Depression During Pregnancy: Is the Developmental Impact Earlier in Boys? A Prospective Case-Control Study

Priscille Gerardin, MD, PhD; Jaqueline Wendland, PhD; Nicolas Bodeau, MSc;
Armelle Galin, MSc (Psych); Stéphanie Bialobos, MSc (Psych); Sylvie Tordjman, MD, PhD;
Philippe Mazet, MD, PhD; Yves Darbois, MD, PhD; Jacky Nizard, MD, PhD;
Marc Dommergues, MD, PhD; and David Cohen, MD, PhD

Objective: Animal studies have shown sex differences in the impact of prenatal maternal stress on the offspring. The aim of this prospective case-control study was to assess the effect of prenatal depression on newborn and 1-year-old infant characteristics as related to gender, controlling for confounding variables.

Method: We screened 205 pregnant women from April 2004 to November 2006 for depressive symptoms. Inclusion in the prenatal depression group (n = 34) was based on meeting *DSM-IV* criteria for major depressive episode. We excluded postnatal depression from the control group (n = 79) by routine screening at 2 and 6 months. Newborn and 1-year-old infant characteristics were evaluated with the Neonatal Behavioral Assessment Scale (NBAS) and the Infant-Toddler Social and Emotional Assessment, respectively.

Results: Despite our use of numerous exclusion criteria (eg, at-risk pregnancy, preterm delivery), prenatal depression highly correlated with anxiety and stress scores. Male newborns of mothers with prenatal depression had lower scores than controls on the motor skills and regulation of states NBAS clusters (*P* = .03 and *P* = .026, respectively). At 1 year, infants of prenatally depressed mothers presented higher scores on generalized anxiety (*P* = .002), particularly in males (*P* = .009); activity/impulsivity (*P* = .042); and sleep problems (*P* = .023) than controls.

Conclusions: As in animal studies, depression during pregnancy may affect infant development in a way that is related to gender. Early gender differences observed to be associated with depression, stress, and anxiety during pregnancy may be a key to understanding the higher prevalence in males of child psychiatric disorders.

J Clin Psychiatry 2011;72(3):378–387
© Copyright 2010 Physicians Postgraduate Press, Inc.

Sex differences have been found in animal studies that examined the relationship between prenatal maternal stress and outcome of the offspring. Few longitudinal studies have investigated the association between depression, stress, and anxiety experienced by the mother during pregnancy and newborn development, and very few have reported results for each gender separately.

Maternal depression is one of the most common complications of the prenatal and postpartum periods. Recent studies have found that between 10% and 20% of women experience depression during their pregnancy, a rate probably higher than that of postnatal depression.[1–4] Yet, until quite recently, antenatal depression was described only as a strong risk factor for postnatal depression, not as a risk per se.[5–8]

Research on maternal depression has focused primarily on postpartum effects on mother-infant interactions, whereas much less attention has been given to antenatal depression disorder and its possible effects on child development.[9–12] The negative effects on infant development have typically been assumed to derive from the infants' disturbed early interactions with their depressive mothers. However, for most studies, the mother's emotional prenatal status was unknown.

Newborns of prenatally depressed mothers show lower scores on orientation, motor behavior, and state regulation[13,14]; display more irritability and less robustness[15]; and may cry excessively.[16] Several studies of clinical samples report a link between prenatal depression and later child development, in particular a more difficult temperament[17,18] or more negative affect in the offspring at 6 months postpartum.[19] In some studies, prenatal depression was associated with prenatal anxiety[18,20] or other cumulated risk factors, such as pregnancy-related anxiety, parenting stress, and job strain during pregnancy. More recently, findings from Deave et al[21] suggest that some effects on child development (developmentally delayed infants at 18 months of age, measured by a developmental questionnaire) ascribed to postpartum depression may be partially due to depressive symptoms during pregnancy. However, most of these studies had no neonatal measurement and consequently could not explore possible predictive links between neonatal and later effects of prenatal depression on child development. It is noteworthy that a study by Dayan et al[22] showed a significant association between prenatal depression and spontaneous preterm birth.

In summary, the consequences of prenatal depression have been poorly investigated, especially when we consider (1) the presence of several prenatal confounding factors such as stress, anxiety during pregnancy, low socioeconomic background, and/or major environmental stressor; (2) possible cumulative effects of stress, anxiety, and depression during pregnancy, as they co-occur in a substantial amount of cases; (3) the presence of perinatal or postnatal factors that

are known to affect development, such as prematurity and maternal postnatal depression; and (4) the lack of study of possible differential effects according to gender. Furthermore, only a few studies have addressed the combined effects of prenatal stress, depression, and anxiety on early infant outcome, and little is known about the complex connections between these risk factors. There is growing evidence from independent prospective studies that if a mother is stressed during pregnancy, her child is at greater risk of later psychopathology.[23] Furthermore, there is now some evidence that stress may impact on infant temperament via in utero effects.[24]

Regarding gender, only a few studies have reported results for each gender separately. Talge et al[24] argued that psychopathologic outcomes are often characterized by skewed gender distributions and that this may represent an important issue for future investigations. Gender differences have been found in infants and children whose mothers experienced emotional difficulties, such as stress or anxiety,[9,12] but none of the previous studies examined developmental characteristics in newborns.

Thus, prospective studies on prenatal depression and child development are needed in order to control for the effects of confounding variables, including low socio-economic status, malnutrition, and substance use–related problems[14]; other comorbidities such as anxiety and/or postnatal depression; stress during pregnancy; neonatal complications related to preterm delivery; and low birth weight. Gender effects should also be examined.

The aims of this prospective case-control study were (1) to examine the effect of prenatal depression on newborn characteristics and on infant development at age 1 year, as related to the infant's gender; (2) to take into account comorbid variables such as anxiety and stress; and (3) to exclude confounding variables (eg, prematurity, major environmental stressor, maternal postnatal depression).

METHOD

Design

This 20-month prospective longitudinal case-control study included several data collection time points during pregnancy and the postpartum period up to 12 months (± 1 month). Figure 1 summarizes the routine instruments used in this research according to time and mother/newborn status. Mothers were recruited in the prenatal care ward of La Pitié-Salpêtrière Hospital in Paris, France, where there are, on average, 2,300 births per year. The first mother was included in April 2004, and the last mother/infant evaluation was performed in November 2006. The study protocol was approved by the Ethics Committee of the University of Paris VI (Pitié-Salpêtrière Hospital, Paris, France; April 2004).

Participants

Mothers were recruited during their pregnancy. They were included if they fulfilled the following criteria: provision of

Figure 1. Routine Instruments and Measures Used in the Study for Mothers and Infants According to Time
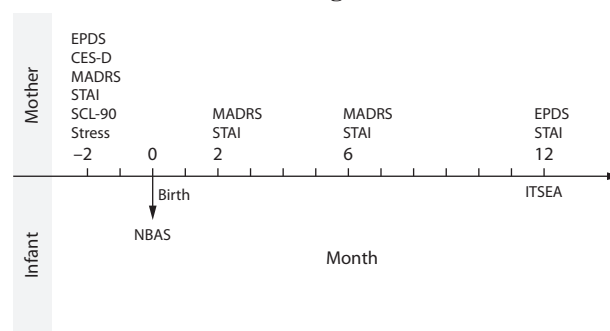
Abbreviations: CES-D = Center For Epidemiologic Studies Depression Scale, EPDS = Edinburgh Postnatal Depression Scale, ITSEA = Infant-Toddler Social and Emotional Assessment, MADRS = Montgomery-Asberg Depression Rating Scale, NBAS = Neonatal Behavioral Assessment Scale, SCL-90 = Symptom Checklist-90, STAI = State-Trait Anxiety Inventory, Stress = Sensations During Pregnancy and Life Events Questionnaire.

written informed consent to participate in the study, fluency in French, age of 20 to 38 years, and primiparity. Exclusion criteria were severe biomedical complications (acute or chronic physical diseases such as diabetes, metabolic diseases, hypertension, gestosis); multifetal pregnancies; signs of fetal malformation; drug, alcohol, or cigarette (more than 15 per day) consumption; psychotic depression; other chronic psychiatric diseases of the expectant mother except major depressive episode without psychotic features; and, after the birth of the child, prematurity. Of note, antidepressant or mood stabilizer medications are not recommended in France during pregnancy unless there is a history of psychotic depression during a previous pregnancy. Since we included only primiparous women, we did not expect to encounter any patients taking psychotropic medication. We hoped that this selection strategy would result in a community sample that had a relatively low risk of complications (during pregnancy, at birth, neonatal) and related stress. We planned to include 3 mothers per week on average because, since the key period of the study was birth, we had only 2 days for the newborn examinations.

A total of 205 mothers meeting inclusion criteria were approached and screened. Fourteen of them were excluded due to 1 or more of the exclusion criteria. Twelve mothers refused to participate because of the length of the study (18 months). Data on the reasons for noninclusion were routinely collected for screened women fulfilling the inclusion criteria. There were no statistical differences between the inclusion and the refusal groups in terms of age, sociodemographic status, or family status (single or part of a couple), except for cultural origin (French women were 87.8% of recruited mothers and 58% of mothers who refused). After an explanation of the research protocol, 164 mothers were then included. All of them provided informed consent to participate in the study. Fathers were also informed and gave their consent.

The first interview conducted by research psychologists took place during the third trimester of pregnancy (beginning of the eighth month) at the maternity hospital. This interview included the collection of sociodemographic information; screening measures with the Edinburgh Postnatal Depression Scale (EPDS), the Center For Epidemiologic Studies Depression Scale (CES-D), and the Montgomery-Asberg Depression Rating Scale (MADRS); systematic assessment for *DSM-IV* major depressive episode (MDE) criteria; the Sensations During Pregnancy and Life Events Questionnaire; the Symptom Checklist 90-Revised (SCL-90-R); and the State-Trait Anxiety Inventory (STAI). Inclusion in the prenatal depression group was based on a MADRS score ≥ 15 and *DSM-IV* criteria for MDE confirmed by the Mini-International Neuropsychiatric Interview (MINI). The second interview took place 3 days after delivery, at the maternity hospital, and was scheduled to evaluate the newborn's neurobehavioral characteristics with the Neonatal Behavioral Assessment Scale (NBAS) by a psychologist blind to the mother's prenatal status. At 2 and 6 months postpartum, mothers were interviewed with the MADRS at the maternity hospital, and the same criteria for depression as during pregnancy were used. At 1 year, the mothers were sent questionnaires at home regarding depression (EPDS) and child development (Infant-Toddler Social and Emotional Assessment [ITSEA]).

Mother's Assessments

Information on sociodemographic (age, education, origin, marital status), obstetric, and somatic factors was obtained from the medical records kept by the obstetricians or during the immediate postpartum period for variables related to birth and feeding practices.

Because of the lack of specific scales for depression during pregnancy, 3 scales for the diagnosis of depression were used. The MADRS[25] is a 10-item diagnostic scale used to measure the severity of depressive episodes in patients with mood disorders. After a clinical interview, the diagnostic scale is then used to assess patient mood changes. A cutoff score of 15 or more has been found to identify most seriously depressed women. The MADRS was translated into French and was found to have good psychometric properties.[26] The CES-D[27] is a 20-item self-report questionnaire, with well-established reliability, designed for use with the general population, that measures the level of depressive symptomatology within the last week with a cutoff score of 16 or more. Each item is scored on a 4-point scale of frequency of occurrence of the symptom ranging from rarely or none of the time (0) to most or all the time (3). It was also translated into French and found to have good psychometric properties.[28] The EPDS[29] is a 10-item self-report scale designed as a screening instrument for postnatal depression. Each item is scored on a 4-point scale (0–3), the minimum and maximum total scores being 0 and 30, respectively. Scores are transformed so that higher scores indicate a higher intensity of depressive symptoms. The EPDS evaluates the intensity of depressive symptoms within the previous 7 days. A cutoff score of 12 or more has been found to identify most seriously depressed women. The threshold of 12 was defined according to previous studies using the French validated version for research purposes.[30]

The MINI[31] is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for *DSM-IV* and *ICD-10* psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies and to be used as a first step in outcome tracking in nonresearch clinical settings.

Trait and state anxiety were assessed with the STAI form A and B.[32] This 20-item questionnaire asks about the presence of stable (trait) and current (state) anxiety symptoms. The STAI was translated into French by Bruchon-Schweitzer and Paulhan[33] and was found to have good psychometric properties.

The SCL-90[34] is a general questionnaire of psychiatric symptoms, validated for the French population by Pariente et al.[35] It includes 9 symptom scales and 3 global scores. We used the paranoid and psychotic symptom scales to exclude psychotic women.

The Sensations During Pregnancy and Life Events Questionnaire was developed and validated in France by Tordjman et al.[36] It includes 3 parts: general data (parity, sociodemographic status, medical history), stressful sensations during pregnancy, and life events questionnaire. Perceived stress assessment for each sensation or event during pregnancy is evaluated on a 5-point scale (ranging from 1 = not at all to 5 = extremely). The intent of this questionnaire is to assess stress reactivity for each trimester of pregnancy, taking into consideration some moderator variables (such as predictability, social support, or coping strategies) and discriminating chronic stress from acute stress, which may have a differential effect on fetal development.[36]

Infant's Assessment

Newborn data were obtained using the NBAS,[37] a standardized assessment in which neonatal behavior is elicited in response to a large range of stimuli. Scores can be reduced to 7 clusters, as proposed by Lester et al[38]: (1) habituation (ability to respond and to inhibit discrete stimuli while asleep), (2) orientation (ability to attend to visual and auditory stimuli and quality of overall alertness), (3) motor skills (motor performance and quality of movements and tone), (4) range of states (infant's arousal and state lability), (5) regulation of states (infant's ability to regulate his or her states when facing increasing levels of stimulation), (6) autonomic stability (signs of stress related to homeostatic adjustments of the central nervous system), and (7) reflexes (number of abnormal reflexes). The reflexes dimension, which assesses only neurologic abnormalities, is rarely used in research and was not used in this study. The autonomic stability dimension was
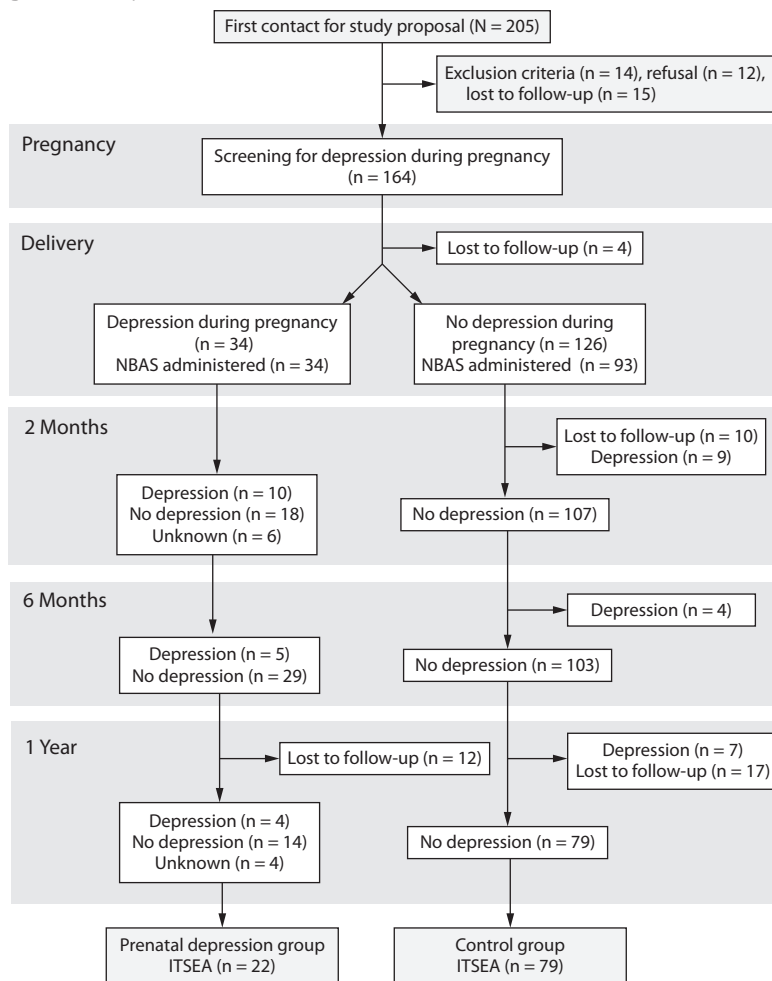
also excluded from the analysis due to the frequency of missing values. The NBAS was performed 3 days after birth. Psychologists were trained in a French Brazelton Training Center for use of the NBAS.

Social-emotional problems and competencies at 1 year were assessed with the ITSEA,[39] an adult-report questionnaire that measures social-emotional problems and competencies in 12- to 36-month-olds. The version used here includes 3 problem domains (externalizing, internalizing, and dysregulation) and the competence domain.[40] Three additional scales assess more clinical symptoms: the maladaptive scale, the social relatedness scale, and the atypical scale. The externalizing domain consists of scales that address activity/impulsivity, aggression/defiance, and peer aggression. The internalizing domain includes inhibition to novelty, separation distress, depression/withdrawal, and general anxiety scales. The dysregulation domain consists of sleep, negative emotionality, eating, and tactile sensitivity scales. The competence domain includes the following scales: attention, compliance, imitation/play, mastery motivation, prosocial peer relations, and empathy. Psychometric properties and criterion validity were good, as ITSEA problems and competencies domains were correlated with laboratory observations of attachment status, emotional regulation, and task mastery in a sample of 12-month-olds.[41] The French version shows the same latent factor structure, with good intrascale reliability.[42,43] However, dimensions that did not show good internal consistency in the French version were excluded from the analysis: depression/withdrawal, imitation and play, mastery motivation, and the 3 additional indices (maladaptive, social relatedness, and atypical).

Data Analysis

SPSS version 12.0.1 for Windows and R version 2.7.0 (SPSS Inc, Chicago, Illinois) were used for statistical computations. The Fisher exact test was used to determine whether the distributions of delivery characteristics and feeding practices were equal among mothers with prenatal depression and mothers without prenatal depression. The Student t test was used for the statistical comparison of the length and the weight of newborns for each group of mothers (the assumption of normality was assessed with the Shapiro-Wilk test, and the assumption of equal variances was assessed with an F test). In the case of a nonnormal distribution, the nonparametric Mann-Whitney test was applied. Finally, the association between continuous variables was measured using Pearson correlation. A 2-tailed P value $< .05$ was considered significant for all analyses.

RESULTS

Characteristics of the Study Groups

Prenatal depression was based on MADRS scores greater than 15. Approximately 20% of the mothers were depressed during the study period, including 14% for whom depression started during pregnancy. Those who exhibited depression only during the postpartum period were excluded from the study (Figure 2). Finally, 34 mothers were included in the prenatal depression group and 79 in the control group. The correlations between the 3 depression scales used during pregnancy were high ($r_{MADRS \times CES-D} = 0.72$, $r_{MADRS \times EPDS} = 0.66$, $r_{EPDS \times CES-D} = 0.76$). However, the mean EPDS score was below the usual severity threshold, suggesting that this self-report questionnaire designed to screen for postnatal depression may not be adapted for screening for depression during pregnancy.

Figure 2. Study Flowchart

Abbreviations: ITSEA = Infant-Toddler Social and Emotional Assessment, NBAS = Neonatal Behavioral Assessment Scale.

Table 1 summarizes the sociodemographic, pregnancy, delivery, and newborn characteristics of mothers included in the study according to their prenatal depression status. As expected, mothers came mostly from middle-to-high socioeconomic levels. (Sociodemographic level was categorized as low, middle, or high according to type of profession [National Institute of Statistics and Economic Studies criteria[44]] and level of education.) The 2 groups did not differ in any of the assessed sociodemographic characteristics or in marital situation, maternal age, or weight gain during pregnancy. There were also no differences in gestational age, methods of delivery, or neonate's birth weight and length. Apgar scores assessed 5 and 10 minutes after delivery showed good physiologic condition for all neonates. Two neonate parameters differed between groups: head circumference and weight (Table 1), but values for both groups were in the normal range.

As expected, mothers with prenatal depression showed significantly higher depression scores on all the study instruments. Despite our inclusion and exclusion criteria, depressed mothers during pregnancy still experienced a significantly higher number of stressful life events and had significantly higher scores on the life events reactivity to stress scale. Similarly, pregnancy sensation scores were significantly higher for depressed mothers. Finally, state and trait anxiety scores were significantly higher for mothers who were depressed during pregnancy.

Mothers who were depressed during pregnancy differed from control mothers in their feeding practices: in both groups, approximately 75% of mothers chose to breastfeed their infant, but 14% of depressed mothers used mixed feeding practices and 27% of control mothers used bottle feeding.

Neonatal Assessment

Analyses of the NBAS scores were performed taking into account both depression status and infant's gender (Table 2). Intragroup comparisons for female and male newborns revealed no significant difference for the prenatal depression group. However, for the control group, female newborns had significantly better scores on the habituation cluster. Between-group comparisons showed that male newborns of nondepressed mothers had higher scores than those of mothers with depression during pregnancy on motor skills and on regulation of states clusters. Furthermore, comparisons between total scores (males + females) for control and depressed groups showed that control newborns had better scores on regulation of states. Finally, on almost all clusters and for both groups, female newborns had higher scores on the NBAS dimensions.

Infant Development at Age 1 Year

Evaluation of infant socioemotional behavioral characteristics at age 1 year took into account the mother's

Table 1. Sociodemographic, Pregnancy, Delivery, and Newborn Characteristics of Mothers With Prenatal Depression and Controls

Characteristic	Prenatal Depression (n = 34)	Controls (n = 79)	P
Sociodemographic characteristics			
Mother's age, mean ± SD, y	29.8 ± 4.8	30.2 ± 4.2	.64
Father's age, mean ± SD, y	32.5 ± 6.9	31.4 ± 4.9	.63
Single, %	9	8	1
French citizen, %	88	95	.24
Socioeconomic status, %[a]			.52
High	42	54	
Middle	48	38	
Low	9	8	
Pregnancy characteristics, mean ± SD			
Weight gain, kg	11.3 ± 7.4	9.7 ± 6.8	.33
MADRS score	19.4 ± 4.3	6.0 ± 4.0	<.001***
EPDS score	7.3 ± 6.1	3.9 ± 3.7	.03*
CES-D score	23.1 ± 8.8	9.7 ± 6.2	<.001***
STAI A score	44 ± 14.8	30.6 ± 8.5	<.001***
STAI B score	42 ± 8.9	32.6 ± 8.1	<.001***
Sensations During Pregnancy and Life Events Questionnaire results, mean ± SD			
No. of life events	15.1 ± 8.1	9.6 ± 6.6	.003**
Life events reactivity score	51.2 ± 31.5	25.1 ± 20.4	.008**
No. of pregnancy sensations	31.3 ± 16.4	16.1 ± 8.9	<.001***
Pregnancy sensations reactivity score	96.8 ± 54.6	41.6 ± 28.7	<.001***
Delivery characteristics, %			
Type of delivery			.06
Vaginal	76	91	
Cesarean section	24	9	
Epidural	100	91	
Newborn characteristics, mean ± SD			
Head circumference, cm	35.4 ± 1.7	34.8 ± 1.3	.039*
Weight, g	3620 ± 480.0	3387 ± 441.0	.029*
Length, cm	50.3 ± 2.0	49.3 ± 2.2	.08
Apgar 5-minute score	10 ± 0.2	10 ± 0	.13
Apgar 1-minute score	9.9 ± 0.3	9.8 ± 0.5	.65
Feeding practices, %			
Bottle	11	27	.013*
Breast	75	72	
Mixed	14	1	

[a]Sociodemographic status was categorized as low, middle, or high according to type of profession (National Institute of Statistics and Economic Studies criteria) and level of education.
*Significant (P < .05). **Highly significant (P < .01). ***Extremely significant (P < .001).
Abbreviations: CES-D = Center For Epidemiologic Studies Depression Scale, EPDS = Edinburgh Postnatal Depression Scale, MADRS = Montgomery-Asberg Depression Rating Scale, STAI = State-Trait Anxiety Inventory.

depression status during pregnancy and the infant's gender (Table 3). Some items of the aggression/defiance scale, which showed significant results, are detailed in Table 3; otherwise, only global scale scores are presented. Intragroup analysis revealed no significant difference between male and female infants for the group of mothers who were depressed during pregnancy. For the control group, female infants had higher scores than males on the dimensions related to social/relational competencies, such as compliance and prosocial peer relation.

Between-group comparisons showed that male infants of prenatally depressed mothers presented significantly higher generalized anxiety scores than control male infants. Total scores (male + female) of generalized anxiety were

Table 2. Neonatal Behavioral Assessment Scale (NBAS) Scores (mean ± SD) at Birth for Infants of 34 Mothers With Prenatal Depression and 93 Controls

	Prenatal Depression			Controls			Group Comparisons: Prenatal Depression vs Controls		
NBAS Dimension	Males[a] (n = 16)	Females[b] (n = 11)	Males vs Females, P	Males[c] (n = 38)	Females[d] (n = 26)	Males vs Females, P	Males, P	Females, P	Total, P
Habituation	5.4 ± 1.8	6.4 ± 1.5	.31	5.3 ± 2.0	6.7 ± 1.4	.03*	.848	.62	.914
Orientation	4.6 ± 1.9	5.6 ± 1.2	.234	4.7 ± 1.8	5.3 ± 1.7	.167	.897	.922	.702
Motor skills	4.3 ± 0.8	4.8 ± 0.8	.124	4.9 ± 0.8	4.7 ± 1.0	.495	.03*	.656	.163
Range of states	3.1 ± 0.9	3.5 ± 0.7	.254	3.5 ± 0.7	3.2 ± 0.9	.37	.145	.537	.704
Regulation of states	3.7 ± 1.9	4.8 ± 1.5	.081	5.0 ± 1.6	5.4 ± 1.5	.353	.026*	.366	.045*

[a]Ns range from 11 to 16. [b]Ns range from 5 to 11. [c]Ns range from 23 to 38. [d]Ns range from 15 to 26.
*Significant (P < .05).

Table 3. ITSEA Scores (mean ± SD) at 1 Year for Infants of 22 Mothers With Prenatal Depression and 79 Controls

	Prenatal Depression			Controls			Group Comparisons: Prenatal Depression vs Controls		
ITSEA Dimension	Males[a] (n = 13)	Females[b] (n = 7)	Males vs Females, P	Males[c] (n = 42)	Females[d] (n = 32)	Males vs Females, P	Males, P	Females, P	Total, P
Externalizing symptoms									
Activity/impulsivity	0.6 ± 0.4	0.8 ± 0.4	.497	0.6 ± 0.4	0.4 ± 0.4	.228	.46	.076	.042*
Peer aggression	0.3 ± 0.3	0.3 ± 0.3	1	0.2 ± 0.2	0.2 ± 0.2	.552	.215	.38	.127
Aggression/defiance	0.4 ± 0.2	0.5 ± 0.3	.381	0.4 ± 0.3	0.3 ± 0.2	.78	.706	.203	.124
Defiance	0.9 ± 0.5	1.0 ± 0.6	.464	0.8 ± 0.4	0.8 ± 0.5	.818	.911	.342	.272
Relational defiance	0.1 ± 0.2	0.3 ± 0.4	.063	0.2 ± 0.3	0.2 ± 0.2	.734	.16	.222	.87
Dispositional aggression	0.3 ± 0.3	0.3 ± 0.3	.64	0.2 ± 0.4	0.2 ± 0.3	.65	.152	.231	.029*
Oppositional/defiant aggression	0.2 ± 0.3	0.3 ± 0.4	.605	0.1 ± 0.2	0.1 ± 0.3	.59	.179	.038*	.017*
Internalizing symptoms									
Generalized anxiety	0.2 ± 0.2	0.2 ± 0.2	1	0.1 ± 0.1	0.2 ± 0.2	.137	.009**	.199	.002**
Separation distress	1.0 ± 0.5	0.9 ± 0.4	1	0.9 ± 0.4	0.9 ± 0.4	.588	.662	.854	.38
Inhibition to novelty	0.9 ± 0.5	0.7 ± 0.3	.441	0.7 ± 0.5	0.7 ± 0.5	.921	.176	.985	.161
Dysregulation symptoms									
Sleep	0.5 ± 0.5	0.5 ± 0.3	.873	0.3 ± 0.5	0.3 ± 0.4	.722	.119	.127	.023*
Negative emotionality	0.6 ± 0.4	0.7 ± 0.5	1	0.5 ± 0.3	0.5 ± 0.3	.555	.376	.521	.094
Eating	0.3 ± 0.2	0.2 ± 0.2	.439	0.2 ± 0.3	0.3 ± 0.2	.31	.121	.823	.324
Tactile sensitivity	0.4 ± 0.3	0.4 ± 0.2	.313	0.3 ± 0.2	0.3 ± 0.3	.816	.552	.22	.139
Competence									
Compliance	0.9 ± 0.3	0.9 ± 0.3	.749	0.9 ± 0.4	1.2 ± 0.3	.001***	.936	.065	.236
Attention	1.1 ± 0.5	1.2 ± 0.5	.718	1.3 ± 0.5	1.3 ± 0.5	.835	.276	.704	.197
Empathy	0.7 ± 0.6	0.7 ± 0.5	.659	0.7 ± 0.5	0.9 ± 0.6	.099	.834	.718	.88
Prosocial peer relations	0.8 ± 0.5	0.9 ± 0.5	.701	0.8 ± 0.4	1.1 ± 0.5	.003**	.914	.576	.823

[a]Ns range from 10 to 13. [b]Ns range from 6 to 7. [c]Ns range from 35 to 42. [d]Ns range from 24 to 32.
*Significant (P < .05). **Highly significant (P < .01). ***Extremely significant (P < .001).
Abbreviation: ITSEA = Infant-Toddler Social and Emotional Assessment.

also reliably higher in the depression group as compared to the control group. Groups did not differ on other internalizing symptoms. For externalizing symptoms, female infants in the depression group showed more oppositional/defiant aggression behaviors than controls. These behaviors were also significantly more frequent for the whole group of infants (males + females) of prenatally depressed mothers compared to infants in the control group. This was also the case for dispositional aggressive behaviors. Similar results were found when we examined the activity/impulsivity scores: infants of prenatally depressed mothers, on average, had significantly higher scores than control infants. Finally, infants of mothers who were depressed during pregnancy presented significantly more symptoms of sleep problems compared to infants in the control group.

DISCUSSION

Prenatal Depression Effects on Fetus' Development: Are Boys Particularly at Risk?

This is the first prospective study that addresses the question of whether depression during pregnancy may affect newborn development as related to the infants' gender. Timing of assessments included 2 particular points: (1) before the infant's third day of life, when differences may not be ascribed to mother-newborn interaction effects, and (2) at 1 year of age.

Studies of neonatal sex differences in behavioral and physiologic reactivity prior to socialization show that female newborns have higher (which means better) scores on several NBAS items and clusters.[45,46] However, Canals et al[47]

found no significant sex-related differences 3 days after birth using the NBAS. At 4 weeks, they found variability on some NBAS clusters (orientation and autonomic stability), which may suggest that these items may be influenced by interaction with the environment. The results of the present study, which was conducted with a substantial sample of neonates, support the notion that female newborns have better performance than male newborns on the NBAS assessment.

The current study provides new data regarding prenatal depression effects on newborn characteristics and gender differences. Taken as a whole (females + males), control newborns had better scores on the regulation of states cluster than newborns of prenatally depressed mothers. Furthermore, prenatal maternal depression may have a greater impact on male newborns: male newborns of mothers depressed during pregnancy had significantly lower scores on motor skills and regulation of states clusters than control male newborns. To date, none of the previous studies have examined prenatal depression effects on developmental characteristics in newborns as related to the infants' gender. Studies on maternal postnatal depression already showed that male infants appear to be more vulnerable, but effects were supposed to be attributable to qualitative differences in the way depressed mothers interact with boys and girls. For example, mothers with depressive symptoms are more likely to show intrusive behavior toward sons than toward daughters[10] and less likely to focus their speech on sons than on daughters.[48] The current results support the hypothesis that maternal prenatal depression affects boys and girls differently, as early as birth, suggesting that male and female fetuses are not affected in the same way in the womb, as discussed later in this article.

Regardless of gender effects, the results of the present study are in agreement with those of previous research that found a link between maternal depression and a perturbation of the newborn's regulation of states and related characteristics.[14,16,49,50] However, in previous research, mothers and newborns had several concurrent risk factors, such as a variety of ethnicity, low to middle socioeconomic status, prematurity, and low birth weight. Field et al[14] have in fact observed that the large proportion of unexplained variance in neonatal neurobehavioral profiles points to additional potential factors that were not accounted for in their study.

The present study also shows that prenatal depression may have lingering effects on infant development and that these may vary according to the infant's gender. Both internalizing and externalizing symptoms, at 1 year of age, were significantly more frequent for infants of the depressed group. Globally (males + females), infants of prenatally depressed mothers had higher scores of generalized anxiety than control infants, whereas male infants of depressed mothers presented significantly more signs of generalized anxiety than controls. As for externalizing symptoms, female infants of the depression group showed more oppositional/defiant aggression behaviors than controls. Oppositional/defiant aggression, activity/impulsivity, and dispositional aggression were also significantly more frequent for the whole group of infants

of prenatally depressed mothers. Furthermore, infants of mothers depressed during pregnancy presented significantly more symptoms of sleep problems compared to controls. In a prospective study, Carter et al[9] found that maternal depressive symptoms, from pregnancy to 30 months postpartum, play a larger role in the emergence of problem behaviors for boys than for girls, but the authors had no neonatal measurement of infants' characteristics, and prenatal and postnatal depression status were merged. In that study, daughters of depressed mothers had elevated Child Behavior Checklist externalizing symptom scores compared with daughters of nondepressed mothers, which is consistent with our findings on oppositional/defiant aggression behaviors. Also, the authors found a trend for girls to be rated higher than boys on the competence dimension.[9] The present results support this notion, but only for the control group. Control female infants had higher scores than males on the dimensions related to social/relational competencies such as compliance and prosocial peer relation. However, given that two-thirds of our mothers with prenatal depression also had postnatal depressive symptoms, it is likely that infant's status at 1 year was related to both prenatal and postnatal effects. To assess differential effect of prenatal and postnatal depression, we performed a sensitivity analysis that was the same analysis as in Table 3 except with only infants of mothers with prenatal depression (n = 14; 7 girls, 7 boys) despite lack of power due to small groups. ITSEA scores remained significantly different between cases and controls for dispositional aggression and oppositional/defiant aggression ($P = .029$ and $P = .019$, respectively), which means that prenatal depression plays a role in this effect. Generalized anxiety and sleep trended toward a significant difference between groups ($P = .07$ and $P = .1$, respectively), meaning that both prenatal and postnatal depression may mediate this effect. In contrast, we found no difference in activity/impulsivity between groups ($P = .16$), meaning that most of the effect is mediated by postnatal depression.

Animal Models: Evidence for Sex Differences

Before we discuss how prenatal depression may affect development, some data from animal models should be mentioned. A wide range of studies in humans have pointed out the role of chronic low-grade stress in the etiology of depression[51] and also in postpartum depression.[8] The different types of stress procedures applied to pregnant rodents are well documented and have been shown to produce several behavioral and biologic dysfunctions, both in the mother[52] and in the pups.[53,54] Animal studies have underlined the behavior of the adult offspring of a mother stressed during pregnancy. They showed that the behavior of the adult offspring can be deeply altered if the mother was exposed to prenatal stress.[53,55–57] We know from these animal studies that prenatal factors can influence male and female offspring in different ways in nonhuman mammals.[58] For example, in rats and mice, feminization of sexual behavior has been described in males[59] as well as demasculinization of sexual behavior.[60]

Guinea pig females were described as presenting behavioral masculinization, whereas males showed behavioral infantilization if their mothers were exposed to prenatal stress.[61] For Kaiser and Sachser,[58] the major consequences of prenatal social stress are less pronounced male-typical behavior of the sons and a behavioral masculinization of the daughters. For many aspects of behavior, prenatal stress affects the offspring in a sex-specific and sex-reversed way, involving a complex variety of neuroendocrine pathways.

How Prenatal Depression May Affect Development

Although in the present study we selected a low-risk population (eg, middle/high socioeconomic status, low prevalence of immigrants, no prematurity) and had a control group for potentially confounding intrapartum variables, we still found, in the prenatal depression group, significantly higher scores for state and trait anxiety, stressful life events and reactivity, and pregnancy sensations. Therefore, it is likely that these psychopathologic dimensions are associated because of a shared biologic/psychological background. The mechanisms of the transmission of maternal emotional state to the fetus are still unknown, and the question of whether these mechanisms may vary in regard to the child's gender is even less explored. Although certain biologic measurements were not performed in this study, biopsychosocial research regarding this subject should be carried out in the future. Depression has been associated with a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis that is also a biologic marker of stress. This dysregulation may have a direct effect on fetal development. Some studies suggest that stress during pregnancy is also associated with neuronal death and abnormal development of the neuronal structures in the fetal brain via the glucocorticoids.[62,63] Hansen et al[64] found that a major stressful life event (death of an older child during pregnancy) increases the prevalence of fetal malformations, in particular malformations of the cranial-neural crest, and suggested that very severe prenatal stress may play an essential role during organogenesis. However, life events such as the death of an older child during pregnancy may be more closely related to depression than to stress. Increased serum cortisol and catecholamine levels may affect placental function by altering uterine blood flow and inducing uterine irritability.[65,66]

Newborns of depressed mothers, like their mothers during pregnancy, have higher cortisol and lower dopamine and serotonin levels, and they are likely to have a lower birth weight.[14] Indeed, newborns of prenatally depressed mothers are described as physiologically less developed: they have greater relative right frontal electroencephalographic asymmetry (possibly due to reduced left hemisphere activation), lower vagal tone, and less optimal scores on the Brazelton neonatal assessment (NBAS), as previously mentioned. Diego et al[67] argued that these physiologic alterations might derive not only from prenatal depression per se but probably also from the duration of the depressive symptoms. In the context of prenatal depression, prenatal stress seems to be a good model for depression as well.[68] Although

there are few data on the link between depression during pregnancy and newborn gender and behavioral differences, the available studies suggest that there are marked gender differences in the relationship between birth weight and the stress response, with boys who were smaller at birth having an enhanced HPA response to stress.[69] This observation is supported by increasing animal evidence that fetal programming of the HPA axis is different for each gender.[70,71] Cortisol level would appear to be a mediating variable, with elevation resulting from prenatal stress in several forms including depression, anxiety, anger, and daily hassles.[72]

Besides these biologic hypotheses, prenatal depression may also affect development through distortions in early mother/infant interactions. Compared to nondepressed women, women with depressive symptoms during pregnancy have been shown to handle and interact with their newborns differently in the immediate postpartum period.[73] Further, depressed mothers have been described as emotionally unavailable and unresponsive during their early interactions with their infants.[74]

Strengths and Limitations

This study is the first to explore, prospectively, the predictive value of prenatal depression on newborn behavioral characteristics and gender effects. The newborn's assessments with the NBAS not only provide an independent infant measurement but also were performed blind to the psychological status of the mother. An array of possible confounders for fetus or newborn development were obtained, and inclusion and exclusion criteria were used to limit their possible occurrence, leading to groups with low-risk status (eg, middle/high socioeconomic status, low prevalence of immigrants, no prematurity). These variables did not differ between the 2 groups except for prenatal stress, prenatal anxiety, and pregnancy sensation, suggesting that these pathologic dimensions are inherently associated. However, given (1) the prospective design, (2) our strict inclusion and exclusion criteria, (3) the duration of the study, and (4) the fact that the NBAS assessment requires optimal conditions, not always attained,[75] we obtained a relatively small sample size for some analyses (eg, ITSEA female data in the depression group), which may limit generalization of the findings. Furthermore, the present findings may be subject to criticism of respondent biases because part of the prenatal depression ratings and ratings of infant temperament characteristics and problem behaviors were obtained through maternal report.[76] However, given that we found concordant findings with an independent observation at birth, the results based on self-report data (ITSEA) seem valuable. Regarding the 1-year data, our analysis included several mothers who continued to show depressive symptomatology after delivery. Although we performed a sensitivity analysis with only infants of mothers with prenatal depression, we consider this result only exploratory. Finally, we did not explore family history of mood disorders, although it may be an important variable (eg, higher genetic vulnerability).

Clinical Implications

Prenatal depression appears to be a risk factor for child development, in particular for boys. Perturbation of newborn characteristics is in itself a risk factor for postnatal depression and disturbed mother-infant interaction.[75,77] A process of negative mother-infant reciprocities might arise from both infant and maternal characteristics. Gender differences observed in relation to depression during pregnancy may be a key to understanding the higher male prevalence of child psychiatric disorders. Thus, these differences should be more systematically explored in studies on mother and infant emotional development, and specifically focused in clinical practice. This study highlights the need for more integrated work between child psychiatrists/developmental psychologists and antenatal health care providers (eg, obstetricians, prenatal nurses, and family doctors) and for specific education on screening for depression, anxiety, and stressors during pregnancy.

Author affiliations: Department of Medical Pediatrics and Child and Adolescent Psychiatry, Rouen University Hospital and University of Rouen, Rouen, France (Dr Gerardin); Clinical Psychopathology and Neuropsychology Laboratory, Paris Descartes University (Dr Wendland); Department of Child and Adolescent Psychiatry, APHP (Assistance Publique—Hôpitaux de Paris), Groupe Hospitalier Pitié-Salpétrière, Paris (Drs Wendland, Mazet, and Cohen; Mr Bodeau; and Mss Galin and Bialobos); Department of Child and Adolescent Psychiatry, Université de Rennes 1, Rennes; and Laboratoire de la Psychologie de la Perception, CNRS (Centre National de la Recherche Scientifique), Paris (Dr Tordjman); Department of Gynecology-Obstetrics, APHP, Groupe Hospitalier Pitié-Salpêtrière, Université Pierre et Marie Curie, Paris (Drs Darbois, Nizard, and Dommergues); and CNRS UMR 8189, Psychologie et Neurosciences Cognitives, Paris (Dr Cohen), France.

REFERENCES

1. de Tychey C, Spitz E, Briançon S, et al. Pre- and postnatal depression and coping: a comparative approach. *J Affect Disord*. 2005;85(3):323–326.
2. Lee DT, Chan SS, Sahota DS, et al. A prevalence study of antenatal depression among Chinese women. *J Affect Disord*. 2004;82(1):93–99.
3. Marcus SM, Barry KL, Flynn HA, et al. Treatment guidelines for depression in pregnancy. *Int J Gynaecol Obstet*. 2001;72(1):61–70.
4. Stowe ZN, Hostetter AL, Newport DJ. The onset of postpartum depression: implications for clinical screening in obstetrical and primary care. *Am J Obstet Gynecol*. 2005;192(2):522–526.
5. Austin MP. Antenatal screening and early intervention for "perinatal" distress, depression and anxiety: where to from here? *Arch Women Ment Health*. 2004;7(1):1–6.
6. Da Costa D, Larouche J, Dritsa M, et al. Psychosocial correlates of prepartum and postpartum depressed mood. *J Affect Disord*. 2000;59(1):31–40.
7. Heron J, O'Connor TG, Evans J, et al, ALSPAC Study Team. The course of anxiety and depression through pregnancy and the postpartum in a community sample. *J Affect Disord*. 2004;80(1):65–73.
8. Robertson E, Grace S, Wallington T, et al. Antenatal risk factors for postpartum depression: a synthesis of recent literature. *Gen Hosp Psychiatry*. 2004;26(4):289–295.
9. Carter AS, Garrity-Rokous FE, Chazan-Cohen R, et al. Maternal depression and comorbidity: predicting early parenting, attachment security, and toddler social-emotional problems and competencies. *J Am Acad Child Adolesc Psychiatry*. 2001;40(1):18–26.
10. Hart S, Field T, Del Valle C, et al. Depressed mothers' interactions with their one-year-old infants. *Infant Behav Dev*. 1998;21(3):519–525.
11. Lovejoy MC, Graczyk PA, O'Hare E, et al. Maternal depression and parenting behavior: a meta-analytic review. *Clin Psychol Rev*. 2000;20(5):561–592.
12. O'Connor TG, Heron J, Glover V; ALSPAC Study Team. Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *J Am Acad Child Adolesc Psychiatry*. 2002;41(12):1470–1477.
13. Jones NA, Field T, Fox NA, et al. Newborns of mothers with depressive symptoms are physiologically less developed. *Infant Behav Dev*. 1998;21(3):537–541.
14. Field T, Diego M, Dieter J, et al. Prenatal depression effects on the fetus and the newborns. *Infant Behav Dev*. 2004;27(2):216–229.
15. Abrams SM, Field T, Scafidi F, et al. Newborns of depressed mothers. *Infant Ment Health J*. 1995;16(3):233–239.
16. Zuckerman B, Bauchner H, Parker S, et al. Maternal depressive symptoms during pregnancy, and newborn irritability. *J Dev Behav Pediatr*. 1990;11(4):190–194.
17. McGrath JM, Records K, Rice M. Maternal depression and infant temperament characteristics. *Infant Behav Dev*. 2008;31(1):71–80.
18. Davis EP, Glynn LM, Schetter CD, et al. Prenatal exposure to maternal depression and cortisol influences infant temperament. *J Am Acad Child Adolesc Psychiatry*. 2007;46(6):737–746.
19. Huot RL, Brennan PA, Stowe ZN, et al. Negative affect in offspring of depressed mothers is predicted by infant cortisol levels at 6 months and maternal depression during pregnancy, but not postpartum. *Ann N Y Acad Sci*. 2004;1032(1):234–236.
20. Austin MP, Hadzi-Pavlovic D, Leader L, et al. Maternal trait anxiety, depression and life event stress in pregnancy: relationships with infant temperament. *Early Hum Dev*. 2005;81(2):183–190.
21. Deave T, Heron J, Evans J, et al. The impact of maternal depression in pregnancy on early child development. *BJOG*. 2008;115(8):1043–1051.
22. Dayan J, Creveuil C, Marks MN, et al. Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. *Psychosom Med*. 2006;68(6):938–946.
23. Wurmser H, Rieger M, Domogalla C, et al. Association between life stress during pregnancy and infant crying in the first six months postpartum: a prospective longitudinal study. *Early Hum Dev*. 2006;82(5):341–349.
24. Talge NM, Neal C, Glover V; Early Stress, Translational Research and Prevention Science Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry*. 2007;48(3–4):245–261.
25. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
26. Lempérière T, Lépine JP, Rouillon F, et al. Comparison of various tools for evaluating depression apropos of a study on Athymil 30 mg [in French]. *Ann Med Psychol (Paris)*. 1984;142(9):1206–1214.
27. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385–401.
28. Fuhrer R, Rouillon F. La version Française de l'échelle CES-D. *Psych Psychol*. 1989;4:163–166.
29. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry*. 1987;150(6):782–786.
30. Guédeney N, Fermanian J, Guelfi JD, et al. Premiers résultats de la traduction de L'Edinburgh Postnatal Depression Scale sur une population parisienne. *Devenir*. 1995;7:69–92.
31. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
32. Spielberger CD, Gorsuch RL, Lushene RE. *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologists Press; 1983.
33. Bruchon-Schweitzer M, Paulhan I. *Manuel du State-Trait Anxiety Inventory (STAI)*. Paris, France: Edition du Centre de Psychologie Appliquée; 1993.
34. Derogatis LR. *SCL-90 Revised Version Manual I*. Baltimore, MD: Clinical Psychometric Research Unit, Johns Hopkins University School of Medicine; 1977.

35. Pariente P, Lepine JP, Boulenger JP, et al. The Symptom Check-List 90-R (SCL-90 R) in a French general psychiatric 708 outpatient sample; is there a factor structure? *Psychiatr Psychobiol*. 1989;4:151–157.

36. Tordjman S, Granier-Deferre D, Cabrol C, et al. Empirical and Factor Validation Study of the "Sensations During Pregnancy and Life Events Questionnaire." Presented at: 37th Annual Meeting of the International Society for Developmental Psychobiology; June 25–28, 2004; Aix-en-Provence, France.

37. Brazelton TB. *Neonatal Behavioral Assessment Scale*. London, England: Mac Keith Press; 1984.

38. Lester BM, Als H, Brazelton TB. Regional obstetric anesthesia and newborn behavior: a reanalysis toward synergistic effects. *Child Dev*. 1982; 53(3):687–692.

39. Carter AS, Briggs-Gowan M. *The Infant-Toddler Social and Emotional Assessment (ITSEA)*. New Haven, CT: Department of Psychology, Yale University; 1993.

40. Briggs-Gowan M, Carter AS. Preliminary acceptability and psychometrics of the Infant-Toddler Social and Emotional Assessment (ITSEA): a new adult-report questionnaire. *Infant Ment Health J*. 1998;19(4): 422–445.

41. Carter AS, Little C, Briggs-Gowan MJ, et al. The Infant-Toddler Social and Emotional Assessment (ITSEA): comparing parent ratings to laboratory observations of task mastery, emotion regulation, coping behaviors, and attachment status. *Infant Ment Health J*. 1999;20(4):375–392.

42. Bracha Z, Perez-Dias F, Gerardin P, et al. A French adaptation of the Infant-Toddler Social and Emotional Assessment. *Infant Ment Health J*. 2004;25(2):117–129.

43. Bracha Z, Gerardin P, Perez-Diaz F, et al. Évaluation du développement socioémotionnel de l'enfant d'un à trois ans: validation de la version française de l'Infant-Toddler Social and Emotional Assessment. *Neuropsychiatr Enfance Adolesc*. 2007;55(4):194–203.

44. National Institute of Statistics and Economic Studies (INSEE) Web site. http://www.insee.fr. Accessibility verified October 15, 2010.

45. Davis M, Emory E. Sex differences in neonatal stress reactivity. *Child Dev*. 1995;66(1):14–27.

46. Lundqvist C, Sabel KG. Brief report: the Brazelton Neonatal Behavioral Assessment Scale detects differences among newborn infants of optimal health. *J Pediatr Psychol*. 2000;25(8):577–582.

47. Canals J, Fernandez-Ballart J, Esparo G. Evolution of neonatal behavior assessment scale scores in the first month of life. *Infant Behav Dev*. 2003;26(2):227–237.

48. Murray L, Kempton C, Woolgar M, et al. Depressed mothers' speech to their infants and its relation to infant gender and cognitive development. *J Child Psychol Psychiatry*. 1993;34(7):1083–1101.

49. Lundy B, Field T, Pickens J. Newborns of mothers with depressive symptoms are less expressive. *Infant Behav Dev*. 1996;19(4):419–424.

50. van der Wal MF, van Eijsden M, Bonsel GJ. Stress and emotional problems during pregnancy and excessive infant crying. *J Dev Behav Pediatr*. 2007;28(6):431–437.

51. Brown GW. Psychosocial factors and depression and anxiety disorders: some possible implications for biological research. *J Psychopharmacol*. 1996;10(1):23–30.

52. Power KL, Moore CL. Prenatal stress eliminates differential maternal attention to male offspring in Norway rats. *Physiol Behav*. 1986;38(5): 667–671.

53. Henry C, Kabbaj M, Simon H, et al. Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. *J Neuroendocrinol*. 1994;6(3):341–345.

54. Maccari S, Piazza PV, Kabbaj M, et al. Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. *J Neurosci*. 1995;15(1 Pt 1):110–116.

55. Clarke AS, Wittwer DJ, Abbott DH, et al. Long-term effects of prenatal stress on HPA axis activity in juvenile rhesus monkeys.

Dev Psychobiol. 1994;27(5):257–269.

56. Pardon MC, Gérardin P, Joubert C, et al. Influence of prepartum chronic ultramild stress on maternal pup care behavior in mice. *Biol Psychiatry*. 2000;47(10):858–863.

57. Newport DJ, Wilcox MM, Stowe ZN. Maternal depression: a child's first adverse life event. *Semin Clin Neuropsychiatry*. 2002;7(2):113–119.

58. Kaiser S, Sachser N. The effects of prenatal social stress on behaviour: mechanisms and function. *Neurosci Biobehav Rev*. 2005;29(2):283–294.

59. Dahlöf LG, Hård E, Larsson K. Influence of maternal stress on offspring sexual behaviour. *Anim Behav*. 1977;25(4):958–968.

60. Harvey PW, Chevins PFD. Crowding or ACTH treatment of pregnant mice affects adult copulatory behavior of male offspring. *Horm Behav*. 1984;18(2):101–110.

61. Sachser N, Kaiser S. Prenatal social stress masculinizes the females' behaviour in guinea pigs. *Physiol Behav*. 1996;60(2):589–594.

62. Uno H, Eisele S, Sakai A, et al. Neurotoxicity of glucocorticoids in the primate brain. *Horm Behav*. 1994;28(4):336–348.

63. Uno H, Lohmiller L, Thieme C, et al. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques, I: hippocampus. *Brain Res Dev Brain Res*. 1990;53(2):157–167.

64. Hansen D, Lou HC, Olsen J. Serious life events and congenital malformations: a national study with complete follow-up. *Lancet*. 2000;356(9233): 875–880.

65. Glover V. Maternal stress or anxiety in pregnancy and emotional development of the child. *Br J Psychiatry*. 1997;171(2):105–106.

66. Jefferson T. What are the benefits of editorials and non-systematic reviews? *BMJ*. 1999;318(7176):135.

67. Diego MA, Field T, Hernandez-Reif M, et al. Prepartum, postpartum, and chronic depression effects on newborns. *Psychiatry*. 2004;67(1): 63–80.

68. Morley-Fletcher S, Darnaudery M, Koehl M, et al. Prenatal stress in rats predicts immobility behavior in the forced swim test. Effects of a chronic treatment with tianeptine. *Brain Res*. 2003;989(2):246–251.

69. Phillips DI, Jones A. Fetal programming of autonomic and HPA function: do people who were small babies have enhanced stress responses? *J Physiol*. 2006;572(Pt 1):45–50.

70. Wadhwa PD. Psychoneuroendocrine processes in human pregnancy influence fetal development and health. *Psychoneuroendocrinology*. 2005;30(8):724–743.

71. Welberg LAM, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. *J Neuroendocrinol*. 2001;13(2):113–128.

72. Field T, Diego M. Cortisol: the culprit prenatal stress variable. *Int J Neurosci*. 2008;118(8):1181–1205.

73. Livingood AB, Daen P, Smith BD. The depressed mother as a source of stimulation for her infant. *J Clin Psychol*. 1983;39(3):369–375.

74. Field T. Maternal depression effects on infants and early interventions. *Prev Med*. 1998;27(2):200–203.

75. Sutter-Dallay A-L, Murray L, Glatigny-Dallay E, et al. Newborn behavior and risk of postnatal depression in the mother. *Infancy*. 2003;4(4): 589–602.

76. Boyle MH, Pickles AR. Influence of maternal depressive symptoms on ratings of childhood behavior. *J Abnorm Child Psychol*. 1997;25(5): 399–412.

77. Murray L, Stanley C, Hooper R, et al. The role of infant factors in postnatal depression and mother-infant interactions. *Dev Med Child Neurol*. 1996;38(2):109–119.