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Outline and aims of this thesis

The main purpose of this thesis is to focus on the role of prenatal maternal stress in relation to infant development in a prospective longitudinal design. In this design, data was gathered on various aspects of maternal and fetal aspects. In Table 2.1 the design is presented. The aspects in italics in Table 2.1 reflect data on which this thesis reports. The gray parts on Figure 2.1 summarize the focus of this thesis. The relationships between prenatal maternal stress and fetal behavior and birth outcome (represented in Figure 2.1 by means of white arrows) will be discussed in an accompanying thesis entitled 'The effects of maternal stress on fetal development' by P.G. Robles de Medina.

Table 2.1 Design of the large prospective study of which a part is discussed in this thesis.

	Time period	Maternal measures	Fetal/Infant measures	General measures/ combination maternal-infant measures
<i>Pregnancy</i>	15 - 17 weeks	General demographic information Socio-economic status Smoking and drinking habits Stress questionnaires Cortisol in saliva during ultrasound Cortisol (saliva) day curve	Ultrasound recording of fetal behavior and fetal heart rate during 1 hour	
	24 weeks	ACTH & β -endorphin in plasma (subsample)		
	27 - 28 weeks	Stress questionnaires Pregnancy complaints Smoking and drinking habits Cortisol in saliva during ultrasound Cortisol (saliva) day curve	Ultrasound recording of fetal behavior and fetal heart rate during 1 hour	
	32 weeks	ACTH & β -endorphin in plasma (subsample)		
	37 - 38 weeks	Stress questionnaires Pregnancy complaints Smoking and drinking habits Cortisol sample in saliva during ultrasound Cortisol day curve	Ultrasound recording of fetal behavior and fetal heart rate during 2 hours	
<i>Birth</i>			Gestational age Birth weight Apgar score 1/5 minutes	General information on delivery (duration, mode of delivery etc.) Complications Medication use
<i>Neonatal</i>	10 \pm 2 days postpartum	Stress questionnaires Neonatal perception questionnaire General information on health status of the baby	Neurological status (Prechtl) of the baby Head circumference	Observation of Mother-Infant-Interaction during bathing session
<i>Infancy</i>	2 months		Cortisol day curve in subsample	
	3 months	Stress questionnaires Infant temperament questionnaire (ICQ) General information on health status of the infant	Bayley Scales of Infant Development (BSID) Head circumference Vagal tone during BSID in subsample	
	4 months		Cortisol day curve in subsample	
	5 months		Cortisol day curve in subsample	
	8 months	Stress questionnaires Infant temperament questionnaire (ICQ) General information on health status of the infant	Bayley Scales of Infant Development (BSID) Head circumference Vagal tone during BSID in subsample	Observation of Mother-Infant-Interaction during semi-structured play-session and BSID
	2 years; data collection on-going	Stress questionnaires Childrearing questionnaire Marital status questionnaire Child Behavior Checklist (CBCL) Infant temperament questionnaire General information on health status of the infant	Bayley Scales of Infant Development (BSID) Head circumference Vagal tone during BSID in subsample	Observation of Mother-Infant-Interaction during semi-structured play-session and BSID

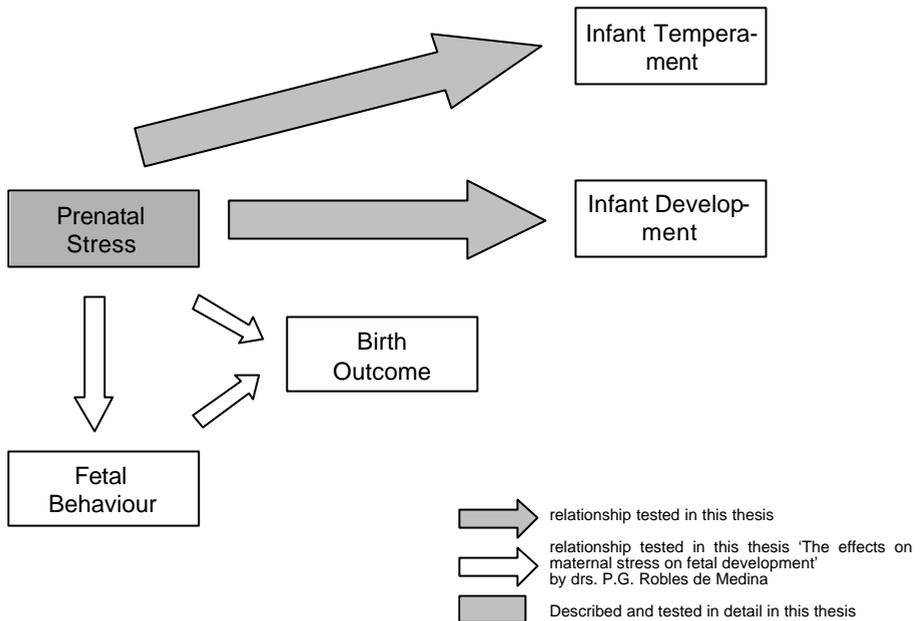


Figure 2.1. Schematical presentation of the tested relationships in this thesis presented in gray.

The present thesis addresses the following specific aims:

1. To provide a summary of the preclinical literature of the effects of prenatal stress;
2. To clarify the concept of prenatal stress;
3. To test the hypothesis that prenatal stress in humans has adverse effects on the mental and motor development and on the temperament of the infant.

The influence of prenatal maternal stress on animal offspring is systematically reviewed (chapter 3). First, the prenatal stress paradigm in animal experimental studies is described, after which the effects of prenatal stress on behavior of rodent offspring and nonhuman primate offspring is discussed separately. The mechanisms underlying alterations in offspring behavior and development due to prenatal stress are reviewed, with a main focus on the role of the maternal hypothalamic-pituitary-adrenal (HPA) axis. Transduction of stress from the mother to the fetus may involve transplacental transport of maternal stress hormones to the fetus, maternal stress-induced release of placental hormones that may enter the fetal circulation and maternal stress-induced effects on the blood flow to the placenta. These possibilities are elaborated. An important effect of prenatal stress is an altered HPA axis regulation in the offspring. Several mechanisms underlying this effect are discussed. In addition, the effect of prenatal stress on the brain opioid system and brain neurotransmitter systems (serotonergic, noradrenergic, dopaminergic and cholinergic system) are described. Modification by postnatal influences on the prenatal stress effects in animals are briefly summarized. Finally, the relevance of animal prenatal stress models for the human and implications for human psychopathology are discussed.

Although the evidence of harmful effects of prenatal maternal stress on the developing fetal brain and offspring development and behavior is abundant, animal findings cannot be extrapolated directly to the human situation. Besides the differences in brain development and potential transfer mechanisms of maternal stress hormones to the fetus, a major problem concerns the concept of prenatal stress used in animal studies which differs from stressors that may be encountered in human pregnancy. Therefore, it is important to conceptualize and operationalize clearly what is meant by prenatal stress in human pregnancy. Various concepts of prenatal stress have been used by researchers who have studied the harmful effects of stress during pregnancy on birth outcome. A second aim of this thesis is therefore to analyze the concept of prenatal stress in detail in a sample of nulliparous pregnant women. For that purpose, various aspects of prenatal stress in human pregnancy were studied. First, **chapter 4** focuses on a unique element of human pregnancy: pregnancy-related anxieties. Confirmatory factor analysis was carried out on a questionnaire aimed to assess these anxieties to test the structure, internal consistency, stability and change of pregnancy-related anxieties. To test if prenatal anxiety is a syndrome that may be differentiated from general anxiety and other personality factors, multiple regression analysis was performed.

Second, coping with stress is another aspect of human pregnancy that has not received much attention thus far. Especially, studying coping in a normal risk population of pregnant women may give more insight into coping processes that naturally occur during pregnancy. This topic will be addressed in **chapter 5**. The potential mediating role of coping on the distress response is elaborated in **chapter 6**.

Third, in **chapter 7**, multidimensional models of prenatal stress will be formulated and tested by means of structural equation modeling. These models incorporate various aspects of stress that may cause an emotional response, i.e. distress. According to the stress model of Lazarus and Folkman (1984) several factors can be differentiated: stress-provoking factors, stress-mediating or -moderating factors and a stress-resulting factor. Pregnancy-related anxieties may provoke a stress response and are therefore included as stress-provoking factors, besides more common potentially stress-provoking factors like daily hassles and life events. Stress-mediating or -moderating factors included in the present study are coping style (as described in chapter 5), social support and neuroticism. Finally, a latent construct of distress is formulated by means of several questionnaires that measure the amount of perceived stress or anxiety.

After describing the emotional aspects of pregnant women in chapter 4 through 7, resulting in a multidimensional model of distress in pregnancy, the possible harmful effects of prenatal maternal distress on the infant at the age of 3 and 8 months is analyzed in the remaining chapters to address the third aim of this thesis. From animal studies, described in chapter 3, we learned that prenatal stress may result in neuromotor and attentional problems in the offspring. Therefore, in **chapter 8** the focus is on the influence of prenatal stress on infant mental and motor development at these ages. In **chapter 9**, the temperament of the infant after exposure to prenatal maternal stress is the topic of study. In both chapters, exploratory analyses are carried out to test for the possible role of the HPA axis in mediating the effects of prenatal stress.

Finally, in **chapter 10**, a general discussion of our findings is presented and recommendations for future research are provided.

