seckl, 2001). Prenatal damages are generally possible by application of medical substances, drugs, toxins, radiation, infections, hormones, metabolic illness and hypoxia of the pregnant woman (Newman & Newman, 2009; Petermann et al., 2004; Stauber & Weyerstahl, 2005). Commonly, the highest sensitivity exists during phases of rapid cell division in the developing organs or nervous system (Cameron & Demerath, 2002; Kajantie & Phillips, 2006). The most highly sensitive time for exogenous teratogenic noxis is the time between the conception and

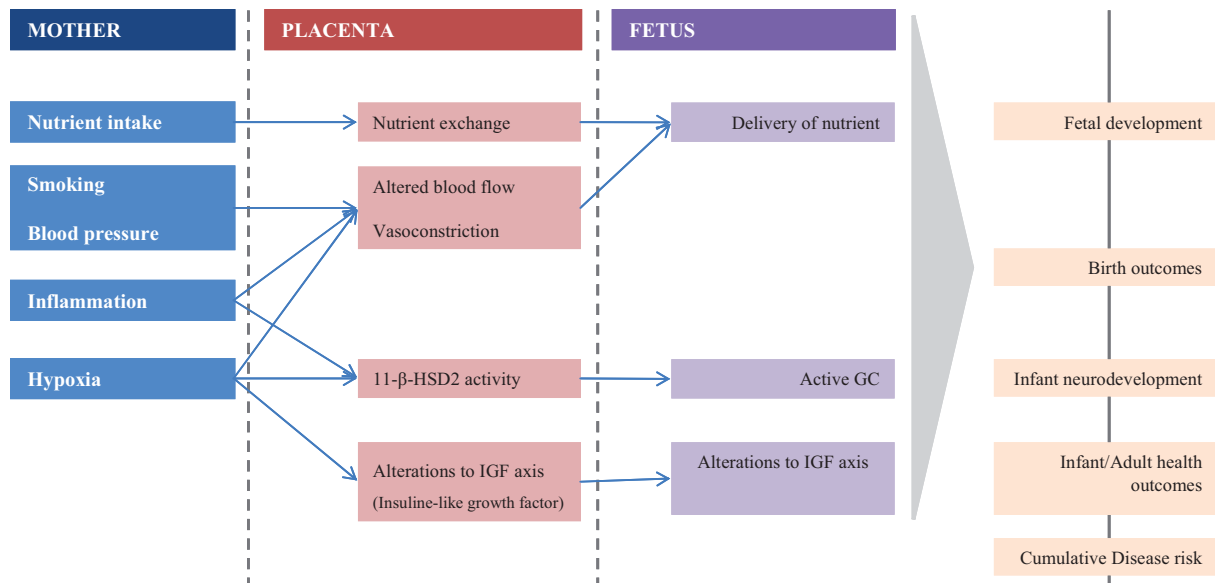
the 10th GW, which is why miscarriages might often occur during the first trimester. The central nervous system is especially vulnerable to morphological damages in the 3rd to 6th GW. Up to the 6th GW, physiological defects are possible (Bühling & Friedmann, 2004; Stauber & Weyerstahl, 2005). In addition to these severe damages in the fetal pregnancy period (up to the 8th GW), discreet physiological changes might occur, which can be persistent for a long time and have a long-term impact on the childhood and adolescence (Bühling & Friedmann, 2004; Seckl, 2001). Such alterations are based on the fetal programming hypothesis, which will be explained in section 4.2.1 and presents the background for the long-term impact of prenatal stress. Before proceeding with further risk factors and complications during a pregnancy, the conceptual framework of the entity mother, placenta and the fetus will be described, since the developing organism and the host environment are in interaction at every stage. They influence each other in a process of simultaneous reciprocal determinism and accordingly can have benign or malicious effects on the newborn (Bühling & Friedmann, 2004; Fowden et al., 2009; Lupien et al., 2009; Petermann et al., 2004; Van den Berg et al., 2009).

2.1.2 Maternal-Placental-Fetal Entity

Generally, through the entire fetal time, the fetus is nourished, provided with oxygen and protected through the mother's body and blood supply. Therefore, the body of the mother is connected with the developing fetus environment. The connection organ is the placenta, which begins to develop upon implantation of the fertilized cell in the endometrium (inner membrane of the mammalian uterus). Functions of the placenta are: nutrition, metabolic, immune and endocrine function (Carsten & Lu, 2004; Devereux et al., 2001; 2002; Emmert & Gerstorter, 2005; Hofmann & Geist, 1999). Figure 4 illustrates some interactions between the

mother and placenta and fetus, which are crucial for the control of fetal growth and health disturbances.

Figure 4. Maternal-Placental-Fetal interactions and potential consequences for psychosomatic health in children and adolescents (adapted from Murphy et al.; Wadhwa & Frederenko; in Hodgsen & Coe, 2005)



In the following, the neuroendocrine function and the mother's HPA-Placenta- and fetal HPA system will be described due to their importance for this work.

Parallel to the proceeding of the gestational week, there is an increase in corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and cortisol due to the secretion of CRH through to the placenta in addition to the mother's and fetus CRH production. Placental CRH has a stimulating effect on both the mother's and fetus secretion of ACTH through the pituitary (Egarter & Husslein, 1998; Wadhwa et al., 1997) and this consequently leads to increased cortisol levels in the mother and fetus. In contrast to the negative feedback loop to the hypothalamus and pituitaries, heightened cortisol levels have a

stimulating effect in the CRH-expression of the placenta (Egarter & Husslein, 1998; Wadhwa & Federenko; in Hodgson & Coe, 2005). The crucial protective factor, which protects the fetus from overexposure to GC, is the placental 11- β -hydroxysteroid dehydrogenase type 2 (11- β -HSD2). By 11- β -HSD2, glucocorticoids are oxidated into inactive derivatives (Kerzner et al., 2002; Stewart et al., 1995; Vackova et al., 2009; Wadhwa & Federenko; in Hodgson & Coe, 2005; Welberg et al., 2000). Although the underlying mechanisms are still not fully understood, various lines of research provide sufficient evidence that the maternal, placental and fetal neuro-endocrine systems play a critical role in fetal maturation, physical processes and parturition (Ehlert et al., 2003; Wadhwa et al., 1997; Wadhwa & Federenko; in Hodgson & Coe, 2005). The maternal-placental-fetal (MPF) neuroendocrine axis promotes in early gestation uterine quiescence and in late gestation uterine contractility. There seems to be a shift from a progesterone-dominant to an estrogen-dominant uterine environment over the course of the gestation. This process results in promoting labor, expression of oxytocin receptors and synthesis of prostaglandins (Challis et al., 2000; Ehlert et al., 2003; Grammatopoulos et al., 1999; Smith, 2001; Wadhwa et al., 1997; Wadhwa & Federenko; in Hodgson & Coe, 2005). Women in preterm birth have significantly elevated CRH-levels, in some studies already in the 15th GW, preceding the onset of spontaneous preterm birth, (Holzman et al., 2001; Wadhwa, 1998; Warren et al., 1992) as compared to controls. In contrast, women delivering postterm (> 41 GW) have lower levels of CRH (McLean et al., 1995; Wadhwa, 2004). The MPF neuroendocrine axis seems to be stress-sensitive (Wadhwa & Federenko; in Hodgson & Coe, 2005; Wadhwa, 2004). Clinical evidence suggests that the mechanism of placental CRH production over the course of gestation might be elevated by an adverse intrauterine environment characterized by physiological stress (Hobel et al., 1999; Wadhwa & Federenko; in Hodgson & Coe, 2005). Elevated CRH in the mother or fetus has been observed in women with occurrence of pregnancy complications such as pre-eclampsia,

reduced uteroplacental perfusion, intrauterine infection, and in cases where fetal distress has led to elective preterm childbirth (Wadhwa & Federenko; in Hodgson & Coe, 2005). Numerous in vitro studies have shown that CRH is released from cultured placental cells in a dose-response manner as a reaction to all of the major biological effectors of stress, including cortisol, epinephrine and norepinephrine as well as proinflammatory cytokines (Petraglia et al., 1987; 1989; 1990). Significant correlations among maternal HPA axis stress hormones ACTH and cortisol and placental CRH were found in vivo studies (Erickson et al., 2001; Petraglia et al., 1990). Furthermore, maternal psychological stress is significantly correlated with maternal HPA axis hormones ACTH and cortisol. Accordingly, in some studies, direct associations were found between maternal psychosocial stress and placental CRH function (Erickson et al., 2001; Hobel et al., 1999). Adverse prenatal stress effects on the fetus and child development as well as consequences for psychosomatic health are described in section 4.2.

In the next section, other risk factors such as numerous complications are briefly presented, which can appear during the pregnancy and might be very stressful and painful for the mother and fetus. Such adverse prenatal conditions might even have life-threatening effects on the fetus/newborn.

2.1.3 Complications of Pregnancy and their Treatment

In course of a pregnancy, different complications with negative influences on the fetus can emerge, including (Wen et al., 2004; Lopez Bernal, 2007):

- Pregnancy hypertension, which has a prevalence of 1.47% in Switzerland (StatSanté, 2007a)
- Preeclampsia, with a prevalence of 2.78% in Switzerland (StatSanté, 2007); 3-5% of all pregnancies (Kajantie & Phillips, 2006)