Prenatal Stress and Mixed-Handedness

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ABSTRACT: Atypical lateralization, as indicated by mixed-handedness, has been related to diverse psychopathologies. Maternal prenatal stress has recently been associated with mixed-handedness in the offspring. In the present study, this relationship was investigated further in a prospective, methodologically comprehensive manner. Stress levels were determined three times during pregnancy by means of questionnaires and measurements of cortisol levels. The handedness of 110 6-y-old children (48 boys) was determined by independent observers. Mixed handedness was defined as using the opposite hand for one or more of the tested activities. Logistic regression analysis showed that more maternal daily hassles in late pregnancy and maternal mixed-handedness increased the chance of mixed-handedness in the offspring. In contrast, more pregnancy-related fear in late pregnancy and a longer duration of gestation were associated with a smaller chance of being mixed-handed. Prenatal stress measured during the first two periods of pregnancy or determined by cortisol was not related to mixed-handedness in the offspring. In conclusion, reported and physiologic measures of prenatal stress in a moderately stressed pregnant population were only partly related to offspring mixed-handedness. (*Pediatr Res* 62: 586–590, 2007)

According to the fetal programming hypothesis, the environment *in utero* can alter the development of the fetus during particular sensitive periods, with a permanent effect on the set point of physiologic systems and the phenotype in later years (1).

Maternal prenatal stress has been shown to affect postnatal physical, behavioral, emotional, temperamental, and physiologic outcome of the offspring (2). In animals, maternal prenatal stress has also been linked with atypical laterality in the offspring (3–5). In humans, reduced brain asymmetry and less right-handedness have been proposed as indicators of disturbances in normal brain development and to be related to psychopathology (6). Atypical lateralization, as indicated by mixed-handedness, has been associated with autism (7), dyslexia (8), attention-deficit/hyperactivity disorder (9), and schizophrenia (10).

Two recent studies investigated the possible association between maternal prenatal distress (11) and anxiety (12) and offspring mixed-handedness. Obel and colleagues (11) reported that the 3-y-old children of mothers who had experi-

enced more distress and stressful life events during the third trimester of pregnancy had a three- to fourfold higher prevalence of mixed-handedness. Glover *et al.* (12) reported a significant association between prenatal anxiety measured at 18 wk of pregnancy and mixed-handedness of the 42-mo-old offspring. Furthermore, the authors found a positive relationship between maternal mixed-handedness and offspring mixed-handedness.

The two studies measured handedness through parental reports, and although both found maternal prenatal stress to be associated with mixed-handedness, their results differed with respect to the period in pregnancy in which stress exerted this effect.

The goal of the present study was to investigate this subject further by using independent behavioral observations instead of parental report to determine the offspring's handedness. Observations of the child's handedness were expected to be more objective than asking a parent which hand the child used to perform certain actions. Furthermore, prenatal stress was measured in early, middle, and late pregnancy and by both self-report and saliva levels of the stress hormone cortisol. This makes the present study methodologically more comprehensive than earlier studies on the subject.

METHODS

The present study is part of an ongoing longitudinal prospective investigation of the influence of prenatal factors on fetal behavior and postnatal development. The study started in 1996. Subjects were recruited from a population of pregnant women of the Outpatient Clinic of the Department of Obstetrics of the University Medical Center Utrecht (UMCU) in Utrecht, The Netherlands, between January 1996 and July 1998.

Participation was on a voluntary basis. Written informed consent was obtained from the mothers and verbal informed consent from the children. The UMCU's ethical committee for experiments on human beings approved the study.

The children participating in this study had been followed since their mothers' pregnancy as part of an ongoing prospective longitudinal study of the effects of prenatal stress in mothers on the cognitive and behavioral development of their children (13–19).

With the exception of two boys who did not want to participate in this part of the study, the study group was the same as described in Gutteling *et al.* (16) (for more details, please refer to that article).

Observational data were collected from 110 (48 boys and 62 girls) children. The mean age of the participating children was 6.7 y (SD = 0.7 y) and ranged from 5.4 y to 8.0 y. Of the 110 mothers, 98 completed the questionnaire on handedness, as did 92 fathers. Reasons for not completing

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Abbreviations: HPA, hypothalamic-pituitary-adrenal; STAI, State-Trait Anxiety Inventory

the questionnaire were lack of interest and lack of time. Furthermore, some fathers were not living with their children and had therefore not received the questionnaire.

Psychosocial measures. Psychosocial stress was assessed with five questionnaires. First, the frequency of daily hassles was measured with the Everyday Problem List (20). This self-report questionnaire was used to assess the number of daily hassles during the past 2 mo. Mothers completed the list by marking yes or no on 49 items that were very diverse in nature (e.g. "You had to wait long for an appointment").

The second measure was the impact score on the Life Events Questionnaire (21). The Life Events Questionnaire was used to measure the negative emotionality or impact of the subjects' life events (such as a divorce or moving) of the past year (at 15–17 wk of gestation) or the past 2 months (at 27–28 wk of gestation and at 38–39 wk of gestation). The impact score of this questionnaire is based on the Social Readjustment Rating Questionnaire (22). The higher the impact score, the more life event–related negative emotionality had been experienced by the subject.

Pregnancy-related anxieties were assessed as indicators of psychosocial prenatal stress. These were determined by a Dutch version of the Pregnancy Related Anxiety Questionnaire-Revised (PRAQ) (23). This self-report questionnaire consists of 34 items and has three subscales. In this study sample, only two subscales were used in this study: fear of giving birth (three items) and fear of bearing a mentally or physically handicapped child (four items). Questions concern specific fears and worries related to pregnancy. The Dutch version of the Perceived Stress Scale (PSS) of Cohen and Williamson (24) was used to measure perceived stress. The PSS measures the amount of stress subjects experienced during the past month, on a 4-point Likert scale varying from never to always (e.g. "how often have you felt nervous and 'stressed'").

Finally, the State-Trait Anxiety Inventory (STAI) (25) measured general anxiety in two ways, namely, state anxiety, which is conceptualized as a transitory emotional anxiety, and trait anxiety, which refers to a relatively stable proneness to anxiety. The STAI-state contains 20 statements that ask the respondent how she feels at the moment (e.g. "I feel upset"). Individuals respond to each item on a 4-point Likert scale, indicating the frequency with which each strategy is used (not at all to very much so). The STAI-trait contains 20 statements that ask the respondent how she generally feels (e.g. "I am a steady person"), and which are also answered on 4-point Likert scales ("almost never" to "almost always").

Endocrinological measures. Maternal salivary cortisol levels were determined as a measure of hypothalamic-pituitary-adrenal (HPA) axis function. Samples were collected with Salivettes (Sarstedt Inc.) in each of the three periods of pregnancy on a preselected day every 2 h between 0800 and 2000 h to obtain day curves. Samples were stored at -20°C until analysis. The cortisol concentrations were measured without extraction, using an in-house competitive radioimmunoassay with polyclonal anticortisol-antibody (K7348). [1,2– ^3H (N)]-Hydrocortisone (NET 185, NEN-DUPONT, Dreiech, Germany) was used as a tracer after chromatographic 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 ($n = 20$). More details on the collection of the saliva samples are described in earlier reports on this longitudinal study (17,18).

Because earlier results in this longitudinal project showed associations between prenatal morning cortisol and postnatal child characteristics (14,15,17), the 0800-h values of each pregnancy period were used as independent variables. Additionally, the mean values, area under curve, and slopes of the cortisol curves for each pregnancy period were included as independent variables in an exploratory fashion. SPSS version 12.1 was used to calculate the slope that consisted of the seven diurnal measurements. It was calculated as follows: we performed general linear modeling using the mothers as the random factor, the slope as the dependent factor, and the seven cortisol variables (0800 h to 2000 h) as the covariates. The beta values of the main effects were considered the slope. This slope in cortisol levels throughout the day is related to the shape of the circadian curve and to recovery from daily stress. The area under the curve was determined as follows: (0800-h measure + 1000-h measure) + (1000-h measure + 1200-h measure) + (1200-h measure + 1400-h measure) + (1400-h measure + 1600-h measure) + (1600-h measure + 1800-h measure) + (1800-h measure + 2000-h measure).

Child handedness. The children were visited at home. During the visit, the children's handedness was determined. Besides the handedness determination, two cognitive tests were performed as well (16). Trained research assistants who were blind to information about maternal prenatal stress evaluated the handedness of the child by scoring which hand the child used to show how they would perform eight daily activities.

The children were sitting on a chair behind a desk while they pretended to perform the activities. Scores were right, left, or both hands. With one exception (see below), the eight activities were those used by Obel and

colleagues (11): drawing, buttering bread, holding a toothbrush, using scissors, holding a fork or a spoon, holding an ice cream, taking sweets from a bag, and throwing a ball. We replaced Obel and colleagues' activity of taking sweets from a bag with taking a balloon from a bag. Children actually performed this action because the balloon was a gift that was presented in the body midline. All activities were performed once.

In the present study, mixed-handedness was scored, in line with the definition of Obel *et al.* (11), when the child performed at least one activity with the opposite hand to that with which the child performed the remaining activities. If a child performed an activity with both hands simultaneously, this activity was not used for determining that child's handedness.

To check the reliability of the handedness scoring, the first author rescored the handedness of 11 of the children from videotapes (10% of the study population, chosen at random). The interrater reliability was 100%.

Parent handedness. The handedness of both of the biologic parents was determined with an 11-item Dutch questionnaire that the parents completed shortly after the home visit. Nine items were identical to those on the scale used by Glover *et al.* (12): with which hand do you write?, draw?, throw a ball?, hold a racket?, clean your teeth?, cut with a knife?, use a hammer?, strike a match?, and use an eraser? We replaced the two remaining items of the Glover *et al.* questionnaire (deal cards and thread a needle) with stir with a spoon and hold a bottle opener. When the parents used the same hand for the 11 activities, they were accordingly classified as decisively right- or left-handed. If the parents reported preferring to use the opposite hand for any of the activities, they were classified as mixed-handed.

Covariates. Several possibly relevant variables were included as covariates. Maternal smoking and use of alcohol were measured by self-report during the first period of pregnancy and scored as 0–1 variables. Seventeen mothers had smoked during pregnancy, and 19 had consumed alcohol. Social economic status was defined by the mother's educational level: low educational level (primary school, $n = 4$), middle educational level (high school, $n = 60$), and high educational level (college or academic education, $n = 46$). Birth weight (mean = 3393 g, SD = 496), gestational age (mean = 40.1 wk, SD = 1.1 wk), maternal age (mean = 32.26, SD = 5.03 y), maternal mixed-handedness, paternal mixed-handedness, and both parents being mixed-handed, and the child's sex were also included as covariates in the analyses.

Missing values. About 10% of the prenatal stress data, which were measured three times during pregnancy, were missing. For each particular variable at each particular assessment moment, the missing values were replaced with the mean score of the group as a whole. Although the imputation with group means smoothes the data by reducing differences between persons, it was preferred over other alternatives such as imputation with the subject's score on the missing variable at another assessment moment because the stress variables were not stable throughout pregnancy (*i.e.* increased or decreased over time) (Table 1).

Fisher exact tests for each variable showed no significant difference in the number of missing values between the mothers of mixed-handed and non-mixed-handed children.

Statistical analyses. Logistic regression analyses were used to analyze the data; these analyses provide the opportunity to correct for possible confounders. All the covariates mentioned above were put into the analyses together with the prenatal stress factors. To investigate whether mixed-handedness could be predicted from the two different types of prenatal stress variables, logistic regressions with stepwise analyses, with computer-derived steps were carried out separately for the maternal psychosocial stress factors and for the maternal cortisol data. With all tests, p values <0.05 were considered statistically significant.

RESULTS

Mixed-handedness. Eighty-three children, five of whom were left-handed, did not use the opposite hand for any of the eight activities (75.5% of the sample), whereas 27 children, four of whom were mainly left-handed, were classified as mixed-handed (24.5% of the sample).

Fifteen children used the opposite hand for one activity (13.6% of the sample), and one of them was mainly left-handed (*i.e.* used the left hand for the remaining activities). Six children used the opposite hand for two activities (5.5% of the sample); none of them were mainly left-handed. Six children used the other hand for three activities (5.5% of the

Table 1. Descriptives

	First period				Second period				Third period			
	MH		NMH		MH		NMH		MH		NMH	
	<i>n</i>	Mean	<i>n</i>	Mean	<i>n</i>	Mean	<i>n</i>	Mean	<i>n</i>	Mean	<i>n</i>	Mean
Psychosocial variables												
Daily hassles	26	9.58	77	10.04	26	8.19	83	8.28	23	7.30	78	6.86
Perceived stress	26	28.31	82	27.89	26	27.52	83	28.17	23	27.52	78	27.36
Fear of giving birth	19	5.32	64	5.64	19	5.00	63	5.59	19	4.68	64	5.83
Fear of bearing a handicapped child	19	8.42	64	9.39	19	7.37	63	8.57	19	7.12	63	8.67
State anxiety	26	33.88	83	32.50	26	30.77	84	31.26	21	31.62	79	29.97
Trait anxiety	26	34.00	81	35.26	26	31.73	79	34.37	23	33.04	78	33.55
Cortisol variables												
Early morning cortisol	19	18.74	69	20.79	20	24.30	64	23.76	12	23.42	48	24.12
Mean cortisol	18	10.28	59	10.65	16	15.33	57	14.31	10	17.30	32	16.72
Cortisol slope	14	-2.49	65	-2.48	16	-1.66	58	-1.42	12	-4.02	42	-4.31
AUC	18	120.17	59	123.44	16	180.73	57	168.32	10	207.58	32	199.55

MH, mixed handedness; NMH, nonmixed handedness; AUC, area under the curve.

sample), and three of them were mainly left-handed. One of these children was a girl who used her right hand for three activities, her left for three other activities, and both hands for the remaining two activities.

Fisher exact tests showed that there were no significant differences in which specific activities were responsible for children being classified as mixed-handed.

Gender differences in mixed-handedness were not found: 29.6% of the boys were ($n = 14$) and 21% of the girls ($n = 13$) were mixed-handed (Fisher exact test, $p = 0.08$). Of the parents, 14.3% of the mothers ($n = 14$) and 22.8% of the fathers ($n = 21$) were mixed-handed (not significantly different, Fisher exact test, $p = 0.73$). The proportion of mixed-handed children in our study was comparable with that reported in other studies: 24.5% versus 18.4% in the study of Glover *et al.* (12) and 8.2%–35%, depending on the definition, in the study of Annett (26). Obel and colleagues (11) reported a lower proportion of mixed-handedness (6.2%).

Relationship between maternal prenatal psychosocial stress and endocrinological stress. Descriptives of the psychosocial and endocrinological stress scores are given in Table 1.

Correlations (Spearman or Pearson, where appropriate) were performed to investigate the relationship between maternal prenatal psychosocial and endocrinological stress variables. No significant correlations were found for any of the three pregnancy periods (correlation coefficients between 0.01 and 0.19).

Relationship between prenatal psychosocial stress and mixed-handedness. The prenatal psychosocial stress factors measured during the three periods in pregnancy were analyzed together (Table 2). No significant effects of prenatal stress on handedness in children were found for the first or second period of pregnancy. However, prenatal stress in the third period of pregnancy (wk 37–38) was associated with mixed-handedness. More daily hassles, less fear of giving birth to a handicapped child, and maternal mixed-handedness were associated with more mixed-handedness. A longer gestation was associated with a smaller chance of being mixed-handed.

Because the study group was relatively small and to have a better chance of detecting associations between prenatal stress and mixed-handedness, *post hoc* analyses with a stricter definition of mixed-handedness were also carried out. Mixed-handed children, defined as those who performed at least two activities with the opposite hand to that with which the child performed the remaining activities (11% of the children), were compared with the 75.5% of the children who performed all the activities with the same hand. The results were almost identical to those obtained with the broader definition of mixed-handedness. Again, more daily hassles in the third period of pregnancy, less fear of giving birth to a handicapped child in late pregnancy, a shorter gestation, and maternal mixed-handedness were associated with a larger chance of being mixed-handed. In addition, a trend was found for trait anxiety

Table 2. Mixed-handedness in children and maternal psychosocial prenatal stress: a logistic regression analysis with stepwise method

	B	Wald	<i>p</i>	OR	95% CI	
					Lower	Upper
Fear of a handicapped child third period	-0.55	9.87	0.002*	0.58	0.41	0.81
Longer duration of gestation	-0.10	6.33	0.01†	0.91	0.84	0.98
Daily hassles third period	0.21	6.51	0.01†	1.24	1.05	1.46
Maternal mixed-handedness	2.02	5.46	0.02†	7.53	1.38	40.93

CI, confidence interval; OR, odds ratio.

The psychosocial variables of all three pregnancy periods were included in this analysis. Only the last step is presented.

* $p < 0.01$; † $p < 0.05$; Wald's $df = 1$.

Table 3. Maternal prenatal cortisol levels and mixed-handedness in children

Predictors	<i>p</i>
Mean cortisol level in the first period of pregnancy	0.75
Mean cortisol level in the second period of pregnancy	0.89
Mean cortisol level in the third period of pregnancy	0.51
Early morning cortisol in the first period of pregnancy	0.48
Early morning cortisol in the second period of pregnancy	0.48
Early morning cortisol in the third period of pregnancy	0.42
AUC in the first period of pregnancy	0.64
AUC in the second period of pregnancy	0.95
AUC in the third period of pregnancy	0.52
Cortisol slope in the first period of pregnancy	0.44
Cortisol slope in the second period of pregnancy	0.89
Cortisol slope in the third period of pregnancy	0.51

The logistic regression analysis with stepwise method, in which the cortisol variables of all three pregnancy periods were included, resulted in a nonsignificant model. The table presents the *p* values for the cortisol variables.

measured in late pregnancy to be associated with a larger chance of being mixed-handed (OR = 1.19, *p* = 0.06).

Relationship between prenatal endocrinological measures and mixed-handedness. The maternal prenatal cortisol levels measured during the three periods in pregnancy were analyzed together. No significant effects of maternal cortisol on child mixed-handedness were found (*p* values are presented in Table 3).

DISCUSSION

In this study, we investigated whether maternal prenatal stress was associated with mixed-handedness in the offspring. Stress was assessed in three pregnancy periods by means of self-report and by measuring cortisol concentrations in saliva. Independent observations of the children's behavior were used to score the handedness of the 6-y-old offspring.

Our main finding was in the expected direction, *i.e.* children whose mothers had reported more daily hassles in late pregnancy had a 1.24 greater chance of being mixed-handed than did children whose mothers had reported fewer daily hassles in late pregnancy. Our *post hoc* analysis using a stricter definition of mixed-handedness additionally showed that mothers with greater trait anxiety had a tendency to have children with a greater chance of mixed-handedness. This supports the idea that maternal prenatal stress, measured as general stress, may influence lateralization as measured with mixed-handedness. The results are also in line with the findings of the other two recent studies (11,12), which also found a relationship between general stress, instead of specific pregnancy anxiety, and mixed handedness.

However, in our study, we also found that a late pregnancy-specific pregnancy anxiety, namely, fear of bearing a handicapped child, was negatively associated with mixed-

handedness (OR = 0.58). Thus, the children whose mothers had reported more pregnancy-related anxiety had a smaller chance of being mixed-handed.

These apparently contradictory results could be explained by possible differences in late pregnancy lifestyle that go together with maternal reports of general stress and pregnancy-related anxiety in that period. Mothers reporting high levels of general stress in the form of daily hassles (and trait anxiety) would very probably be leading active, stressful lives at the end of their pregnancies. This could result in heightened activity of both the HPA axis and the sympathetic-adrenomedullary axis, with an accompanying decrease in blood flow to the uterus. Indeed, earlier research has found maternal general anxiety in late pregnancy to be related to indices of reduced uterine blood flow (27) and alterations in blood flow in the umbilical and fetal middle cerebral arteries (28). In turn, these effects could affect brain development, increasing the chance of mixed-handedness.

Conversely, mothers reporting specific pregnancy anxiety might show a different lifestyle in late pregnancy. It is very possible that women that toward the end of their pregnancy have the specific fear of having a handicapped child take good care of themselves by following a healthy diet, sleeping and resting enough daily, and avoiding hassles and stressful situations. This healthy lifestyle could explain why these women have offspring with a smaller chance of mixed-handedness. More research is needed to determine whether this hypothesis can be accepted as an explanation of how different types of prenatal maternal stress differently affect fetal development.

We did not find effects of prenatal maternal stress measured as life events and of prenatal maternal stress measured during the earlier stages of pregnancy on mixed-handedness. Therefore, the results of our study are only partly consistent with the recently published studies by Obel *et al.* (11) and Glover *et al.* (12).

There are several possible explanations for the differences in results between the studies.

First of all, the most probable reason for not finding the associations previously reported by other authors is a possible lack of power in the present study due to the relatively small sample size.

Second, the studies were carried out at dissimilar ages (6.7 y *versus* between 3.0 and 3.5 y). The possibility exists that effects of maternal prenatal stress on lateralization vary according to the developmental stage that the child is in or that the hand preference of children becomes more evident and stable with increasing age. In this latter case, the earlier results of Obel *et al.* and Glover *et al.* could be indicating that prenatal stress is related to a later stabilization of hand preference and hence to a more frequent categorization as mixed-handed at the age of 3–3.5 y. In other words, prenatal stress could be more related to a delay in the consolidation of handedness than to a stable mixed-handed pattern.

Third, different definitions were used to categorize mixed-handedness. In the present study, mixed-handedness was scored when the child performed at least one activity with the opposite hand, which is in line with the operationalization of Obel *et al.* (11) and with Annett's (26) definition of mixed-handedness as "a

firm preference for different hands for different actions.” Glover *et al.* (12) used a different definition of mixed-handedness. Mixed-handedness was scored when the mother reported two or more of these items for which the child used *either* hand. The differences in results may thus also have been caused by differences in defining mixed-handedness.

No relationship was found between prenatal maternal cortisol levels and offspring mixed-handedness. Earlier results in this longitudinal study showed no relationship between maternal cortisol and the offspring's temperament, behavior, and learning and memory, on the one hand (16), but a positive relationship with offspring cortisol reactivity levels on the other (13,14). This could mean that these types of maternal prenatal variables are generally unrelated, as was also the case in the present study, and have independent effects on the unborn child. In fact, positive correlations between levels of cortisol and self-reported stress are often not found in stress research (29). Moreover, the associations found earlier in our study between maternal prenatal cortisol and cortisol reactivity in the offspring could at least partly be due to genetic relatedness between the mother and her child. Another possibility is that the hormone cortisol does not adequately reflect a pregnant woman's physiologic stress status. Other HPA axis hormones, such as corticotropin-releasing hormone and corticotropin, may be more important indicators of the maternal physiologic stress status.

Although we did not find clear associations between prenatal stress and mixed-handedness, we did find a negative association between gestational age and mixed-handedness. Thus, children who were older at birth were less likely to be mixed-handed. This finding is consistent with the observation that right-handedness is associated with a greater maturity at birth (26). Conversely, because all the children in our study were born after 37 wk of gestation, this finding could be due to chance.

We also found maternal mixed-handedness to be associated with child mixed-handedness. It is known that right-handedness has a genetic component (26), but to our knowledge the genetic component has not been determined for mixed-handedness. It is interesting that Glover *et al.* (12) also found maternal mixed-handedness to be positively associated with the child's mixed-handedness. This points in the direction of a possible genetic component of, as well as a prenatal environmental influence on, the offspring's mixed-handedness.

The overall conclusion from this study is that in women with low to moderate levels of late pregnancy maternal stress, higher levels of daily hassles appear to be associated with more mixed handedness in their school-age offspring. Although our results were only partly consistent with those of earlier studies, the fact that the children were older and that handedness was actually observed instead of being reported by the parents can be considered methodologically strong points that make the results reliable. To gain more insight into whether the inconsistent results between the studies are due to sample sizes, type of data, operationalizations of mixed-handedness, or age, carefully designed studies are needed. Studies should be carried out in large

samples, at different ages, and should include sophisticated behavioral observations for determining handedness.

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