

10

Summary of results and general discussion

10.1 Summary of results

In this thesis on the effects of prenatal stress on infant development, three parts can be differentiated.

The first part introduces the concept of prenatal influences and in particular prenatal stress. The importance of studies on prenatal determinants of later development is elucidated in chapter 1 and evidence of harmful effects of prenatal stress on postnatal development is provided by a review on animal studies on this topic in chapter 3. The aims of this thesis are formulated in chapter 2.

The second part describes and empirically tests the various aspects involved in the psychological stress of pregnant women who are expecting their first child. In this way, the concept of prenatal stress is clarified. The aspects studied include pregnancy-specific anxieties (chapter 4) and coping styles that can be found in normal-risk pregnancy (chapters 5 and 6). As a next step, multidimensional models are described in chapter 7 that specify which elements of stress contribute to perceived distress in early, mid- and late pregnancy.

Finally, the third part attempts to answer the question whether prenatal maternal stress affects infant development (chapter 8) and infant temperament (chapter 9) at the age of 3 and 8 months postpartum.

With regard to the second part of this thesis which aims to clarify the concept of prenatal stress, several topics are addressed:

1. Are pregnancy-related anxieties specific or do they reflect a general predisposition for anxiety?
2. Which aspects of coping can be differentiated in normal-risk pregnancy using the Utrecht Coping List-19?
3. Which coping style is most effective in reducing the level of distress?
4. Which aspects contribute to a multidimensional concept of distress and are these aspects specific for the different periods in pregnancy?

The outcome of these empirically tested questions is now summarized.

10.2 Are pregnancy-related anxieties specific or do they reflect a general predisposition for anxiety?

A sample of 230 nulliparous pregnant women filled out a questionnaire on pregnancy-related anxieties and several other questionnaires covering general personality factors, such as general anxiety, locus of control, appraisal of pregnancy and neuroticism. Three anxieties specifically related to pregnancy were found by means of confirmatory factor analysis; 'fear of giving birth', 'fear of bearing a physically or mentally handicapped child' and 'concern about one's appearance'. Personality factors such as trait anxiety, neuroticism, external locus of control and appraisal of pregnancy explained only a small part of the variance of these fears. Therefore, it is concluded that pregnancy-specific anxiety can be differentiated for a major part from general anxiety and other personality characteristics. Assessment of merely

general anxiety during pregnancy may therefore underestimate the level of anxiety caused by fears specifically related to pregnancy.

10.3 Which aspects of coping can be differentiated in normal-risk pregnancy using the Utrecht Coping List-19?

To answer this question, the Utrecht Coping-List 19 was filled out three times during pregnancy in our sample of pregnant women and the factor structure and its stability throughout pregnancy was determined by means of confirmatory factor analysis. Two important coping factors were found: emotion-focused coping and problem-focused coping. Emotion-focused coping includes for instance expression of feelings to others or reappraisal of the situation, and is typically directed toward regulating affect surrounding a stressful encounter. Problem-focused coping is directed toward alleviating the circumstances which produce stress and includes for instance planning and finding solutions for the problem. Especially in early pregnancy most women depended on emotion-focused coping, whereas emotion-coping scores declined with increasing gestation. Perhaps the event of a first-time pregnancy and all its associated expectations and changes for the future represented a situation that pregnant women wanted to discuss with their partner or close friends in the early period of pregnancy. Furthermore, it is suggested that coping in normal-risk pregnancy is a process rather than a personality trait, and that this process changes across time due to changing demands of the situation.

10.4 Which coping style is most effective in reducing the level of distress?

In a multidimensional model of distress in normal-risk pregnancy, the role of coping was examined. Coping appeared to have direct effects on the level of distress of pregnant women, rather than having a mediating role between general stress-provoking factors and the distress response. A temporal specificity was found for the most effective coping style used to decrease the level of distress. In early pregnancy, emotion-focused coping was most effective in reducing the level of distress, whereas in late pregnancy problem-focused coping was most useful for this purpose.

10.5 Which aspects contribute to a multidimensional concept of distress and are these aspects specific for the different periods in pregnancy?

Results from animal studies showed that prenatal stress has a negative influence on post-natal development and behavior. However, these findings are not readily comparable to results of human studies, since the stressors used in animal studies are not very relevant and comparable to stressors encountered in human pregnancy. Prenatal stress has been opera-

tionalized in numerous ways across human studies on the effects of stress during pregnancy on birth outcome and later development, making it difficult to compare the results of these studies. A multidimensional concept is most likely to describe stress accurately. Therefore, we formulated multidimensional models of prenatal distress for early, mid- and late pregnancy, which were tested by means of structural equation modeling. Stress-provoking (life events, daily hassles, pregnancy-related anxieties and appraisal of pregnancy), stress-mediating or -moderating factors (social support, coping, personality characteristics) and stress-resulting factors (perceived stress, psychological well-being, state anxiety) were included in the theoretical models of prenatal distress. The models found were specific for the early, mid and late periods of pregnancy, but neuroticisms and life events were found to predict distress throughout pregnancy. In addition, in early pregnancy the lack of control a woman perceives to have over the course of pregnancy (secondary appraisal) contributed to increased levels of distress, whereas emotion-focused coping reduced distress. In mid pregnancy, daily hassles and pregnancy-related fears increased the level of distress. In late pregnancy, a pregnancy-related fear (fear of bearing a physically or mentally handicapped child) was positively related to the level of distress and problem-focused coping was negatively associated with the level of distress. The multidimensional models offer more insight into the processes that lead to increased distress levels in pregnant women and were used in this thesis to predict postnatal development.

After testing and describing the factors involved in prenatal maternal stress in humans, the following questions were addressed in the third part of this thesis to address the third aim of this thesis; to test the hypothesis of adverse effect of prenatal stress on mental/motor development and on temperament.

5. Are psychosocial and endocrinologic measures of prenatal maternal stress related to the mental and motor development of infant at 3 and 8 months of age?
6. Are psychosocial and endocrinologic measures of prenatal maternal stress related to temperamental characteristics of infants at 3 and 8 months of age?

The results of the studies on these topics, described in chapter 8 and 9, are now summarized.

10.6 Are psychosocial and endocrinologic measures of prenatal maternal stress related to the mental and motor development of infant at 3 and 8 months of age?

In a prospective study of 170 nulliparous pregnant women and their infants, we examined the effect of early, mid and late pregnancy prenatal stress on the mental and motor development of infants at 3 and 8 months of age, assessed with the Bayley Scales of Infant Development. Prenatally stressed infants had lower scores on both mental and motor developmental indices (MDI and PDI, respectively) at the age of 8 months, after adjusting for several pre-, peri-, and postnatal confounders. On average an 8-point decline in MDI and PDI scores was found after exposure to high levels of psychosocial measures of prenatal stress. Especially

pregnancy-related fears were found to be related to adverse developmental outcome in these infants. High levels of early morning cortisol in late pregnancy were likewise associated with decreased MDI scores in 3-months-old infants, and significantly reduced PDI scores in infants at 3 and 8 months of age.

10.7 Are psychosocial and endocrinologic measures of prenatal maternal stress related to temperamental characteristics of infant at 3 and 8 months of age?

We examined the effects of prenatal psychosocial (distress, daily hassles, perceived stress and pregnancy-specific anxiety) and endocrinologic (cortisol, ACTH) measures, determined in early pregnancy, on infant temperamental characteristics in the first 8 months of life of 170 healthy fullterm infants. The results show that pregnancy-specific fears were related to a decrease in attention regulation during a standard test situation. Perceived stress of pregnant women in early pregnancy and high levels of ACTH in mid-pregnancy showed to be related to increased unadaptability of the infant, even when postnatal stress levels of the mothers were taken into account. These findings are in line with studies with nonhuman primates and suggest that prenatal stress may have a deleterious effect on the behavior of infants, which may be a risk factor for developing psychopathology later in life. The exact psychopathological mechanism of prenatal stress remains unknown, but the results of this study suggest that the HPA axis may play a role.

10.8 General discussion

10.8.1 Importance of pregnancy-specific anxieties

The studies as presented in the third part of this thesis indicate that pregnancy-related anxiety is the most powerful predictor of adverse developmental and behavioral outcome of infants at 8 months of age. In contrast, no strong evidence was found for a negative effect of the multidimensional construct of distress on infant development and temperament in the first 8 months of life. Since pregnancy-related anxiety is an albeit minor part of the higher-order construct of prenatal distress in mid- and late pregnancy, as was described in chapter 7, the separate measurement of these anxieties resulted in stronger effects on development and temperament of the infant. In the second part of this thesis, we showed that pregnancy-related anxiety can be regarded as a relatively distinctive syndrome which can be differentiated from general anxiety for a major part. Thus, pregnancy may be regarded as a special period in life accompanied by unique anxieties related to the event of pregnancy, which should not be overlooked when testing the effect of prenatal maternal stress on birth outcome and postnatal development. It is interesting to find that these pregnancy-related anxieties are predictive of infant outcome, since they may be regarded as a unique element of human pregnancy. Nonhuman primate studies have found similar results of prenatal maternal stress on offspring development and behavior, but have used very different stressors. It

seems highly unlikely that a nonhuman primate or other animal model could be able to test pregnancy-related anxiety effects on the offspring. Therefore, more human research on these anxieties is warranted. Daily hassles showed no linear effect on infant development or temperament, whereas pregnancy anxiety did, suggesting a dose-response relation for pregnancy anxiety and perhaps a threshold effect for daily hassles. This thesis has focused only on negative aspects of stress. In future research, we will test the effect of uplifts that may be regarded as stressors as well.

The multidimensional concept of distress in early pregnancy was only able to predict very low (<P25) scores of mental development. No other associations were found between this concept of distress and motor development or temperament. It was found that distress throughout pregnancy was predicted for approximately 70% by neuroticism throughout pregnancy. An interpretation of these findings could be that in our sample of normal risk middle class women, the overall neuroticism and therefore distress level was rather low. In high-risk populations (e.g. low social class) neuroticism may be more frequently found. Several trends were found for a negative effect of distress on development and temperament, but no significant differences were found, suggesting that the power of the construct may have been too low. The models of distress found in our sample should be replicated in another study, before we can draw conclusions on its significance for prenatal stress research.

10.8.2 Effects of prenatal stress at 8 rather than at 3 months

It is of interest that we find most effects of prenatal stress on development and temperament when the infant has reached the age of 8 months. At this age, a major developmental transition occurs, termed by Emde (1984) the onset of focused attachment and by Stern (1985) the discovery of intersubjectivity. Infants at this age develop stranger anxiety and separation protests appears. These changes thus involve qualitatively different social experiences for the infant (Zeanah et al., 1997) and the demands on the infants may therefore have been increased as well. Our test situation may have been more challenging for the infants at the age of 8 months, because of their increased social awareness and stranger anxiety, resulting in a more pronounced difference between infants exposed to high versus low prenatal maternal stress. Daily life may also put more strain on the prenatally stressed infant at this age, and the maternal report of elevated unadaptability suggests that prenatally stressed infants may be at risk for increased sensitivity to novel situations and stranger anxiety.

10.8.3 Interrelationships between prenatal stress effects on mental/motor development and on temperament

In the present thesis we tested the effects of prenatal stress on infant development separately from the effects on temperament. However, mental development scores (MDI) at 8-months-old infants were negatively correlated with unadaptability ($r = -.19$, $p < .05$) and posi-

tively correlated with test-affectivity and goal-directedness ($r = .37$, $p < .005$ and $r = .34$, $p < .005$, respectively). Motor development scores (PDI) of 8-months-old infants were not related to maternal reports of infant temperament, but were positively correlated with test-affectivity ($r = .30$, $p < .005$).

Since test-affectivity and goal-directedness reflect observed behavior during the Bayley Scales of Infant Development, it is not surprising to find the positive associations with MDI and PDI scores. Unadaptability was determined by maternal report and the moderate negative correlation with MDI scores is therefore of more interest. Difficulty in adapting to novel environments, such as the test situation in this study, and to new persons (the testleader), may have underestimated the MDI scores of infants with high scores on unadaptability. Another interpretation may be that the general unadaptability of an infant results in an increased risk for developmental delay. Unadaptability is negatively correlated with exploration (data not shown) which may reduce the infant's exposure to new stimuli, thereby hampering learning by experience. Therefore, we performed exploratory analysis that included unadaptability as a covariate in an ANCOVA that tested the effect of prenatal stress on MDI scores. After adjusting for the significant covariate unadaptability, the effects of daily hassles and pregnancy anxiety on MDI remained significant, although the significance level of the effect was reduced (from $p < .005$ to $p < .01$). We performed similar exploratory analysis on the effects of prenatal stress on temperament, while adjusting for developmental scores. MDI and PDI were not found to be significant covariates for the effect of stress on difficulty and unadaptability rated by maternal report and thus the effect of prenatal stress on temperament remained significant. To test the potentially mediating role of temperamental characteristics on the prenatal stress effects on development, and conversely, the mediating role of developmental scores in the relationship between prenatal stress and infant temperament in more detail, we aim to test path analytic models by means of structural equation modeling in the future. This fascinating interaction between developmental delays and temperamental difficulties after prenatal stress offer many possibilities future research on prevention and interventions programs as well.

10.8.4 Sensitive periods?

It is still questionable if a sensitive period for the effect of prenatal maternal stress on the developing fetal brain exist. Our results suggest that early and mid-pregnancy might be periods of increased vulnerability for small variations in the fetal physiological environment, caused by maternal stress, although no strong evidence for this hypothesis was found. First, the potential mediating role of the HPA axis reactivity of pregnant women was only explored in the present study and it was found that some effects of high cortisol in late pregnancy and high ACTH in mid-pregnancy were found on infant development and infant temperament, respectively. However, no relation was found between these endocrinologic measures of stress and the psychosocial measures of stress. These findings are in line with the general finding that only moderate or no correlations exist between psychological and endocrinologic stress measures. We do not know if pregnancy-related anxiety is able to cause small variations in the fetal physiological environment. At least, no evidence was found for an elevated stress hormone level in relation to pregnancy-related anxiety. In future studies we shall

analyse the relationship between cortisol day curve data and prenatal stress measures with refined statistical techniques such as multilevel modeling. Second, several limitations of the studies in this thesis should be taken into account when drawing conclusions on possible sensitive periods. A limitation of our studies is that we did not gather endocrinologic data in a very early period of pregnancy but started collecting data only from 15 weeks gestation onwards. Although for pragmatic reasons it might be hard to accomplish, it would certainly be preferred to focus on the early period of the first trimester in particular, since this reflects a period of generation of neurons and neuronal migration. Studies have indicated that cell neuronal migration is highly sensitive to various perturbations, such as toxins, viruses and genetic mutations. Moreover, to be able to test more precisely for a specific sensitive period for the harmful effects of stress another design is needed in which stress is inflicted only in a particular period of pregnancy and compared to the effects on infant development and behavior of stress exposure in another period of pregnancy. For such a design, a naturally occurring disaster such as the explosion of a fireworks storage in a residential quarter of Enschede, a town in the Netherlands, offers a well-circumscribed stressor. Infants of women living in the hitten residential quarter who were in their first trimester of pregnancy when exposed to this stressor may be compared to infants of women who were in their second or third trimester of pregnancy at the time of this disaster.

In sum, although our sample consisted of normal-risk pregnant women and healthy full-term infants, we still were able to find a small effect of prenatal stress on the development of infants in the first 8 months of life. We expect that in high-risk populations, these adverse effects of prenatal stress may be much more profound, especially if accumulating prenatal and postnatal risk factors, such as maternal smoking or alcohol-intake and adverse lifestyles, exist. The results of this thesis may then be regarded as a frame of reference.

10.9 Implications for clinical practice

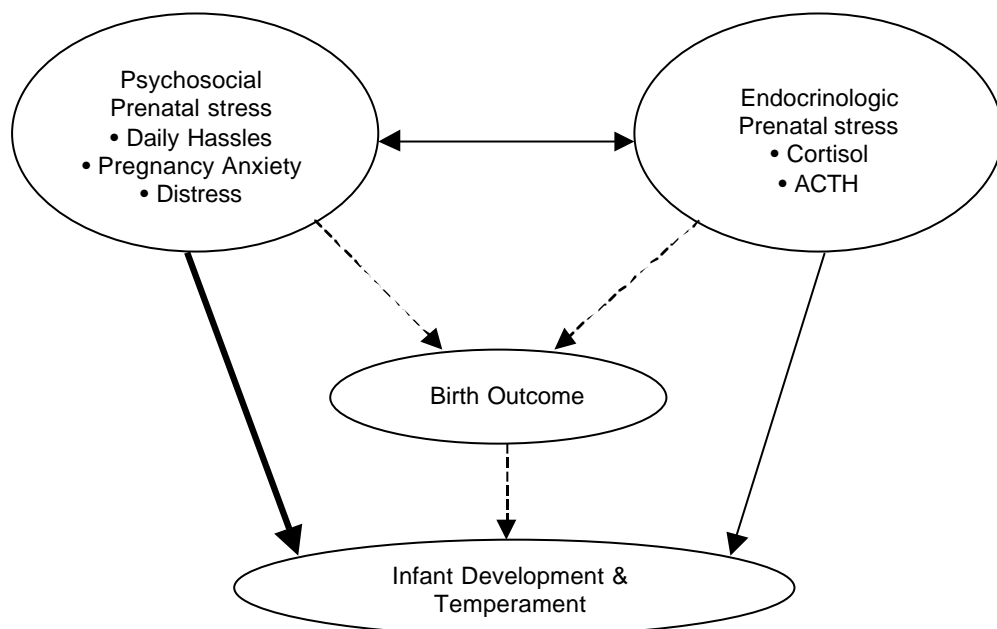
Several implications for clinicians working with normal risk pregnant women may be deduced from the present thesis. First, since pregnancy-related anxieties, such as fear of giving birth and fear of bearing a physically or mentally handicapped child, are related to adverse infant development and temperament, they deserve more attention. The short questionnaire on these anxieties, as described in chapter 4, offers a tool to investigate the amount of pregnancy-related anxiety in patients. In early pregnancy a cut-off score of 8 for both fear for giving birth and fear of bearing a handicapped child may be regarded as a risk for the fetus. Providing information and reassurance may lower these fears, especially in nulliparous women. Second, although it might be impossible to avoid stress during pregnancy, it is important that women become more aware of the possible adverse effects stress may have on their fetus. The findings of the present human study first need to be replicated, but the results of animal studies strongly point to the negative effects of prenatal stress. Therefore, without alarming pregnant women, one should consider that prevention of stress during pregnancy is advisable.

Several intervention studies have aimed to reduce distress during pregnancy, focusing on general stress and social support aspects, and thereby prevent adverse birth outcome. The results of these existing intervention programs are inconclusive. Our results suggest that per-

haps the focus of attention should be shifted towards alleviating pregnancy-specific anxiety in order to prevent adverse birth and developmental outcome.

10.10 Recommendations for future research

Several recommendations for future research may be deduced from Figure 10.1. *Figure 10.1 In this thesis we have tested the thick line representing the relationship*



between psychosocial prenatal stress and infant development and temperament. The thinner line on the right hand side reflects the explored relationship between endocrinologic prenatal stress and infant development and temperament. We do not know as yet how psychosocial prenatal stress and endocrinologic prenatal stress are related. The interrupted lines reflect several paths that may be tested in the future.

First, prenatal stress may result in premature birth or low birth weight, thereby increasing the risk of developmental and behavioral problems later in life. Including both premature and at term born infants in a study will help to test for this effect. Second, more attention should be given to the role of the HPA axis reactivity in pregnant women, and the association between endocrinologic and psychosocial measures of stress in pregnancy. Since animal studies have found that the HPA axis reactivity of prenatally stressed offspring was altered, this offers an opportunity for research in human infants' HPA axis reactivity as well. Other recom-

recommendations include research on gene/environment interaction with regard to individual sensitivity to prenatal stress effects.

Moreover, to be able to test the effect of stronger stressors on fetal and infant development, it is advisable to prospectively study the effects of disasters. Retrospective studies of the effect on the developing fetus of such severe stressors, like the Flood in 1953 and the German Invasion during WO II in the Netherlands, suggested an effect on later psychopathology. Prospectively designed studies are preferable for many reasons. Several years ago an El-Al Boeing 747-F crashed into two apartment buildings in the Bijlmermeer, a suburb of Amsterdam. Thirty-nine people were killed on the ground, more than 260 people lost their apartments and 800 people experienced the disaster at close range. More recently, a fireworks storage, located in a residential quarter, exploded in Enschede, a town in the Netherlands, leaving many people homeless and wounded, while 18 were killed. It would be advisable if pregnant women of these populations of victims would be asked shortly after the occurrence of such a disaster to participate in a prospectively designed study on the effect of such severe stressors on their fetus. Ethical principles are of course involved and should be carefully considered. From a scientific point of view, however, much can be learned for future prevention of developmental and behavioral problem in infants, if strong stress effects on the developing fetus can be examined prospectively.