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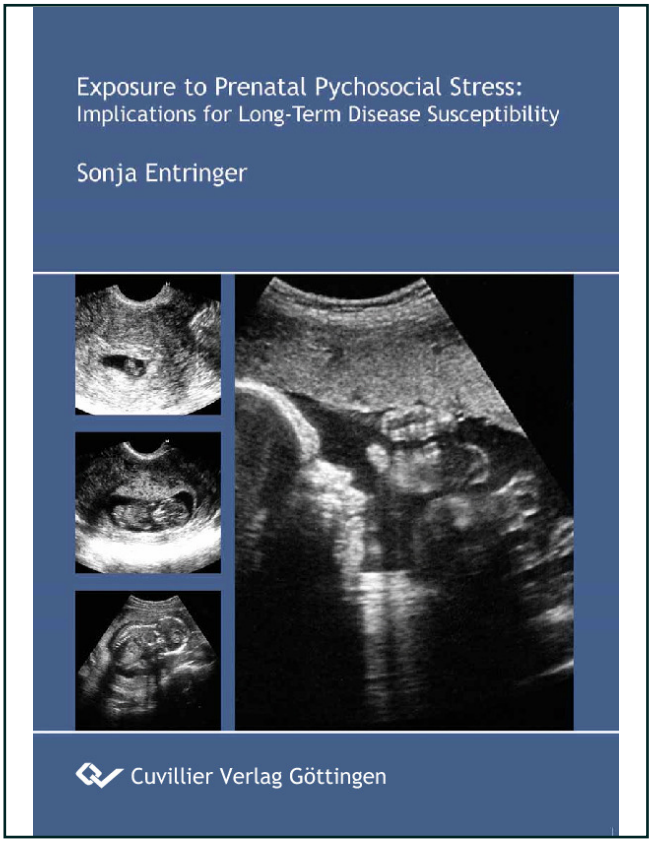
Exposure to Prenatal Psychosocial Stress:



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Chapter 1

INTRODUCTION AND OBJECTIVE OF THE THESIS

1.1 Introduction

The believe that a mother's emotional state during pregnancy may influence the development of her fetus has existed since ancient times across all cultures. References to this notion can be found in an ancient Indian text - the Mahabharata - thought to have been written about 1050 BC, in the Old and New Testaments, in the writings of early Greek physicians such as Hippocrates, and in the works of a number of scholars through the Middle Ages into the present century (Wadhwa, 1998).

Since the mid-1950s, research examining the effects of psychosocial stress of the mother during pregnancy appeared in the literature. In 1981, Simpson et al. in New Zealand observed a negative association between birth weight and blood pressure. Barker and colleagues then investigated the link between birth weight and coronary heart disease (CHD) more generally and found an inverse relationship between birth weight and risk of CHD and type 2 diabetes (Barker and Osmond, 1988; Barker et al., 1989; Barker, 1990). The notion that the risk of suffering from chronic disease depends in part on environmental influences acting early in life has been called the "fetal origins of health and disease" paradigm (Barker, 1990), and extensive research has been conducted in this field since the early 90s. It could be confirmed in several epidemiological studies across the world that low birth weight and small body size are associated with a significantly increased risk of physical and mental disease in adult life, including hypertension, coronary heart disease, type 2 diabetes mellitus, endocrine cancers, depression and other cognitive and affective disorders (Barker, 1998; Mellemkjaer et al., 2003; Michels, 2003; Sallout and Walker, 2003; Gluckman and Hanson, 2004a). These observations are independent of adult size and established risk factors, such as obesity, unfavorable lipid profile or smoking. Moreover these effects extend continuously across the normal range of distribution of birth weight or small-for-gestational age at birth (Barker, 2002; Gluckman and Hanson, 2004b).

It is unlikely that birth phenotype (i.e., birth weight, size at birth, length of gestation) plays a causal role in increasing the risk of adult disease. Instead, birth phenotype is more likely a crude reflection of developmental processes in intrauterine life that underlie health and disease risk in later life (Osmond and Barker, 2000; Morley et al., 2002; Gluckman and Hanson, 2004b). In other words,

the observed relationship between disease risk and birth size does not imply a causal role of being born small but primarily reflects the sensitivity of fetal growth to adverse intrauterine influences (Gluckman and Hanson, 2004b). Several studies of the effects of adverse early environment have focused on the role of prenatal nutritional factors. It has been proposed that psychosocial stress of the mother during pregnancy represents yet another adverse environment that may contribute to both birth phenotype and the physiology of the developing organism (Wadhwa and Federenko, 2006, see figure 1). In humans, maternal psychosocial stress during pregnancy has been shown to predict low birth weight (Paarlberg et al., 1995; Paarlberg et al., 1999; Wadhwa et al., 2001) and preterm delivery (Hedegaard et al., 1993; Paarlberg et al., 1995; Wadhwa et al., 2001), and as mentioned earlier, these birth phenotypes have been linked with disease risk later in life. Experimental studies in animals provide convincing evidence for a causal role for prenatal stress in influencing critical developmental and health outcomes over the life span (for reviews see Weinstock, 2001; Kofman, 2002; Maccari et al., 2003). Human studies of exposure to maternal psychosocial stress and anxiety during pregnancy mainly focused on birth outcomes, fetal development, infant and child behavior and adult psychopathology. To the best of my knowledge there are no human studies available looking at a direct link between prenatal stress exposure and changes in physiological systems in adult life.

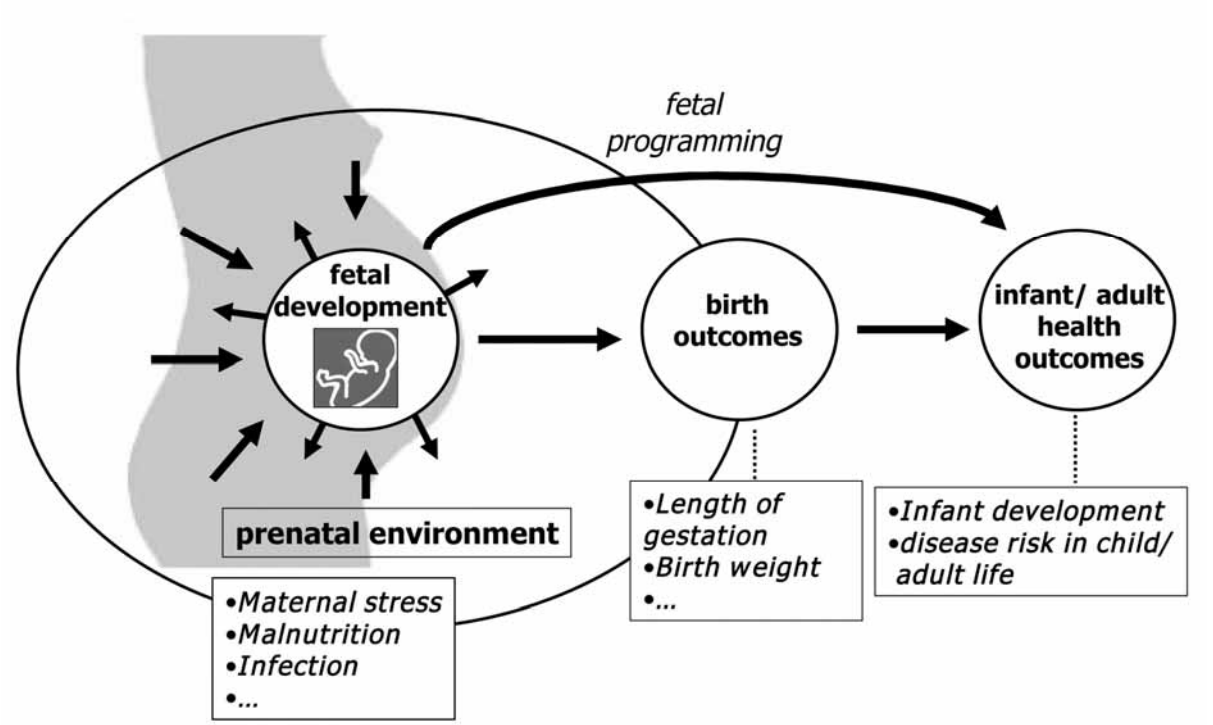

Figure 1.1: Conceptual framework of the thesis (see Wadhwa and Federenko, 2006)

1.2 Objective and Outline of the Thesis

The major objective of the study presented in this thesis was to examine the direct association between maternal psychosocial stress during pregnancy and measures of their offspring's physiology as adults, focusing on endocrine, metabolic and immune parameters.

After presenting an overview of the outline in the present chapter (chapter 1), the second chapter (chapter 2) provides the theoretical background of this thesis. Evidence linking psychosocial stress of the mother during pregnancy with fetal development, adverse birth outcomes, and mental health outcomes over the lifespan in humans is discussed, putative physiological mechanisms that may mediate these effects are described and the issue of developmental programming of health and disease is addressed. The outcomes of stress during pregnancy can be broadly classified into those affecting primarily the mother (e.g., maternal complications during pregnancy or following delivery, and labor and delivery parameters such as length of labor, mode of delivery, and maternal postpartum affect), and those affecting primarily the fetus, e.g., spontaneous abortion, fetal growth and maturation, gestational age at birth, neonatal complications, indices of infant development, and childhood and adult mental and physical disorders (see Wadhwa, 1998). The focus of the present thesis is on human studies investigating the impact of maternal psychosocial stress during pregnancy on health and disease of the developing individuum later in life. Outcomes concerning primarily the mother, and the effects of birth outcomes (like weight at birth and length of gestation), as well as maternal complications during pregnancy *per se* on the developing child are not addressed in this thesis.

Chapters 3, 4 and 5 present findings of my own study on metabolic, endocrine, and immune parameters in adults whose mothers experienced severe psychosocial stress during their pregnancies. The study was conducted under the supervision of Dr. Stefan Wüst, Dr. Pathik Wadhwa, and Dr. Hellhammer, and in collaboration with Robert Kumsta, Dr. Edward Nelson and Irmgard Layes. I wrote three independent manuscripts that will be submitted for publication in different journals. The paper drafts are written in a way that they can be read separately, each with its own introduction, methods, results and discussion section, in case the reader wants to be informed on a certain aspect of the thesis only. To make

reading of a single chapter more convenient, abbreviations are introduced anew in each chapter. Because not all of the assessed parameters could be investigated in every subject, the number of subjects slightly differs in the three sets of result on the metabolic, endocrine and immune system described in chapter 3-5.

In chapter 6, the findings from the previous three chapters are summarized and drawn together, followed by a general discussion of the findings and giving an outlook for future research directions.

Chapter 2

THEORETICAL BACKGROUND

2.1 Human Studies on Psychosocial Stress during Pregnancy

Prenatal stress paradigms in animals expose pregnant females to an experimentally controlled stressful situation (e.g., immobilization, restraint, electric tail shocks, crowding) that leads to changes in the maternal physiology and presumably to alterations in the fetal environment. Although the paradigms differ regarding timing, intensity, frequency and duration of the stress applications, it can be concluded from these studies that prenatal stress has the propensity to negatively influence critical developmental and health outcomes over the life span, including changes in brain morphology and behavior, sexual differentiation, (re)activity of the autonomic nervous, neuroendocrine, immune and reproductive systems, physical and mental health as well as longevity (for reviews see Weinstock, 2001; Kofman, 2002; Maccari et al., 2003; Weinstock, 2005).

Since experimental studies using prenatal stress paradigms cannot be conducted in humans, different approaches are used to investigate the consequences of exposure to maternal stress during pregnancy. There are several methodological issues concerning the design of human studies. First of all, most studies have been performed retrospectively. One problem related to retrospective studies is the likelihood of a recall bias (Gorin and Stone, 2000). Secondly, it is impossible to exclude all postnatal potentially confounding factors in human studies. A few recent studies used prospective designs which provide the opportunity to control for some confounding factors that could influence possible outcomes of prenatal stress exposure, such as malnutrition during pregnancy, socio-economic statues, obstetric factors, postnatal nutrition, mother-child-interaction, etc. Huizink et al. (2004) propose to distinguish between exposure to self-reported stressors and naturally occurring stressors with regard to human studies of prenatal stress during pregnancy. Self-reported stressors are stressors that are not objectively measured but that reflect subjective feelings of stress of pregnant women which can be assessed by questionnaires. Naturally occurring stressors include exposure to a natural disaster (e.g., flood, earthquake), man-made disasters (e.g., war, unpredictable aircraft noise) or severe traumatic experience (death of a child, spouse). According to Huizink et al. (2004), the latter type may be more comparable with uncontrollable experimental stressors in animal studies. The authors further differentiate between stress-provoking factors (e.g.,

life events, daily hassles), and stress-resulting factors (e.g., perceived stress). Some studies used maternal anxiety during pregnancy as a marker of prenatal stress because anxiety may be associated with perceived stress. In the following section, some of the major studies and findings conducted in humans on the effects of psychosocial stress and anxiety of the mother during pregnancy on the developing fetus and on development during childhood, as well as on psychopathology are presented.

2.1.1 Prenatal Stress and Fetal Development

Spontaneous Abortion

Spontaneous abortion (SAB) is among the most frequent adverse pregnancy outcomes, occurring in approximately 40 % of all pregnancies and in 15 % of all clinically recognized pregnancies (Wadhwa, 1998). It is a commonly held belief that extreme severe life stressors may trigger spontaneous abortion. A prospective study of more than 3900 women in northern California examined psychosocial stress in the work place and found that stressful work was associated with a two- to threefold increased risk of SAB in three groups of women: over 32 years of age, cigarette smokers, and primigravid (woman in her first pregnancy) (Fenster et al., 1995). Another study investigated 192 women visiting a medical center after spontaneous abortion (Neugebauer et al., 1996). The results indicate that women who experienced negative life events after conception had a two- to fourfold increase in the risk of chromosomally normal spontaneous abortion. In contrast, Auvinen et al. (2001) found no relation between the Chernobyl fallout in 1986 and rate of stillbirths, pregnancy loss and induced abortions in Finland.

Fetal Malformations

A study of more than 22.000 births in Santiago, Chile, in the 9-month period following a large earthquake revealed a significant overall increase in the incidence of fetal malformations (facial cleft palate), with the largest increase in the cohort of babies born 6 months after the earthquake (Montenegro et al., 1995). Also, structural malformations like craniofacial malformations have been found to be related with the (unexpected) death of an older child (Hansen et al., 2000). In another study, Nimby and colleagues (1999) showed that structural malformations

can also emerge in the context of increased psychosocial problems during pregnancy, especially conflicts with the partner or members of the family.

Fetal Behavior

A considerable number of studies examined whether maternal stress or anxiety during pregnancy is related to fetal behavior. Anecdotal and non-controlled reports from the pre-ultrasound years have suggested that prenatal maternal stress, anxiety, and emotions affect fetal functioning, as evidenced by increased fetal heart rate and motility (Van den Bergh, 1992). Three studies have evaluated the immediate relationship between maternal anxiety or maternal stress during pregnancy and fetal behavior in the first half of pregnancy and found no observable effect on spontaneous motor activity (Bartha et al., 2003; Buitelaar et al., 2003; Niederhofer and Reiter, 2004). Groome et al. (1995) demonstrated that fetuses of mothers with high trait anxiety scores assessed with the Spielberg State and Trait Anxiety Inventory between week 38 and 40 spent more time in quiet sleep and exhibited less gross body movements when in active sleep. DiPietro and colleagues (1999; 2002) showed an overall increased percentage of body movements and fetal heart rate variability and accelerations in fetuses whose mothers reported higher levels of perceived stress and emotions, more pregnancy-related hassles, and a negative valence toward pregnancy. In contrast, results from earlier reports of this group showed reduced fetal heart rate variability and poorer movement fetal heart rate coupling in fetuses of women with high perceived stress (DiPietro et al., 1996b, 1996a). One study reported that stress experienced in early pregnancy (life events and daily hassles during the last 3 months) had an observable effect on fetal behavior as early as at 28 weeks (Mulder et al., 2001), and self-reported measures of state and trait anxiety were positively associated with fetal motor activity during ultrasound observation (Van den Bergh et al., 1989). These findings are in line with the observation of dramatically increased fetal movements during acute maternal panic caused by an earthquake (Ianniruberto and Tajani, 1981). A number of studies recently investigated the effects of induced maternal stress, emotions, and hormonal changes on fetal functioning. Changes in fetal heart rate and motility that occurred during a maternal cognitive challenge (arithmetic test or Stroop color-word matching test) were compared with values obtained during pre-and post-test periods (Monk et al., 2000; DiPietro et al., 2003). The observed effects