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Psychosocial and endocrinologic measures of prenatal stress as predictors of mental and motor development in infancy

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Submitted

8.1 Abstract

Background: Animal studies have found that maternal stress during pregnancy can influence the developing fetus, resulting in delay of motor and cognitive development. These effects may be mediated by the hypothalamic-pituitary-adrenal (HPA) axis.

Objective: To investigate the effect of prenatal maternal stress on motor and cognitive (mental) development in a prospective design.

Methods: Self-report data about various aspects of prenatal stress (pregnancy specific anxiety, daily hassles and an overall construct of distress) were collected in nulliparous women in early, mid- and late pregnancy. In addition, cortisol in saliva and ACTH plasma levels (mid and late pregnancy) were determined. The development of the infant was measured at 3 and 8 months by means of the Bayley Scales of Infant Development.

Results: Complete data were available of 170 term-born infants. A high level of pregnancy specific anxiety (mid and late pregnancy) predicted a lower mental and motor development index score at the age of 8 months ($p < .005$) High amounts of daily hassles in early pregnancy were associated with a significant decrease of mental development at 8 months ($p<.01$). Early morning values of cortisol in late pregnancy were negatively related to both mental and motor development at the age of 3 months (mental development and motor development; $p <.05$ and $p < .005$, respectively) and 8 months (motor development; $p<.01$). All results were adjusted for a large number of covariates. Psychological and endocrinologic stress measures were unrelated in early and mid pregnancy. In late pregnancy rather moderate assocations were found between cortisol levels determined at 8 AM and daily hassles ($r=.27$, $p<.05$) and distress ($r=.25$, $p<.05$).

Conclusion: Prenatal stress, in particular pregnancy specific anxiety, appears to be one of the determinants of delay in motor and mental development in infants of 8 months of age and may be a risk factor for later developmental problems. Further systematic follow-up of the present sample is planned.

8.2 Introduction

In a series of studies, Schneider and co-workers have shown that prenatal stressors adversely affect the motor and mental development of rhesus monkeys (Schneider 1992a; Schneider 1992b; Schneider et al., 1992; 1999). Exposure to mild stress during mid pregnancy, operationalized as three noise bursts over a 10 minute period five times a week, resulted in decreased motor maturity, as evidenced by a delay in learning to self-feed, low muscle tone, inferior balance reactions, a slowed response speed, poorer coordination and a declined attention in the first months of life in comparison to control infants (Schneider, 1992a). These effects of a mild stressor could be mimicked by prenatal exposure to adrenocorticotropic hormone (ACTH) during a 2-week period (Schneider, 1992b). Recently, Schneider et al. (1999) showed that these effects were most profound after exposure to stress in early gestation, but could still be found after mid to late gestational stress. The same mild prenatal stressor appeared to have a negative effect on cognition as well. A delay in object permanence was found on a sequence of Piagetian tasks after prenatal stress (Schneider et al., 1992).

Most human studies on prenatal stress have focused on pregnancy outcome. Stress in pregnancy has been associated with premature delivery and lower birth weight adjusted for gestational age (Dunkel-Schetter, 1998; Copper et al., 1996; Lou et al., 1994; Wadwha et al., 1993). In a prospective study, it was even found that prenatal maternal stress was associated with a reduced head circumference (Lou et al., 1994). The effect on fetal head growth may reflect suboptimal brain development and may be a predictor of impaired cognitive development (Hack et al., 1991; Stanley et al., 1989; Greisen & Petersen, 1989; Ounsted et al., 1988; Chase et al., 1972). Retrospective reports indicated that infants of high-anxious pregnant women have lower scores on the mental scale of the Bayley Scales of Infant Development than infants of low anxious women (Davids et al., 1963) and that stress during pregnancy was associated with delays in early motor development and increased amounts of behavioral problems (Meijer, 1985; Stott, 1973).

We were able to identify one prospective study on the effect of prenatal stress on postnatal development in humans (Van den Bergh, 1990). In a sample of 70 healthy nulliparous women state and trait anxiety scores measured in the third trimester of pregnancy were positively correlated with a difficult temperament of the infant at 10 weeks and 7 months after birth. However, no association was found between prenatal general anxiety measures and mental or motor developmental status of the infant at this early age.

The present prospective longitudinal study was designed to examine the effects of stress in human pregnancy on both motor and mental development early in life. We took account of several potential confounders and used multidimensional models of stress in early, mid, and late pregnancy, according to previous findings (Huizink et al., 2000b). These models are specific for the early, mid and late periods of pregnancy and include various stress-provoking (e.g. life events, secondary appraisal of the pregnancy, pregnancy-related anxiety, neuroticism) and stress-mediating factors (coping styles) that contribute to the amount of distress of pregnant women. Previous results also suggested that distress and daily hassles may be relatively unrelated concepts, with different mechanisms underlying the possible effect on birth outcome and later development (Huizink et al., 2000b). In another study, we showed the existence of pregnancy anxieties which were only partly related to personality characteris-

tics; these were regarded as pregnancy-specific stress provoking factors (Huizink et al., 2000a).

The hypothalamic-pituitary-adrenal (HPA) axis has found to be one of the mediators of the effects of prenatal maternal stress on the developing fetus in animal studies (e.g. Weinstock, 1997; Weinstock et al., 1992; Fride et al., 1986; McCormick, et al., 1995). Therefore, physiological parameters reflecting the activity of the maternal HPA axis during pregnancy were also included as predictors of postnatal infant development. For that purpose, cortisol day profiles were assessed in early, mid, and late pregnancy. Adrenocorticotropic hormone (ACTH) was assessed in mid and late pregnancy in a subsample.

The following questions were addressed in this study:

1. Does prenatal maternal stress or anxiety have a negative effect on mental and/or motor development of the infant at the age of 3 and 8 months?
2. Which aspects of prenatal stress or anxiety show negative effects on the infants' developmental status at 3 and 8 months?
3. Can specific periods in pregnancy be identified which are most vulnerable for prenatal stress effects on later infant development?
4. Are indices of maternal HPA axis activity (cortisol and ACTH) related to the infants'developmental status at 3 and 8 months?

8.3 Methods

8.3.1 Participants

All participants in this study were included in a large prospective longitudinal project which investigated the influence of prenatal psychosocial factors on fetal behavior and the postnatal development of children. Subjects were recruited from a consecutive series of referrals to the Outpatient Clinic of the Department of Obstetrics of the University Medical Center Utrecht (UMCU), which is a first-line referral center for low-risk pregnancies with responsibilities for mid-wives as well, between January 1996 and July 1998. The UMCU is located outside the city of Utrecht and attracts a mixed rural and urban population of patients. From a total of 650 invited women, 230 agreed to participate. The main reason for refusing to participate was the time-consuming aspect of the prenatal part of the study, which included ultrasound recordings of the fetus. The study was approved by the ethical committee of the UMCU; participation was on a voluntary basis but written informed consent was required. Only nulliparous women with a singleton pregnancy were included. Characteristics of participants, such as maternal age, socio-economic status, and biomedical risks did not differ from those of non-participants. However, women with full-time jobs were less likely to participate.

Participants were asked to fill out questionnaires three times during pregnancy; at 15-17 weeks (early pregnancy), 27-28 weeks (mid pregnancy), and 37-38 weeks of gestation (late pregnancy). Of the 230 women who completed the questionnaires on the first occasion, 217 completed the questionnaires on the second occasion and 172 on the third occasion. The main reason for the drop in the number of participants towards late pregnancy was delivery

before 37 weeks of gestational age or delivery before the last session of data collection, which was planned near term, had taken place; other reasons were lack of interest, lack of time, stillbirth, pregnancy complications that required intensive follow-up, or relocation to another city.

Only healthy infants born near term (> 37 completed weeks of gestation) were included in the follow-up study after birth, to remain free from confounding factors involved with prematurity or health problems of the infant. The total number of participants, both the mothers and their infants, who completed the postnatal part of the study, which included an examination of the infants' development at 3 and 8 months of age, was 170. The sample of participants consisted largely of caucasian middle class women, although both lower and higher social classes were represented (Table 8.1). On average, the women were 31 years old. The majority of women (93.7%) lived together with their partner, either in wedlock or unmarried. Furthermore, at the time of their inclusion in the study, the majority of women had a paid job (87.4 %), 55.3 % working less than 38 hours a week and 44.7 % working full-time. Of the infants, 84 were boys and 86 were girls.

8.3.2 Psychosocial predictors during pregnancy

To predict infant development we used three aspects of prenatal maternal stress in early, mid, and late pregnancy, which were only moderately intercorrelated (r ranging from -.03 to .26). First, a higher-order distress score was calculated for each period of pregnancy. This score was derived by means of LISREL, a structural equation technique, according to a multidimensional model of prenatal distress that has been described in detail elsewhere (Huizink et al., 2000b). In short, the distress concept in early pregnancy involved a life event impact score, neuroticism, perceived lack of control over the course of pregnancy, and emotion-focused coping. In mid pregnancy, the life event impact score, neuroticism, daily hassles, and pregnancy-related fears (fear of giving birth and fear of bearing a handicapped child) explained significant parts of the variance in distress. In late pregnancy, the distress concept included a life event impact score, neuroticism, fear of bearing a handicapped child and problem-focused coping. Throughout pregnancy, neuroticism was the strongest predictor of distress.

Second, since we found that the frequency of daily hassles was hardly predictive of the amount of distress, it was regarded as an independent predictor of infant development. Daily hassles were measured by means of the Everyday Problem List (Alledaagse Problemen Lijst, Vingerhoets et al., 1989). This Dutch questionnaire is based on a selection of items of other questionnaires, including the Daily Hassles Scale (Kanner et al., 1981), the Everyday Problem Scale (Burks & Martin, 1985) and the Daily Life Experience Questionnaire (Stone & Neale, 1982). It measures the frequency of occurrence of daily hassles in the past month and gives an intensity score which is the subjective experience of the subject of the unpleasantness of the hassles. Examples of items are: 'You could not find important belongings', 'You were trapped in a traffic jam'. In this study, only the frequency score was used in order to stay free from confounding stress provoking and stress resulting factors in the intensity score.

Third, pregnancy-related anxiety was assessed by means of the Pregnancy Related Anxi-

eties Questionnaire-Revised (PRAQ-R), an abbreviated version of the PRAQ developed by Van den Bergh (1990). We used two subscales in the present study: fear of giving birth (3 items) and fear of bearing a physically or mentally handicapped child (4 items). This questionnaire was developed from the PRAQ of Van den Bergh (1990) and consisted of nine items that fitted to a three factor model (3 items per factor): fear of giving birth, fear of bearing a physically or mentally handicapped child, and concern about one's own appearance (Huizink et al., 2000a). Examples of items are: 'I am worried about the pain of contractions and the pain during delivery' (fear of giving birth) and 'I am afraid the baby will be mentally handicapped or will suffer from brain damage' (fear of bearing a physically or mentally handicapped child). The items were answered on a 5-point scale, ranging from 'never' to 'very often'. The Cronbach's alpha's of the subscales were all > .76 throughout pregnancy.

8.3.3 Endocrinological predictors during pregnancy

Two representatives of the HPA axis were determined. Cortisol was measured by determining the concentration of salivary cortisol which has been proven to be a valid and reliable reflection of the unbound hormone in blood (Kirschbaum & Hellhammer, 1989; Meulenberg & Hofman, 1990). Seven saliva samples were collected every two hours between 8:00 AM and 8:00 PM, to obtain cortisol day time curves in each of the three periods of pregnancy. All samples were stored at -70 0C until assayed. Cortisol in saliva was measured without extraction using an in house competitive radio-immunoassay employing a polyclonal anticortisol-antibody (K7348). [1,2]-^{3}H(N)-Hydrocortisone (NET 185, NEN-DUPONT, Dreiech, Germany) was used as a tracer following chromatic verification of its purity. The lower limit of detection was 0.5 nmol/L and interassay variation was 11.0%, 8.2%, and 7.6% at 4.7, 9.7 and 14.0 nmol/L, respectively (n = 20). Reference values for adults are 4-28 nmol/L at 8:00 AM. For each cortisol day profile, the mean, and early morning (8 AM) values were chosen to reflect a part of the maternal HPA axis activity.

At 24 and 32 weeks of gestation, 30 ml of venous blood was collected for the assessment of ACTH in a subsample of subjects (at 24 weeks: n=43, and at 32 weeks n= 37). ACTH was measured using an immunometric technique on an Advantage Chemiluminescense System (Nichols Institute Diagnostics, San Juan Capistrano, USA). The lower limit of detection was 1.0 ng/L and inter-assay variation was 11.4, 10.7 and 6.8% at 11, 68 and 310 ng/L respectively (n = 32).

The correlation coefficients between the psychosocial and endocrinological predictors were calculated. The only significant associations found between the psychosocial and endocrinological predictors, were those between the 8 AM cortisol value in late pregnancy and daily hassles ($r = .27$, $p < .05$) or distress ($r = .25$, $p < .05$) in this period of pregnancy.

8.3.4 Dependent measures of infant development

The main dependent measures were the developmental indices of the infant at the age of 3 and 8 months after birth as assessed by means of the Bayley Scales of Infant Development (BSID; Bayley, 1969) in a stardard test situation. The BSID has been translated and validated

for the Dutch population of infants (van der Meulen & Smrkovsky 1983; 1984) and therefore offers a good tool to investigate the infants' development. The mental scale results in a standard score, the *Mental Developmental Index (MDI)*, and is designed to assess sensory-perceptual acuities, discriminations, and the ability to respond to these; the early acquisition of 'object constancy' and memory, learning, and problem-solving ability; vocalizations and the beginnings of verbal communication; and early evidence of the ability to form generalizations and classifications. The second part of the BSID consists of the motor scale, which results in the *Psychomotor Developmental Index (PDI)*. The motor scale is designed to provide a measure of the degree of control of the body, coordination of the large muscles, and finer manipulatory skills of the hands and fingers.

8.3.5 Potential covariates

Data was gathered on various other aspects besides prenatal stress that may influence infant development. Descriptives of these potential covariates are shown in Table 8.1.

Prenatal factors included maternal age (in years), socio-economic status (SES), smoking and alcohol-intake during pregnancy and biomedical risks. *SES* was defined by educational level and professional level of the pregnant woman and her partner (Westerlaak et al., 1976). *Smoking behavior* was assessed by self-report, expressed as the number of cigarettes per day (cig/day) and categorized in three groups: 1) non-smokers; 2) smoking 1-10 cig/day; 3) smoking > 10 cig/day. The latter group consisted of only 7 subjects, and therefore a dichotomous variable was created: 1) non-smokers (n= 141); 2) smokers (n= 31); > = 1 cig/day. *Alcohol-intake* during pregnancy was likewise determined by self-report, and was expressed as the number of alcohol-containing beverages per week. Only 11 subjects consumed more than 2 alcohol-containing beverages per week and therefore a dichotomous variable was created: 1) non-drinkers (n= 144); 2) drinkers (n = 28); > = 1 drink per week. Our sample thus contained very few heavy smokers or drinkers, and only a relatively small number of modest smokers and drinkers. *Biomedical risk factors* included the use of medication during pregnancy, pre-existent health problems, fertility problems, gynecological risk factors (DES daughters etc.), high bloodpressure, excessive vomitting and diabetes mellitus caused by pregnancy. The risk factors were added up in a categorical variable; scores ranged from 0 - 5.

Perinatal covariates that may confound the effect of prenatal stress on infant development included birth weight (in grams) and gestational age at birth (in weeks). Also, complications during delivery, the use of medication during delivery, fetal distress, and mode of delivery (elective caesarean section or artifical delivery) were taken into account, by calculating a cumulative score of these perinatal complications (range 0-5).

Postnatal potentially covariates included in the present study are postnatal stress levels of the mother which were determined at 3 and 8 months following child birth. *Psychological well-being* was determined by means of the Dutch translation (Koeter & Ormel, 1991) of the General Health Questionnaire (GHQ-30; Goldberg, 1972). This questionnaire contains 30 questions to be answered on a four-point scale. *Perceived stress* was assessed with the Perceived Stress Scale of Cohen & Williamson (1987), using a Dutch translation. It contains 14 items on an individual's perceived stress over the last month to be answered on a 4-point scale, ranging from 'never' to 'always'.

Table 8.1
Descriptives of potential prenatal, perinatal and postnatal confounders

Confounders	
Prenatal	
Maternal age (years) ± SD	31.3 (4.9)
SES	**Educational level mother** * Low 13.6 % Middle 67.5 % High 18.9 % **Educational level partner** Low 23.4 % Middle 59.8 % High 16.8 % **Professional level mother** Low 8.0 % Middle 54.6 % High 37.4 % **Professional level partner** Low 18.0 % Middle 29.2 % High 52.8 %
Smoking	Smokers: n = 29; > = 1 cigarette per day Non-smokers: n = 141
Alcohol-intake	Drinkers: n = 26; > = 1 drink per week Non-drinkers: n = 144
Biomedical risks	No risk: n = 102 Pregnancy complications: n = 30 Medication during pregnancy: n = 25 Risk for fetus of medication: n = 4 Fertility problems: n = 48 IVF: n = 13 High bloodpressure: n = 15 Diabetus mellitus due to pregnancy: n = 3 Gynecological risk: n = 12 Pre-existent disease: n = 12 Mean score (± SD): 1 (1.2)
Perinatal	
Birth weight (grams) ± SD	3385.5 (487.3)
Gestational age at birth (weeks) ± SD	39.6 (1.9)
Perinatal complications	Partus complications: n= 25 Medication during delivery: n=88 Elective caeserean section: n= 24 Artifical delivery due to fetal distress: n=20 Mean score (± SD): 1 (1.3)
Postnatal	
Psychological well-being (GHQ-30) ± SD	3 months postpartum: 4.7 (5.1) 8 months postpartum: 3.6 (5)
Perceived stress ± SD	3 months postpartum: 25.9 (5.8) 8 months postpartum: 25.5 (5.7)

* low level: primary school, high-school education; middle level: secondary school education; high level: college or academic education

8.3.6 Statistical analysis

First, descriptive analyses were performed on all independent and dependent variables. Second, possible categorical or interval scaled covariates (SES, maternal age, gestational age, birth weight, postnatal stress of the mother) were tested for their relationships with the dependent variables by means of correlations (Pearson or Spearman when appropriate) and regression analysis. Only covariates which were significantly related to the dependent variables were included in further analyses on main effects of prenatal stress. Non-linear effects were tested within a MANCOVA with MDI and PDI scores of 3 and 8 months as dependent variables with a high/low contrast on the between-subjects factor that represented the upper and lower quartile scores in the predictors. For ACTH a median split method was used to form two groups, due to the small sample size. Dichotomous covariates (smoking and alcohol-use during pregnancy, infants' sex) were entered as a between-subjects factor in the MANCOVA. In case of a significant multivariate Hotelling's T2 test, univariate analyses were performed subsequently to locate the source of the difference. Linear effects of significant stress predictors were then examined with multiple regression analysis. The clinical relevance of prenatal predictors was explored in logistic regression analyses that attempted to differentiate mental and motor scores in the lowest quartile from scores in the higher quartile. The associations between continuous predictor variables and the dichotomized dependent variables in the logistic regression models are reported as standardized odds ratios (SOR) and 95% confidence intervals (CI). The SOR represents the change in risk due to one standard deviation change in the independent variable. To control for the possibility of chance findings due to the relatively high number of independent and dependent variables, we used multivariate techniques of analysis. With all tests, statistical significance was assumed at the level of $p < .05$.

8.4 Results

8.4.1 Descriptive analysis

In Table 8.2, means, standard deviations and range in scores of the predictors are presented. With regard to the dependent variables, the mean MDI scores were 114.9 (SD 15.0; range 71-150) and 117.7 (SD 15.5; range 76-150) at 3 and 8 months of age, respectively. The mean PDI scores were 101.3 (SD 13.7; range 61-150) and 109.4 (SD 13.5; range 77-150) at 3 and 8 months of age, respectively. The MDI scores at 3 and 8 months of age were significantly correlated ($r = .26$, $p < .0005$), and so were the PDI scores at 3 and 8 months ($r = .23$, $p < .0005$). Stronger associations were found between the MDI and PDI scores at 3 months ($r = .52$, $p < .0005$) and those at 8 months ($r = .38$, $p < .0005$).

Table 8.2
Mean, SD and range in scores of the psychosocial and endocrinologic predictors

Predictors	*Mean*	*SD*	*Range*	*N*
Psychosocial				
Daily hassles T1	9.96	6.3	0-45	170
Daily hassles T2	7.83	5.5	0-26	170
Daily hassles T3	6.41	4.3	0-23	170
Distress T1	-.02	1.0	-2.1-2.6	170
Distress T2	-.02	1.0	-1.2-7.6	170
Distress T3	.00	1.0	-1.2-8.2	170
Fear of giving birth T1	6.17	2.9	3-15	170
Fear of giving birth T2	5.92	2.7	3-15	170
Fear of giving birth T3	5.99	2.7	3-15	170
Fear of handicapped child T1	9.25	3.5	4-20	170
Fear of handicapped child T2	8.56	3.1	4-19	170
Fear of handicapped child T3	8.49	3.2	4-20	170
Endocrinologic				
Mean cortisol T1	10.57	2.3	5.2-19.8	142
Mean cortisol T2	14.38	3.1	6.3-22.3	130
Mean cortisol T3	17.35	3.8	2.8-30.8	85
Cortisol 8 AM T1	19.78	7.4	6-44	142
Cortisol 8 AM T2	23.29	6.8	9.3-41	130
Cortisol 8 AM T3	23.64	6.3	2.5-43	85
ACTH 24 weeks	16.95	9.3	5-44	43
ACTH 32 weeks	25.97	15.7	11-89	37

T1= early pregnancy; T2= mid-pregnancy; T3= late pregnancy.

8.4.2 Tests for the effects of potential covariates

Correlation coefficients were calculated between the infant developmental scores at 3 and 8 months and prenatal (SES, maternal age, biomedical risks), perinatal (gestational age at birth, birth weight and perinatal complications), and postnatal (mothers' stress levels) factors.

Infant mental development at 8 months of age was positively correlated with gestational

age at birth (r = .17, p < .05), birth weight (r = .21, p < .01), and the educational level of the mother (r = .15, p < .05), but negatively correlated with her amount of perceived stress at 3 months after delivery (r = -.28, p < .001). Infant motor development was positively related to gestational age at birth, both at 3 months (r = .17, p < .05) and at 8 months (r = .21, p < .01). No other linear relationships between potential covariates and the dependent variables were found. Multiple regression analysis with the significant correlates of infant development showed independent effects on infant mental development at 8 months of birth weight (F(1,172) = 7.56, p < .01), gestational age at birth (F(1,172) = 7.53, p < .01), and the amount of perceived maternal stress at 3 months (F(1,172) = 6.12, p < .05). These variables explained 4.2%, 4.3%, and 5.6% of the total variance in the MDI scores at 8 months, respectively. These covariates were taken into account in further analyses.

No main effects or interaction effects of the dichotomous variables reflecting smoking, alcohol-intake during pregnancy, or sex of the infant were found on MDI or PDI scores.

8.4.3 Infant mental and motor development in relation to measures of maternal prenatal stress

In this section, the MDI and PDI scores at 3 and 8 months were compared between infants of mothers who had low (<= P25) and high (> = P75) stress levels during pregnancy. This analysis was carried out using MANCOVA (including MDI and PDI scores of the infants at 3 and 8 months of age) and univariate analyses for early, mid, and late pregnancy separately to test for non-linear effects, followed by multiple regression analysis to test for linear effects. Finally, logistic regression was performed. The results are summarized in Table 8.3 and Figures 8.1-8.4.

MANCOVA showed that an overall decrease in MDI and PDI scores of infants whose mothers had reported a high amount of daily hassles in early pregnancy (F(12,188) = 5.43, p <.05), and a high level of fear of giving birth in mid- and late pregnancy (F (12, 188) = 4.37, p <.005 and F (12,188)= 4.02, p <.05, respectively), after adjusting for gestational age at birth, birth weight and the postnatal stress level of the mother. Subsequent univariate analyses showed that the decline in MDI scores at the age of 8 months is significant for daily hassles in early pregnancy, and for fear of giving birth in mid- and late pregnancy (see Figs. 8.1-8.3). No linear effect of psychosocial stress on MDI scores could be found. Univariate analyses furthermore showed that the difference in PDI scores, when comparing women high on fear of giving birth in mid-pregnancy with women low on this fear, was significant in infants at the age of 8 months (see Table 8.3 and Figure 8.4). Multiple regression analysis showed a linear negative effect of fear of giving birth in mid-pregnancy on PDI scores, explaining 5 % of the total variance.

Logistic regression showed that daily hassles and distress in early pregnancy were independent risk factors for low (i.e. <= P25) MDI scores of infants at 8 months of age (SOR = 1.1, 95% CI 1.02 - 1.18 and SOR = 1.7, 95% CI 1.04 - 2.7, respectively). Logistic regression furthermore showed that high levels of fear of giving birth in mid-pregnancy increased the risk of having an infant with a low (i.e. <= P25) PDI score at 8 months of age (SOR=1.3, CI 1.12 - 1.56).

		MANCOVA high/low contrast			Univariate post-hoc analyses			Multiple regression analyses				
Predictors	*Da*	*F*	*df* (m,n)	*P*		*F*	*P*	*β*	R^2 total	*F*	*df*	*P*
Psychosocial												
Early pregnancy					3 months	--	n.s.	--	--	--	--	--
Daily Hassles	MDI	5.43	12,188	<.05	8 months	7.0	<.01	--	--	--	--	n.s.
	PDI				3 months	--	n.s.	--	--	--	--	--
					8 months	--	n.s.	--	--	--	--	--
Mid pregnancy					3 months	--	n.s.	--	--	--	--	--
Fear of giving birth	MDI	4.37	12,188	<.005	8 months	8.35	<.005	--	--	--	--	n.s.
	PDI				3 months	--	n.s.	--	--	--	--	--
					8 months	13.73	<.005	-.21	.05	5.30	16	<.05
Late pregnancy					3 months	--	n.s.	--	--	--	--	--
Fear of giving birth	MDI	4.02	12,188	<.05	8 months	5.34	<.05	--	--	--	--	n.s.
	PDI				3 months	--	n.s.	--	--	--	--	--
					8 months	--	n.s.	--	--	--	--	--
Endocrinologic												
Early pregnancy					3 months	6.38	<.05	-.31	.10	7.19	85	<.01
Daily Hassles	MDI	4.20	12,83	<.01	8 months	--	n.s.	--	--	--	--	--
	PDI				3 months	9.15	<.005	-.28	.14	5.16	85	<.01
					8 months	8.50	<.01	-.28	.08	7.08	85	<.01

n.s. = not significant; -- = not relevant, Da = Developmental aspects

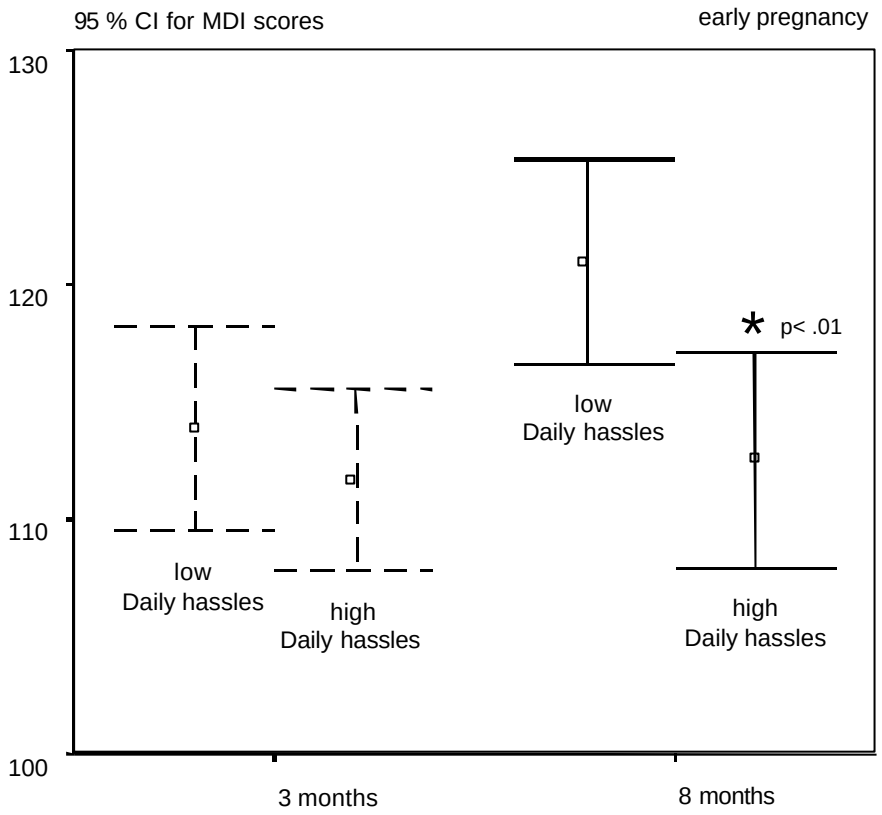

Figure 8.1
The effect of daily hassles in early pregnancy on MDI scores of infants at 3 and 8 months of age.

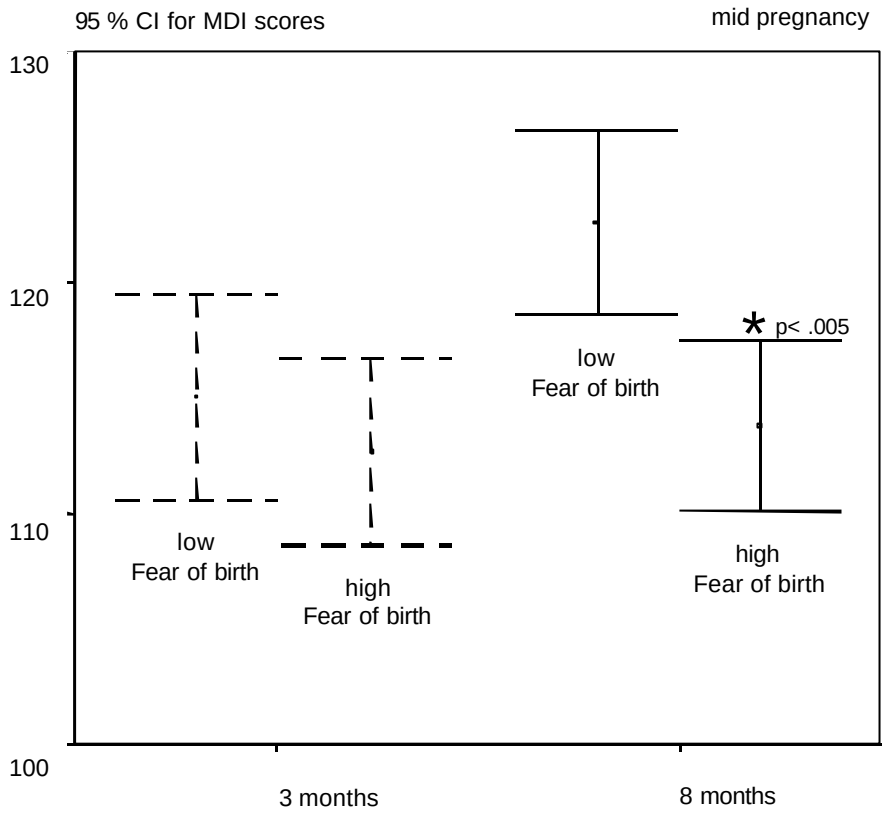

Figure 8.2
The effect of fear of birth in mid-pregnancy on MDI scores of infants at 3 and 8 months of age.

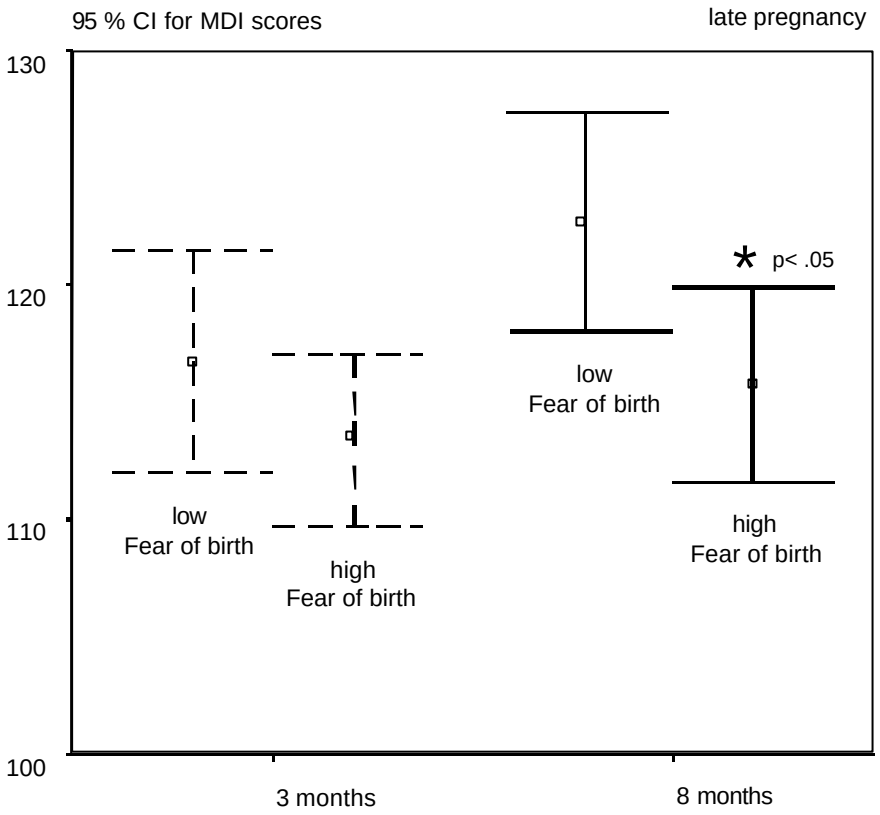

Figure 8.3
The effect of fear of birth in late pregnancy on MDI score of infants at 3 and 8 months of age.

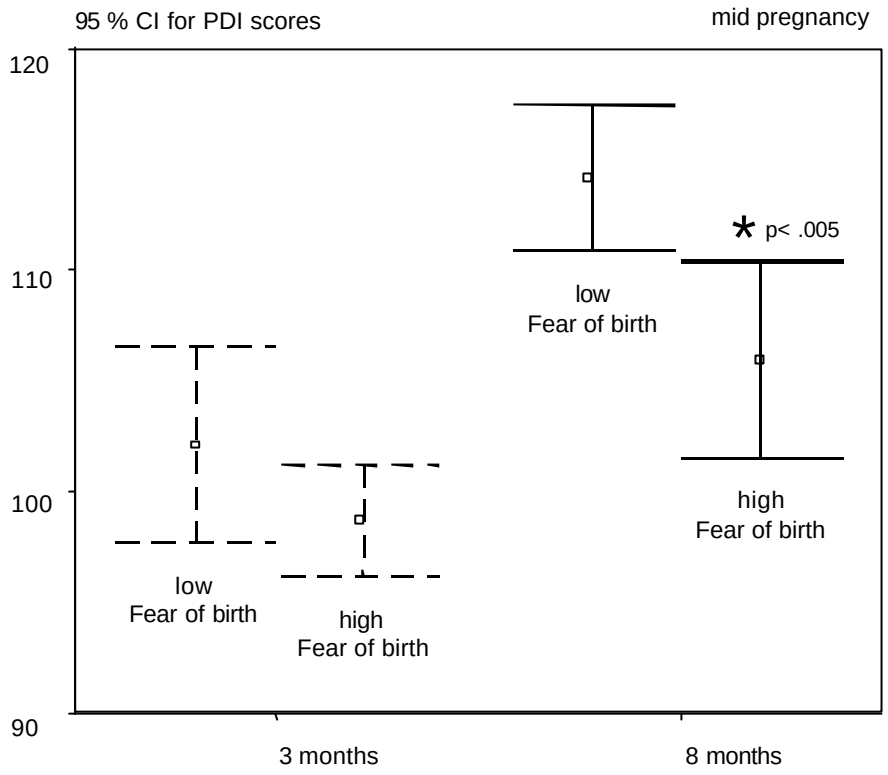

Figure 8.4
The effect of fear of birth in mid-pregnancy on PDI scores of infants at 3 and 8 months of age.

8.4.4 Infant mental and motor development in relation to measures of maternal HPA axis activity during pregnancy

In this section, analyses are presented analogous to those performed above. The results are presented in Table 8.3 and Figures 8.5 and 8.6.

MANCOVA showed that high levels of cortisol at 8 AM in late pregnancy as compared to low levels of cortisol at 8 AM in this period of pregnancy were associated with an overall decrease in MDI and PDI scores ($F(12,83) = 4.20$, $p<.01$), after adjusting for confounders. Subsequently performed univariate analyses showed that the decline in MDI scores was significant in infants at 3 months of age ($F(1,32)= 6.38$, $p< .05$), whereas the effect of high cortisol on PDI was significant for infants at both 3 ($F(1, 32) = 9.15$, $p<.005$) and 8 months of age ($F(1,32) = 8.50$, $p<.01$; see Figs. 8.5-8.6). Multiple regression analyses showed a linear negative effect of cortisol determined at 8 AM in late pregnancy on the MDI scores of 3-months-old infants and on the PDI scores of infants both at 3 and 8 months of age.

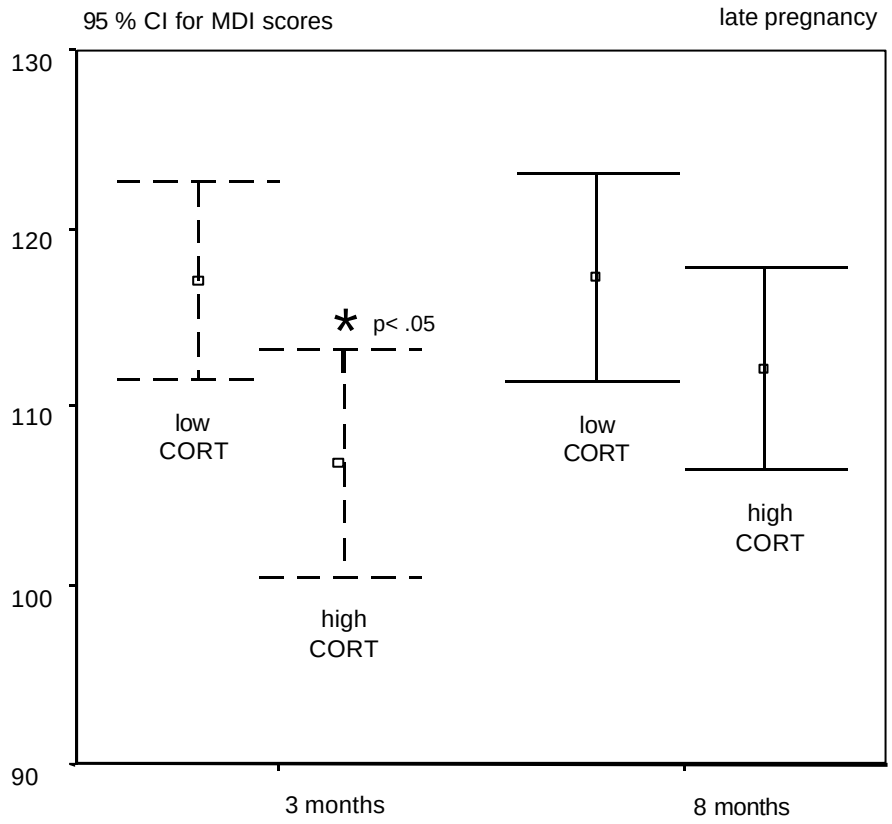

Figure 8.5 The effect of cortisol (CORT) level in saliva at 8 AM in late pregnancy on MDI scores of infants at 3 and 8 months of age.

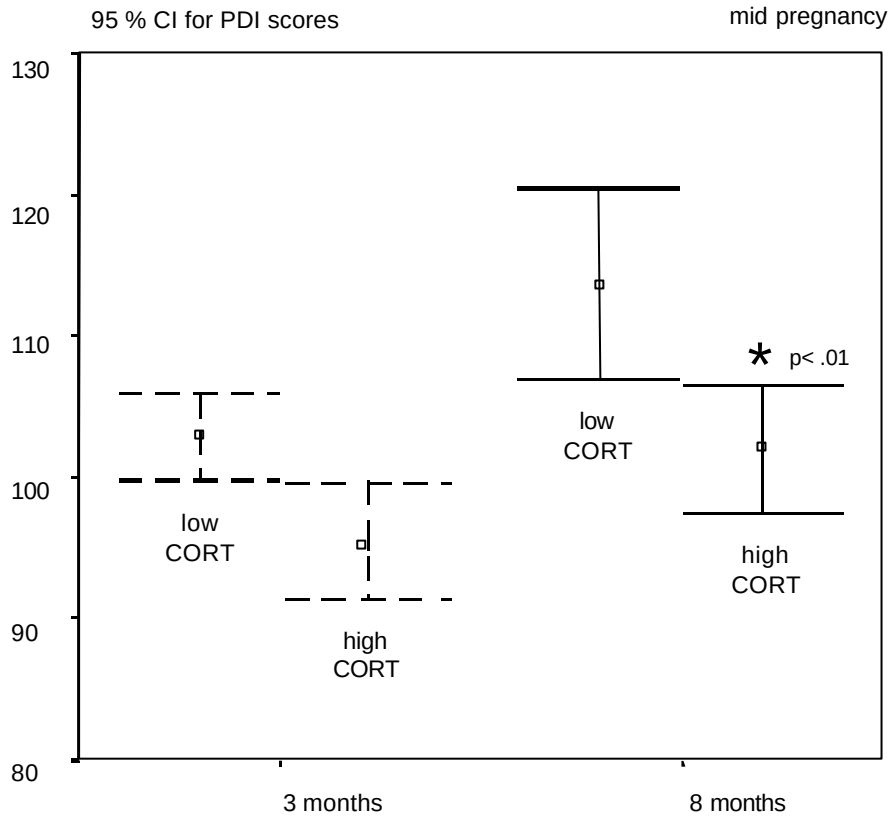

Figure 8.6
The effect of cortisol level in saliva at 8 AM in late pregnancy on PDI scores of infants at 3 and 8 months of age.

8.5 Discussion

The present study examined the effect of prenatal stress on infant development in the first 8 months of life in infants born near term. The results of this investigation indicated that prenatally stressed infants have declined MDI and PDI scores when compared to non-stressed infants. These effects of prenatal psychosocial stress were evident at the age of 8 months postpartum and remained significant after adjusting for possible confounders, such as SES, maternal age, birth weight, gestational age, biomedical risks, perinatal complications, and the mothers' postnatal stress levels (see Table 8.1). On average an 8-point decline in MDI and PDI scores was found after exposure to prenatal maternal stress, as determined by psychosocial measures. The effect on MDI scores was only found when high contrast groups were formed, whereas the negative effect of prenatal maternal stress on PDI scores was also linear.

Although the effects of prenatal stress may seem rather mild, they were adjusted for various pre-, peri- and postnatal covariates and they were found in a sample of fullterm infants. Since prenatal stress has been found to be associated with preterm delivery and low birth weight (Dunkel-Schetter, 1998; Copper et al., 1996; Wadwha et al., 1993), the present study may underestimate the influence of prenatal stress on infant development, possibly mediated by adverse pregnancy outcomes. Moreover, an increased risk of obtaining a MDI or PDI score in the lowest 25th percentile was found for specific stressors in early (daily hassles and distress) and mid-pregnancy (fear of giving birth). Thus, the present findings have clinical relevance. It is important to note that there are wide individual differences in responsivity to stressors among adults (Steptoe et al., 1996; Stansbury & Gunnar, 1994). It is therefore highly unlikely that psychological disturbances such as prenatal stress or anxiety would affect all mothers and their infants in an identical manner. The present study analyzed the effect on a group level, and therefore it could be that we underestimated the effects of stress for especially reactive women and their infants. In addition, the stressors used in this study are naturally occurring stressors and no experimental stressors such as used in animal studies, nor a circumscribed stressor by accident like a period of war of earthquake. Therefore, it is most likely that the prenatal stress levels in our sample are rather mild as compared to stressors used in animal studies. However, our overall results concur with other evidence indicating that prenatal stress administered to pregnancy monkeys induced neuromotor deficits in their offspring (Schneider, 1992; 1992a; 1992b; Schneider et al., 1999). We should note that although the MDI is classified as a 'mental developmental index', between the age of 3 and 8 months over half of the items contributing to the MDI are motor or sensorimotor tasks.

With regard to some potential confounders or modifying factors, we did not find a main effect or modifying effect of the infants' sex on developmental outcome after prenatal stress. Some animal studies have found that the male and female offspring of a low-activity strain of prenatally stressed mothers differed in their postnatal behavior (Stohr et al., 1998), suggesting that sex effects seem relevant to explain different results following the exposure to prenatal stress. In our sample, only very few women were heavy smokers or drinkers and a relatively small number of pregnant women were moderate smokers or drinkers during pregnancy. Therefore, it is not surprising that we did not find a main or interaction effect of smoking or alcohol-intake during pregnancy on infant development.

We furthermore tested which aspects of prenatal stress and anxiety had the most profound adverse effects on MDI and PDI in early infancy. Pregnancy-specific fears had a negative effect on infant development. In particular, an increased level of fear of giving birth during mid-pregnancy was found to be associated with a linear decrease in PDI scores at 8-months-old infants. Daily hassles and the multidimensional concept of distress in pregnancy also had an adverse effect on MDI scores at 8 months. These aspects of stress are only moderately intercorrelated and possibly reflect various aspects of the emotional state of pregnant women. Thus, it appears that various prenatal stress aspects and fear of giving birth were associated with reduced MDI scores at 8 months of age, but the strongest effects were found for pregnancy-related anxiety. Since the stress measures used in the present study are not comparable with the stressors used in non-human primate studies, the present findings should be replicated in another human study. Pregnancy-related anxiety has been found to predict adverse pregnancy outcome as well (Killingsworth Rini et al., 1999), and reflects a unique element of human pregnancy. Rather than studying the effects of life events and daily

hassles on birth outcome and postnatal development, the present findings suggest to focus on anxieties and stressors specifically related to pregnancy in humans.

Our results show evidence for the notion that prenatal stress factors do affect mental and motor development. However, it remains difficult to be clear about which period of pregnancy in particular is involved. First, our prenatal stress measures throughout pregnancy are not independent, that is, they are correlated over time. Second, a direct effect of stress during a particular period in pregnancy on the developing fetus would offer stronger evidence for the assumption that a sensitive period for prenatal stress would exist. These effects are tested as well in our large prospective study and will be described in detail elsewhere (Robles de Medina, 2000). Although we employ cautiousness in drawing conclusions about sensitive periods for prenatal stress, our findings are partly in line with findings of Schneider et al. (1999), who showed that sensitivity to prenatal stress of rhesus macaques peaks during early gestation and tapers off during later gestation. In our study, the strongest effects of prenatal stress on mental development were found in early and mid-pregnancy. The effects tapered off until late pregnancy, but could still be found. For motor development, mid-pregnancy stress exhibited the strongest effects. Early gestation reflects a period of generation of neurons and neuronal migration. Middle gestation is known as a period during which there is neuroblast proliferation. Late gestation and the subsequently postnatal first 18 months of life correspond to the brain growth spurt, a period during which brain weight and developmental processes proceed very quickly (Dobbings & Sands, 1979). Studies have indicated that cell neuronal migration is highly sensitive to various perturbations, such as toxins, viruses, and genetic mutations (Barth, 1987; Caviness et al., 1989; Rakic, 1988). Proper neuronal migration results in an appropriate acquisition of neuron position, which enables communication between early and late forming neurons at the critical developmental stages, before they make their synaptic connections (Rakic, 1985). Thus, theoretically, one would expect a stronger effect of prenatal stress in the early period of pregnancy. However, the negative effect of cortisol on MDI and PDI scores was only found in late pregnancy. These results should be interpreted with caution, since an effect was found for the early morning level of cortisol only, and this value is vulnerable to variation due to the circadian rhythm of cortisol secretion, where early morning values decline steeply around that time. Interestingly, only in late pregnancy, the early morning value of cortisol was moderately correlated with psychosocial measures of stress. Perhaps, this indicates that the HPA axis is reactive to stress only in late pregnancy in humans and may mediate the effects on the developing fetus in this period. Further research is warranted to elucidate this potential pathophysiologic mechanism in more detail.

Although we controlled for postnatal stress levels and psychological well-being in the present study, it is almost impossible to control for all life-style variables of the postnatal environment of the infant. Most likely, a risk profile for postnatal development would predict the development of the infant most accurately. Women high on prenatal stress may have more adverse life-styles, which would contribute to an accumulating negative effect on the infants' development. Postnatal environmental factors may contribute in an additional way to the early programmed vulnerabilty of prenatally stressed infants. In that light, it is interesting to see that the effect of prenatal psychosocial stress and anxiety were only significant when the infant had reached the age of 8 months, although a similar pattern was already found at 3 months. In contrast, the effects of cortisol were already significant for 3 months-old-infants.

Thusfar, the results of existing intervention programs designed to reduce distress during

pregnancy are inconclusive (Villar et al., 1992; Elbourne et al., 1996; Norbeck, 1994). Our results suggest that a focus on pregnancy related anxiety may increase the effectiveness of intervention studies. Moreover, the findings of the present study offer a guideline for future studies on prenatal stress effects in high-risk populations. Although the effects of stress in pregnancy are only mild in this early part of life, animal studies have shown that they could persist until later in life and retrospective human studies suggest that the effects may even increase at a later age. Early neuromotor dysfunction has been found to be associated with academic, cognitive, and behavioral problems at later ages (Gillberg & Gillberg, 1989; Marlow et al., 1993; Brumback, 1993). Already decades ago Bayley (1969) stated: `Motor abilities play important roles in the development of the child's orientation toward its environment, and they influence the quality of its interaction with the environment. Locomotion and control of the body serve to enlarge the potential sphere for new and varied experiences and for individual choices in seeking or avoiding different kinds of experience'. Thus, the effects of prenatal stress on motor development may hamper infant development in various ways. Therefore, a longer follow-up of prenatally stress-exposed children is warranted.

8.6 References

Barth, P.G. (1987). Disorders of neuronal migration. Journal of Neurological Science, 14, 1-16.

Bayley, N. (1969). Bayley Scales of Infant Development. New York: Psychological Corp.

Brumback, R.A. (1993). Is depression a neurologic disease? Behavioral Neurology, 11, 79-104.

Burks, N., and Martin, B. (1985). Everyday problems and life change events: ongoing versus acute sources of stress. Journal of Human Stress, spring, 27-35.

Caviness, V.S., Misson, J.-P. and Gadisseux, J.-F. (1989). Abnormal neuronal migrational patterns and disorders of neocortical development. In A.M. Galaburda (ed.): From reading to neuron, pp. 405-422. Cambridge, MA: MIT Press.

Chase, H.P., Welsh, N.N., Dabiere, C.S., Vasan, N.S. and Butterfield, L.J. (1972). Alterations in human brain biochemistry following intrauterine growth retardation. Pediatrics, 50, 403-411.

Cohen, S., and Williamson, G.M. (1987). Perceived stress in a probability sample of the United States. In S. Spacapan & S. Oskamp (Eds.), The social psychology of health. (pp. 31-47). Newbury Park, California: SAGE Publications.

Copper, R.L., Goldenberg, R.L., Das, A., Elder, N., Swain, M., Norman, G., Ramsey, R., Cotroneo, P., Collins, B.A., Johnson, F., Jones, P., & Meier, A.M. (1996). The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol, 175, 1286-1292.

Davids, A., Holden, R. H., & Gray, G. (1963). Maternal anxiety during pregnancy and adequacy of mother and child adjustment eight months following childbirth. Child Development, 34, 993-1002.

Dobbing, J., & Sands, J. (1979). Comparative aspects of the brain growth spurt. Early Human Development, 3, 79-93.

Dunkel-Schetter, C. (1998). Maternal stress and preterm delivery. Prenatal and Neonatal Medicine, 3, 39 - 42.

Elbourne, D., Oakley, A., and Chalmers, I. (1996). Social and psychological support during pregnancy. In Cholmers (Ed.), Effective care in pregnancy and childbirth.

Fride, E., Dan, Y., Feldon, J., Halevy, G., and Weinstock, M. (1986). Effects of prenatal stress on vulnerability to stress in prepubertal and adult rats. Physiol Behav, 37, 681-687.

Gillberg, I.C. and Gillberg, C. (1989). Children with preschool minor neurological disorders IV: behavior and school achievement at age 13. Developmental Medicine and Child Neurology, 31, 3-13.

Goldberg, D.P. (1972). The detection of psychiatric illness by questionnaire. London, Oxford University Press.

Greisen, G. and Petersen, M.B. (1989). Perinatal growth retardation in preterm infants. Acta Paediatrica Scandinavia, 360 (suppl), 43-47.

Hack, M., Breslau, N., Weissman, B., Aram, D., Klein, N. and Borawski, E. (1991). Effect of very low birth weight and subnormal head size on cognitive abilities at school age. New England Journal of Medicine, 325, 231-237.

Huizink, A.C., Robles de Medina, P.G., Mulder, E.J.H., Visser, G.H.A. and Buitelaar, J.K. (2000a).
Is pregnancy anxiety a relatively distinctive syndrome? Submitted.

Huizink, A.C., Robles de Medina, P.G., Mulder, E.J.H., Visser, G.H.A. and Buitelaar, J.K. (2000b).
Multidimensional models of prenatal distress in normal risk pregnancy. Submitted.

Kanner, A.D., Coyne, J.C., Schaefer, C. and Lazarus, R.S. (1981). Comparison of two modes of stress measurement: daily hassles and uplifts versus major life events. Journal of Behavioral Medicine, 4, 1-39.

Killingsworth Rini, C., Dunkel-Schetter, C., Wadhwa, P.D. and Sandman, C.A. (1999). Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. Health Psychology, 18, 333-345.

Kirschbaum, C., and Hellhammer, D.H. (1989). Salivary cortisol in psychobiological research: A overview. Neuropsychobiology, 22, 150-169.

Koeter, M.W.J. and Ormel, J. (1991). General Health Questionnaire. Nederlandse bewerking. Swets test services.

Lou, H.C., Hansen, D., Nordentoft, M., Pryds, O., Jensen, F., Nim, J., and Hemmingsen, R. (1994). Prenatal stressors of human life affect fetal brain development. Developmental Medicine and Child Neurology, 36, 826-832.

Marlow, N., Roberts, L. and Cooke, R. (1993). Outcomes at 8 years for children with birthweights of 1250g or less. Archives of Disease in Childhood, 68, 286-290.

McCormick, C.M., Smythe, J.W., Sharma, S. and Meaney, M.J. (1995). Sex-specific effects of prenatal stress on hypothalamic-pituitary-adrenal responses to stress and brain glucocorticoid receptor density in adult rats. Brain Res Dev Brain Res, 84, 55-61.

McKinney, W.T. and Moran, E.C. (1979). Animal models for human psychopathology. In W.E. Fann, I. Karacar, A.D. Pokorny and R.L. Williams (Eds.). Phenomenology and treatment of anxiety (pp. 141-151). New York: Spectrum Press.

Meier, A. (1985). Child psychiatric sequelae of maternal war stress. Acta Psychiatrica Scandinavia, 72, 505-511.

Meulen van der, B.F. and Smrkovky, M. (1984). Bayley ontwikkelingsschalen. Thesis. University of Groningen, the Netherlands.

Meulen van der, B.F. and Smrkovky, M. (1983). BOS 2-30. Bayley ontwikkelingsschalen: handleiding. Lisse, The Netherlands: Swets and Zeitlinger B.V.

Meulenberg, P.M.M., and Hofman, J.A. (1990). The effect of oral contraceptive use and pregnancy on the daily rhythm of cortisol and cortisone. Clinica Chimica Acta, 190, 211-222.

Norbeck, J.S. (1994). A program of social support research from concept testing through intervention trials. Utrecht: Campion Press Limited.

Ounsted, O.H., Moar, V.A. and Stott, A. (1988). Head circumference and developmental ability at the age of seven years. Acta Paediatrica Scandinavia, 77, 374-379.

Rakic, P. (1988). Defects of neuronal migration and pathogenesis of cortical malformations. Progressive Brain Research, 73, 15-37.

Rakic, P. (1985). Limits of neurogenesis in primates. Science, 227, 154-156.

Robles de Medina, P.G. (2000). The effects of maternal stress on fetal development. Dissertation.

Schneider, M.L., Roughton, E.C., Koehler A.J. & Lubach, G.R. (1999). Growth and development following prenatal stress exposure in primates: an examination of ontogenetic vulnerability. Child Development, 70, 263-274.

Schneider, M.L. (1992a). The effect of mild stress during pregnancy on birthweight and neuromotor maturation in rhesus monkey infants (Macaca mulatta). Infant Behavior and Development, 15, 389-403.

Schneider, M.L. (1992b). Delayed object permanence development in prenatally stressed rhesus monkey infants (Macaca mulatta). Occupational Therapy Journal of Research, 12, 96-110.

Schneider, M.L., Coe, C.L., and Lubach, G.R. (1992). Endocrine activation mimics the adverse effects of prenatal stress on the neuromotor development of the infant primate. Developmental Psychobiology 25, 427-439.

Stanley, O.H., Flemming, P.J. and Morgan, M.H. (1989). Abnormal development of visual function following intrauterine growth retardation. Early Human Development, 19, 87-101.

Stansbury, K. and Gunnar, M.R. (1994). Adrenocortical activity and emotion regulation. Monographs of the Society for Research in Child Development, 59, 108-134.

Steptoe, A., Fieldman, G., Evans, O. and Perry, L. (1996). Cardiovascular risk and responsivity to mental stress: the influence of age, gender and risk factors. Journal of Cardiovascular Risk, 3, 83-93.

Stohr, T., Schulte Wermeling, D., Szuran, T., Pliska, V., Domeney, A., Welzl, H., Weiner, I. and Feldon, J. (1998). Differential effects of prenatal stress in two inbred strains of rats. Pharmacol. Biochem, Behav., 59, 799-805.

Stone, A.A. and Neale, I.M. (1982). Development of a methodology for assessing daily experiences. In: A. Blaum and E.F. Singer (eds.). Advances in Environmental Psychology. Vol.4. Environment and health. Hillsdale, NJ: Erlbaum

Stott, D.N. (1973). Follow-up study from birth of the effects of prenatal stress. Dev. Med. Child Neurology, 15, 770-787.

Van den Bergh, B. (1990). The influence of maternal emotions during pregnancy on fetal and neonatal behavior. Pre and Peri Natal Psychology Journal, 5, 119-130.

Villar, J., Farnot, U., Barros, F., Victora, C., Langer, A., & Belizan, J.M. (1992). A randomized trial of psychosocial support during high-risk pregnancies. The New England Journal of Medicine, 327, 1266-1271.

Vingerhoets, A.J.J.M., Jeninga, A.J., & Menges, L.J. (1989). Het meten van chronische en alledaagse stressoren: Eerste onderzoekservaringen met de Alledaagse Problemen Lijst (APL) II. Gedrag en Gezondheid, 17, 10-17.

Wadhwa, P.D., Sandman, C.A., Porto, M., Dunkel-Schetter, C., & Garite, T.J. (1993). The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. American Journal of Obstetrics and Gynecology, 169, 858-865.

Weinstock, M. (1997). Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? Neurosci Biobehav Rev, 21, 1-10.

Weinstock, M., Matlina, E., Maor, G.I., Rosen, H., & McEwen, B.S. (1992). Prenatal stress selectively alters the reactivity of the hypothalmaic-pituitary adrenal system in the female rat. Brain Research, 595, 195-200.

Westerlaak, van J.M., Kropman, J.A. and Collaris, J.W.N. (1976). Beroepenklapper. Nijmegen, the Netherlands: Instituut voor Toegepaste Sociologie.