Fetal Heart Rate Reactivity Differs by Women's Psychiatric Status: An Early Marker for Developmental Risk?

CATHERINE MONK, PH.D., RICHARD P. SLOAN, PH.D., MICHAEL M. MYERS, PH.D., LAUREN ELLMAN, B.A., ELIZABETH WERNER, B.A., JIYEON JEON, B.A., FELICE TAGER, PH.D., AND WILLIAM P. FIFER, PH.D.

ABSTRACT

Objective: To determine whether there are differences in fetal heart rate (FHR) reactivity associated with women's psychiatric status. **Method:** In 57 women in their 36th to 38th week of pregnancy (mean age 27 ± 6 years), electrocardiogram, blood pressure (BP), respiration (RSP), and FHR were measured during baseline and a psychological challenge (a Stroop color–word matching task). Subjects underwent the Structured Clinical Interview for *DSM-IV* (SCID) and completed the Spielberger State–Trait Anxiety Inventory prior to testing. **Results:** There was a significant main effect of maternal diagnostic group on FHR reactivity during the Stroop task even after controlling for birth weight and women's BP reactivity ($F_{4,44} = 2.68$, $p = .04$). Fetuses of depressed women had greater heart rate increases compared to fetuses of women with anxiety disorders and those of healthy, low-anxiety women (post hoc comparisons using the Fisher protected least significant difference test; $t = 4.12$, $p < .05$; $t = 4.72$, $p < .01$, respectively). There was a similar pattern comparing fetuses of healthy, high-anxiety women to the same two groups ($t = 3.29$, $p < .05$; $t = 3.99$, $p < .05$, respectively). There were no group differences in FHR during a resting baseline period ($F_{4,52} = 1.2$, $p = .35$). **Conclusions:** Maternal mood disturbance is associated with alterations in children's physiological reactivity prior to birth. *J. Am. Acad. Child Adolesc. Psychiatry,* 2004;43(3):283–290. **Key Words:** antenatal depression, antenatal anxiety, fetal heart rate.

A significant risk factor for developing emotional disturbances is having a parent with a serious psychiatric illness (Nomura et al., 2002). Recent studies demonstrate that the association between parental psychopathology and early indications of alterations in neurobehavioral development reflecting less adaptive regulatory capacities can be identified in toddlers, and even newborns (Dawson et al., 2001; Lundy et al., 1999). Moreover, new research indicates that stress and anxiety during pregnancy are linked to differences in fetal heart rate (FHR) and movement activity that may have implications for future emotion regulation (DiPietro et al., 2000; Groome et al., 1995; Monk et al., 2003). Depression, one of the most common psychiatric illnesses, affects nonpregnant and pregnant women at a comparable rate of approximately 1 out of every 10 women (Llewellyn et al., 1997). The delineation of fetal neurobehavioral profiles associated with women's depression, as well as with other disorders, has significant implications for psychiatric treatment during pregnancy and for the conceptualization and treatment of child psychopathology; this approach also extends into the prenatal period the developmental perspective used in child psychiatry.

For the limited research on pregnant women's emotional states in relation to fetal behavior, life stress has been a focus. Fetuses of pregnant women who report greater life stress have reduced parasympathetic and/or

Accepted September 23, 2003.

Dr. Monk is an Assistant Professor, Dr. Sloan is a Professor, and Dr. Tager is an Assistant Clinical Professor, Department of Psychiatry, Columbia University, New York; Drs. Myers and Fifer are Professors, Departments of Psychiatry and Pediatrics, Columbia University, and Research Scientists, New York State Psychiatric Institute; Ms. Ellman, Ms. Werner, and Ms. Jeon are with the Department of Psychiatry, Columbia University.

This research was supported by the March of Dimes, the National Alliance for Research on Schizophrenia and Depression, the Sackler Institute, and by a Career Development Award MH01928 to C.M.

Correspondence to Dr. Monk, Behavioral Medicine Program, Columbia-Presbyterian Medical Center, 622 West 168th Street, Box 427, New York, NY 10032; e-mail: cem31@columbia.edu.

DOI: 10.1097/01.chi.0000103178.91435.ff

increased sympathetic activation as measured by reduced fetal heart rate variability; measures of heart rate variability are used as noninvasive indices of cardiac autonomic modulation linked in children and adults to less adaptive affect regulation (Bazhenova and Porges, 1997; DiPietro et al. 1996a; Sloan et al., 1994). Moreover, fetuses of highly stressed mothers, who also have faster baseline heart rate (HR), show delayed maturation of the coupling of FHR and movement, which is hypothesized to reflect less mature central nervous system development (DiPietro et al., 1996b). Low socioeconomic status, which often is accompanied by heightened levels of life stress, is associated with higher and less variable FHR throughout the second and third trimesters (Pressman et al., 1998). Finally, elevated stress during pregnancy and in particular stress specific to being pregnant, as well as having an intense emotional style, are associated with greater fetal reactivity assessed at three time points during gestation (DiPietro et al., 2002).

To date, there are only a few published studies examining fetal behavior in women with anxiety, and even fewer with depressive symptoms. Fetuses of more highly anxious women were found on ultrasound examination to move less often during active sleep and overall to spend more time in a quiet sleep state (Groome et al., 1995). One other report found that state anxiety among pregnant women was associated with increased fetal movement (Field et al., 1985). However, this study was based on maternal report of fetal movement, which is less reliable than ultrasound. On the other hand, when examining a subset of fetuses who entered a state with an active, unstable HR, the more anxious the mother, the longer the time fetuses spent in that state (Sjostrom et al., 2002). There also are differences in FHR responses related to women's anxiety status. Fetuses of highly anxious women show an HR increase during women's exposure to psychological stress, while fetuses of low-anxiety women do not exhibit an HR change (Monk et al., 2000, 2003). In response to a vibroacoustic stimulation, fetuses of women reporting elevated levels of depression are slower to return to baseline HR (Allister et al., 2001).

These findings suggest that alterations in neurobehavioral functioning related to poor maternal mood regulation may be identified as early as the in utero period. However, all of these studies have assessed women's moods based on brief, self-report measures. None has used psychiatric interviews that can distinguish between subsyndromal symptoms and illness. In an era when more and more women and physicians are weighing the risks and benefits of pharmacological treatment during pregnancy, it is necessary to uncover any possible effects of untreated maternal mood disorders on fetal behavior. In this research, we investigated associations between a maternal anxiety disorder (AD) or depression and alterations in FHR reactivity. Specifically, we screened pregnant women for mood disorders and collected cardiovascular and FHR data while the women underwent a standardized laboratory challenge paradigm. We hypothesized (1) that during the challenge period, there would be differences in FHR responses related to pregnant women's psychiatric status and (2) that the maternal diagnostic group differences in FHR reactivity would be statistically independent of other correlates of FHR, such as women's acute cardiorespiratory reactivity assessed during the same period.

METHOD

Subjects

Through posted announcements and signs in obstetricians' offices, 64 pregnant, nonsmoking women with singleton fetuses ranging in gestational age from 33 to 39 weeks were recruited at the Columbia-Presbyterian Medical Center (CPMC). Women were excluded from the study if there were any maternal or fetal complications, including hypertension, diabetes mellitus, suspected fetal growth restriction, or a fetal structural anomaly on ultrasound. None of the subjects reported drinking more than two glasses of wine throughout the entire pregnancy. Fifty-nine percent of the sample were Latina, 23% were white, 11% were African American, and 7% were Asian or Dominican Indian. For all subjects, English was the primary language. The mean maternal age was 27 ± 6 years. Fifty-four percent of the sample had completed either high school or 2 to 4 years of college. Thirty-seven percent of the women were married and 32% of them were cohabiting; 49% were primiparas; 52% were working outside the home at least half-time. Because this sample was drawn from an urban hospital and included physicians and support staff as well as patients, there was a large range for average annual family income: 36% of the sample reported an annual income of $0 to $15,000; 11% reported $16,000 to $25,000; 25% reported $26,000 to $50,000; 14% reported $51,000 to $90,000; and 15% reported over $100,000. This study was approved by the CPMC institutional review board. Informed consent was obtained from each subject.

At the time of testing the average gestational age was 36 weeks (SD = 1 week, range 33–39 weeks) as determined by a combination of last menstrual period and sonogram. All fetuses were born after 37 weeks (mean = 40 weeks, range 37–43 weeks), and none was small for dates. The average weight at birth was 3,424 g (SD = 401, range 2,730–4,485 g). Fifty-six percent of the babies were male.

Three subjects with resting diastolic blood pressure (DBP) of more than 90 mm Hg and one with a resting HR of 130 beats per minute (bpm) were excluded from further study. For 2 of the remaining 60 subjects, data collection was incomplete, and they also were removed from analyses. One other subject was excluded

from analyses due to technical problems resulting in poor signal quality. Results are based on data from the remaining 57 subjects. Two of these women were taking selective serotonin reuptake inhibitors (Celexa and Zoloft). We ran all analyses with and without these two subjects included in the dataset.

Procedure

Women made two visits to the laboratory. For the first visit, between the 24th and 26th weeks, they completed demographic questionnaires and were interviewed by a licensed psychologist using the Structured Clinical Interview for *DSM-IV* (SCID) (First et al., 1997). During the third trimester, subjects returned for the psychophysiology session, which began at about 11 A.M. and ended at 1 P.M. After a review of the experimental procedures, they completed a self-report measure of anxiety (Spielberger State–Trait Anxiety Inventory [STAI]) (Spielberger, 1983) and were reinterviewed briefly about their pregnancy and living situation. Information on the collection of physiological data can be found in Monk et al., 2003. Subjects were given instructions regarding a cognitive test, the Stroop task, and were allowed to practice the task for 1 minute. At the start of data collection, subjects were instructed to remain silent throughout the procedures. Subjects rested quietly for a 5-minute baseline and then performed a 5-minute Stroop color–word matching task, followed by a 5-minute recovery period.

Stroop Task

In this version of the Stroop task, the subjects were presented with color names (blue, green, yellow, and red) in colored letters that were either congruent or incongruent with the names. The subject's task was to press the key on the keypad that corresponded to the color of the letters as indicated by a legend on the computer screen. The task was paced by the computer, and an incorrect response or failure to respond rapidly enough resulted in a message indicating "incorrect" on the screen. At 1-minute intervals, the experimenter gave the subject verbal prompts (e.g., to work faster).

Self-Report of Stress

The subjects were asked to rate the stress they experienced on a 1 (none at all) to 10 (extreme stress) scale after each of the three periods of the experiment.

Acquisition and Processing of Maternal and Fetal Signals

Analog electrocardiogram (ECG) and respiration impedance waveforms from a Hewlett Packard 78292A monitor were digitized and collected by a microcomputer. Analog ECG signals were digitized at 500 Hz by a 16-bit A/D card (National Instruments 16XE50). Specially written software was used to mark R waves and create files of RR intervals. Artifacts in the RR interval series were defined as values below 0.4 seconds (HR > 150 bpm) or above 1.5 seconds (HR < 40 bpm). When artifacts were detected, the RR-interval file was examined. Artifacts were rejected or corrected following established procedures (Berntson et al., 1990). Respiration was sampled at 50 Hz. Postacquisition software was used to mark the peaks and troughs of the impedance waveform. These marks were verified by visual inspection and then were used to calculate respiratory rate. BP was acquired on a beat-to-beat basis by an Ohmeda Finapres 2300 monitor. The analog pressure waveform was digitized at 250 Hz. Systolic BP (SBP) and DBP values were marked by peak/trough detection software, and errors in marking were corrected interactively. Fetal HR was recorded via an ultrasound transducer (Advanced Medical Systems, IM76) and passed to the microcomputer acquisition system.

Women's Psychiatric Illness

Based on results from the SCID interview administered between the 24th and 26th gestational week, women with a current major depressive disorder and/or dysthymia were classified as depressed. None of the depressed women had bipolar disorder. Women who currently had a social phobia, a simple phobia, generalized AD, or agoraphobia without panic disorder were classified as having an AD. Women with posttraumatic stress disorder or a comorbid condition were excluded from these analyses as the cell sizes were too small to provide stable results.

Women's Subsyndromal Anxiety

Women's subsyndromal anxiety was assessed using the Trait Anxiety scale of the STAI (Spielberger, 1983), a 20-item, self-report instrument that measures a predisposition to feel "generally" anxious. We chose this instrument because it is associated with alterations in physiology during pregnancy (Teixeira et al., 1999) as well as with fetal characteristics (Groome et al., 1995; Monk et al., 2000). STAI items assessed the extent to which women have a predisposition toward feeling anxious by using a 4-point scale ranging from 1 (almost never) to 4 (almost always) to answer questions about how they generally feel (e.g., "I worry too much over something that really doesn't matter"). Trait Anxiety scores on the STAI can range from a minimum of 20 to a maximum of 80. Although all subjects completed the form, only those who were free of a current psychiatric illness were classified as healthy subjects and then categorized as high, medium, or low anxiety based on a tertile grouping of their Trait Anxiety scores.

Data Reduction and Analyses

We used analysis of variance (ANOVA) and analysis of covariance (ANCOVA) to examine group differences in FHR during the baseline and Stroop periods. Covariates were entered into the model if the univariate correlation with FHR activity was significant at $p < .05$. The possible covariates included women's physiological variables (HR, BP, and respiration rate) as well as the baby's birth weight, which we had found in a previous study to be associated with FHR reactivity, and fetal age at the time of testing. Using standard regression analyses, birth weight was adjusted to 40 weeks gestational age. The FHR and maternal HR, BP, and respiration rate were calculated as the mean values for each of the 5-minute periods (baseline and the challenge task). FHR and maternal physiological reactivity to the task were computed as a within-subject change scores (challenge task–baseline).

RESULTS

Subject Groups

Results from SCID interviews and the trait anxiety questionnaire yielded the following groups: 11 in the depressed group, 11 in the AD group. Three subjects were diagnosed with simple phobia, three with social phobia, three with agoraphobia without panic disorder, and two with generalized AD. Thirty-five subjects without psychiatric diagnoses were further subdivided based on the 80-point Trait Anxiety scale as follows: high anxiety, $n = 11$ (mean 46 ± 7), middle anxiety, $n = 13$ (mean 33.0 ± 3), and low anxiety, $n = 11$ (mean

25 ± 3). Trait Anxiety scores for the two diagnostic groups were AD, mean 39 ± 7, and depressed, mean 41 ± 9. Reported average scores for nonpregnant women from two samples ages 19 to 39 are 35 ± 9 and 36 ± 10 (Spielberger and Sydeman, 1994). Exclusion of the two subjects taking antidepressants did not change any of the results except in one instance, which is noted.

Self-Reports of Stress

There were no significant group differences on women's stress ratings during the baseline period ($F_{4,52} = 0.92$, $p = .27$) or the Stroop task ($F_{4,51} = 0.99$, $p = .29$), and groups did not differ in the increase from baseline to the Stroop task ($F_{4,51} = 1.31$, $p = .37$).

The mean rating during baseline on the 1- to 10-point scale was 1.9 (± 0.2). The mean rating during Stroop was 5.8 (± 0.3), and the average increase, 3.9 (± 0.3), was a significant change ($t = 11.98$, $p < .0001$).

Women's Cardiorespiratory Activity During Baseline

Table 1 reports the mean baseline cardiorespiratory data for women. Based on ANOVAs, no main effect of diagnostic group for any maternal variable during this period was found.

Fetal HR During Baseline

The FHR during baseline by women's diagnostic groups is reported in Table 1. An ANOVA revealed no baseline group differences in FHR ($F_{4,52} = 1.20$, $p = .35$). Next we constructed a correlation matrix to determine which, if any, baseline maternal variables have a univariate relationship with baseline FHR and should be controlled for when examining relationships between women's psychiatric status and FHR during this period. As previously discussed, we also included birth weight and fetal age at time of testing in this examination of univariate associations (Table 2). In the resulting ANCOVA that controlled for maternal HR during baseline, there were no maternal diagnostic group differences in FHR during baseline ($F_{4,50} = 0.99$, $p = .43$).

Women's Cardiorespiratory Responses to Laboratory Challenge

As can be seen in Table 3, women had increases in HR, BP, and respiration rate in response to stress. There were no statistically significant group differences in the magnitude of these responses.

TABLE 1
Mean Maternal HR, BP, and Respiration Rate, and Fetal HR at Baseline by Diagnostic Group

Variable/Group	Baseline (±SE)
Maternal HR (bpm)	
AD	95.2 ± 4.2
Depressed	91.8 ± 3.5
High anxiety	91.2 ± 2.8
Middle anxiety	95.1 ± 3.7
Low anxiety	86.1 ± 3.5
Maternal SBP (mm Hg)	
AD	111.5 ± 4.8
Depressed	122.8 ± 4.4
High anxiety	126.9 ± 4.1
Middle anxiety	121.4 ± 3.8
Low anxiety	118.6 ± 4.4
Maternal DBP (mm Hg)	
AD	69.6 ± 3.5
Depressed	68.7 ± 3.1
High anxiety	77.3 ± 2.3
Middle anxiety	69.8 ± 2.7
Low anxiety	68.6 ± 3.4
Maternal RSP (cpm)	
AD	19.1 ± 3.5
Depressed	20.2 ± 2.1
High anxiety	21.1 ± 1.3
Middle anxiety	21.0 ± 2.4
Low anxiety	22.4 ± 2.8
Fetal HR (bpm)	
AD	143.2 ± 2.7
Depressed	136.8 ± 2.8
High anxiety	139.6 ± 3.6
Middle anxiety	138.6 ± 2.4
Low anxiety	135.5 ± 1.3

Note: Because of technical failure, one subject was missing maternal HR data; six subjects were missing SBP data and seven were missing DBP. Two were missing RSP data and one subject's respiration data was omitted because during baseline it was 5 SD above the mean. HR = heart rate; BP = blood pressure; AD = anxiety disorder; SBP = systolic blood pressure; DBP = diastolic blood pressure; RSP = respiration.

FHR Responses During Women's Exposure to Laboratory Challenge

There was nearly a significant main effect of maternal diagnostic group on FHR reactivity from baseline to the Stroop task ($F_{4,52} = 2.48$, $p = .06$). As with our examination of FRH during baseline, we constructed a correlation matrix to determine which, if any, maternal variables measured during baseline and/or in response to the Stroop task, should be controlled for when examining relationships between women's psychiatric status and FHR responses during maternal challenge. We also included birth weight and gestational age at the

TABLE 2
Correlation Matrix of Maternal Variables During Baseline, Birth Weight, and Fetal Age With FHR During Baseline

	FHR (bpm)
Maternal HR (bpm)	0.32*
Maternal SBP (bpm)	–0.27†
Maternal DBP (bpm)	–0.05
Maternal RSP (cpm)	0.18
Fetal age at time of testing	–0.06
Birth weight (kg)	–0.17

Note: HR = heart rate; FHR = fetal heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RSP = respiration.
† $p < .10$; * $p < .05$.

TABLE 3
Reactivity Values (Stressor Period–Baseline) in Maternal HR, BP, and Respiration Rate, and Fetal HR by Diagnostic Group

Variable/Group	Change Value (±SE)
Maternal HR (bpm)	
AD	3.6 ± 1.5
Depressed	4.3 ± 1.4
High anxiety	2.8 ± 1.6
Middle anxiety	3.2 ± 1.1
Low anxiety	4.1 ± 1.1
Maternal SBP (mm Hg)	
AD	8.4 ± 1.5
Depressed	5.8 ± 3.8
High anxiety	10.0 ± 2.7
Middle anxiety	10.2 ± 2.0
Low anxiety	9.9 ± 2.0
Maternal DBP (mm Hg)	
AD	5.0 ± .9
Depressed	4.8 ± 1.6
High anxiety	5.5 ± 1.6
Middle anxiety	6.0 ± 1.0
Low anxiety	6.3 ± 1.4
Maternal RSP (cpm)	
AD	4.2 ± 3.7
Depressed	3.8 ± 1.8
High anxiety	2.5 ± 1.2
Middle anxiety	2.8 ± 1.9
Low anxiety	3.9 ± 1.9
Fetal HR (bpm)	
AD	–.03 ± .8
Depressed	3.2 ± 1.1
High anxiety	3.0 ± 1.6
Middle anxiety	.5 ± 1.1
Low anxiety	–1.0 ± 1.1

Note: HR = heart rate; BP = blood pressure; AD = anxiety disorder; SBP = systolic blood pressure; DBP = diastolic blood pressure; RSP = respiration.

TABLE 4
Correlation Matrix of Maternal Baseline and Reactivity Variables, Birth Weight, and Fetal Age With FHR Reactivity

	FHR Reactivity (bpm)
Maternal HR baseline (bpm)	–0.04
Maternal HR reactivity (bpm)	0.14
Maternal SBP baseline (bpm)	–0.16
Maternal SBP reactivity (bpm)	–0.32*
Maternal DBP baseline (bpm)	–0.19
Maternal DBP reactivity (bpm)	–0.20
Maternal RSP baseline (cpm)	0.03
Maternal RSP reactivity (cpm)	0.01
Fetal age at time of testing	0.05
Birth weight (kg)	–0.37**

Note: HR = heart rate; FHR = fetal heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RSP = respiration.
* $p < .05$; ** $p < .01$.

time of testing in the examination of univariate relationships (Table 4). In the resulting ANCOVA (Table 5) that controlled for women's SBP responses and birth weight, there was a significant main effect of women's psychiatric status on FHR reactivity. Figure 1 shows the mean FHR reactivity values adjusted for these covariates. Post hoc tests indicated the following significant differences in FHR responses: fetuses of depressed women had greater HR increases compared to fetuses of women with AD; healthy, low-anxiety women; and healthy, middle-anxiety women (post hoc comparisons using the Fisher protected least significant difference [PLSD] test; $t = 4.12$, $p < .05$; $t = 4.72$, $p < .01$; $t = 3.45$, $p < .05$, respectively), and healthy, high-anxiety women had greater HR increases compared to fetuses of women with AD and healthy, low-anxiety women (post hoc comparisons using the Fisher PLSD; $t = 3.29$, $p < .05$; $t = 3.99$, $p < .05$, respectively). When the two

TABLE 5
Analysis of Covariance: Fetal Heart Rate Reactivity by Women's Diagnostic Status, Controlling for Women's SBP Reactivity and Birth Weight

	df	Sum of Squares	Mean Square	*F* Value	*p* Value
Maternal group status	4	128.22	32.05	2.68	.04
Birth weight (kg)	1	146.48	146.48	12.25	.001
SBP reactivity (mm Hg)	1	89.80	89.79	7.51	.01
Residual	44	525.96	11.95		

Note: In this analysis, we deleted the interaction terms after determining that they were not significant. SBP = systolic blood pressure.

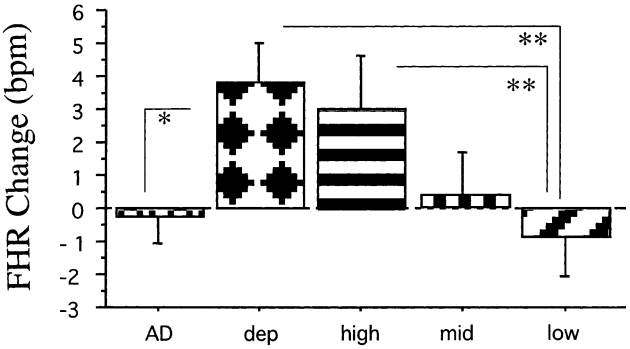

Fig. 1 Differences in fetal heart rate (FHR) reactivity by women's psychiatric status. AD = anxiety disorder; dep = depression as assessed by the Structured Clinical Interview for *DSM-IV*. Other subjects are free of psychiatric illness but classified by Spielberger's (1983) Trait Anxiety scale as high (high subsyndromal anxiety), mid (mid subsyndromal anxiety), or low (low subsyndromal anxiety). $^{*}p < .05$; $^{**}p < .01$.

subjects taking antidepressant medication (selective serotonin reuptake inhibitors) were removed from the ANCOVA, the main effect of women's diagnostic status reached only $p = .10$ significance. Post hoc group comparisons remained the same as in the analysis with all subjects except that the difference between fetuses of depressed versus those of healthy, middle-anxiety women no longer reached significance. Finally, further post hoc tests showed significant FHR responses in the depressed and healthy, high-anxiety groups ($p < .05$) but no significant changes in the other three groups.

DISCUSSION

In the results presented here, we show that third-trimester fetuses of women with Axis I mood disorders, as well as those with elevations in subsyndromal anxiety, have different HR responses during women's exposure to challenge compared to low-anxiety, healthy women. These group differences in FHR responses are independent of women's acute cardiorespiratory reactivity measured during the same period. These data suggest that even prior to birth, there is an association between women's mood disorders and alterations in their children's physiological reactivity.

Although there were no group differences in FHR while women rested during a quiet baseline period, FHR responses during women's exposure to a psychological challenge differed according to women's psychiatric status. Fetuses of depressed women had significant HR increases during the challenge period, whereas fetuses of healthy women with low or middle levels of anxiety showed virtually no response. Interestingly, fetuses of women with AD also had no significant response. In agreement with a prior study from our laboratory (Monk et al., 2000), fetuses of healthy but highly anxious women also had a HR increase. Group differences in FHR response remained while controlling for women's SBP response to challenge (the only maternal variable associated with FHR reactivity) and birth weight. Meanwhile, women's cardiorespiratory measures did not differ statistically by diagnostic group during the baseline or challenge periods.

These findings indicate that the group differences in fetal reactivity are not dependent on group differences in the magnitude of women's acute cardiorespiratory reactivity. Rather, the data suggest that all fetuses were exposed to comparable stimulation from the changes in women's cardiorespiratory activity in response to the Stroop task, yet they had varied HR reactions that were associated with their mother's psychiatric status. This suggests the possibility that by the third trimester, there are traitlike differences in fetal reactivity related to pregnant women's mood. This would be consistent with other studies demonstrating that aspects of newborn physiology and behavior are associated with women's mood during pregnancy (Lundy et al., 1999; Zuckerman et al., 1990). On the other hand, it is possible that the group differences in FHR responses are associated with an unmeasured variable, such as maternal cortisol or fetal movement. In future studies we plan to collect salivary cortisol from pregnant women under stressful situations, to monitor fetal movement, as well as to expand the assessment of other potential physiological correlates.

The identification of fetal differences related to pregnant women's mood also provides evidence for the familial effects of psychopathology *prior to birth*. Similar to research examining the heritability of emotional disturbances, our study cannot disentangle the genetic and environmental influences that may account for this transmission. The fetal HR increase to maternal challenge seen in the offspring of depressed and high-anxiety women compared to those of the other subjects may be a marker of altered neurobehavioral development primarily related to a genetic predisposition. Alternatively, the group differences in FHR may be the product of emotion-based changes in the maternal physiological environment that affect the offspring in utero and possibly, over time, shape developmental outcomes. The significant associations between women's acute, cardiovascular activity and fetal HR during the stress-eliciting challenge task seen here are consistent with this possibility. Similarly, given that baseline

physiological data likely reflect a reaction to the novelty of the overall laboratory testing situation, the association between maternal and fetal HR during baseline also are consistent with this hypothesis. Recent studies further support this hypothesis by showing correlations between pregnant women's anxiety and uterine artery resistance (Teixeira et al., 1999), women's social support and their levels of adrenocorticotropin releasing factor (ACTH) (Wadhwa et al., 1996), and pregnant women's and newborns' levels of stress hormones (Lundy et al., 1999). Moreover, animal studies, in which genetic influences can be largely controlled, show that laboratory-administered stress during pregnancy affects neurobehavioral development, particularly with respect to behavioral and physiological regulatory capacities (Kofman, 2002). Thus, a pathway for the familial transmission of mental illness also might be via the altered intrauterine environment related to maternal psychiatric illness and emotions.

Two lines of research suggest that the alterations in FHR reactivity presented here may be an early indication of future risk for pathology. Four-month-olds who show increased motor and crying behavior in response to novelty go on to develop inhibited temperament and AD at a higher rate compared to other toddlers (Biederman et al., 2001; Kagan and Snidman, 1991). These "high reactive" toddlers are more likely to have a parent with an affective disorder or AD and, according to one study, as fetuses to have lower resting heart period variability (a measure of cardiac autonomic regulation indicative of less parasympathetic control) (Rosenbaum et al., 1988; Snidman et al., 1995). The relative increase in fetal HR during women's exposure to a challenge task that is associated with maternal depression and high trait anxiety may be a marker for a similar biobehavioral profile characterized by greater sympathetic and/or less parasympathetic cardiac control, a general propensity for lower response thresholds and elevated response magnitudes, and slower return to baseline. This response "style" may suggest a heightened risk for inhibited temperament and/or a vulnerability to future stress-induced psychopathology (e.g., Heim and Nemeroff, 1999; Heim et al., 2000).

Although we did not make predictions as to group differences in FHR related to women's specific diagnostic classification, it was somewhat surprising that fetuses of women with AD showed smaller HR increases during maternal challenge than fetuses of women with depression or those with high anxiety. We offer three interpretations for these results. First, the AD group is very heterogeneous. Thus, it is possible that putting into one group women with distinct ADs obscured patterns of FHR responses associated with different subtypes. However, there were too few subjects in each of the AD subgroups to warrant investigation of this hypothesis. Second, birth weight was unevenly distributed among the groups. Specifically, there was a near-significant group difference ($p = .11$) in birth weight and a trend for offspring in the AD group on average to be the heaviest (three of the five highest birth weights recorded in the entire cohort were in the AD group). As described elsewhere, we have found that birth weight is inversely related to FHR reactivity. We included birth weight as a covariate in our analyses, but it may be that this was not an adequate adjustment for the most extreme cases of high birth weight in the AD group. Finally, although there was no difference in the average trait scores between the AD and the depressed women, there may be a difference in the persistence of the anxiety that has implications for fetal development. The majority of women in the AD group were diagnosed with phobias and thus actually may experience their high anxiety on an intermittent basis. In contrast, depressed women, and those in the high-anxiety group, likely have chronic levels of elevated anxiety. Intermittent versus chronic anxiety may be associated with different intrauterine environments, the effects of which may be evidenced by different patterns of FHR reactivity.

Study Limitations

We did not control for fetal sleep state nor did we assess fetal movement in this study. Fetal state, bouts of state transition, and movement patterns each could underlie the group differences in FHR responses and/or serve as another variable by which to characterize variation in fetal behavior associated with women's psychiatric status. In future studies, we plan to include both of these variables. This study was not based on recruitment of a random sample of research subjects; rather, subjects responded to posted advertisements announcing the project. This method of recruitment may result in one or more types of self-selection bias.

Clinical Implications

The identification of differences in FHR reactivity related to women's moods during pregnancy, and in particular the increased FHR reactivity in fetuses of depressed and highly anxious women, underscores the

developmental nature of psychopathology: markers for the future risk for it may be evident as early as the prenatal period. Studies of fetal behavior and development in relation to women's psychiatric status will lead to more informed decisions with respect to the risk/benefit analysis of exposing the fetus to pharmacologically treated versus untreated psychiatric illness. In general, greater attention paid to pregnant women's moods could lead to interventions that would help not only the women, but perhaps their future children as well.

REFERENCES

Allister L, Lester BM, Carr S, Liu J (2001), The effects of maternal depression on fetal heart rate response to vibroacoustic stimulation. *Dev Neuropsychol* 20:639–651

Bazhenova OV, Porges SW (1997), Vagal reactivity and affective adjustment in infants. Convergent response systems. *Ann N Y Acad Sci* 807:469–471

Berntson GG, Quigley KS, Jang JF, Boysen ST (1990), An approach to artifact identification: application to heart period data. *Psychophysiology* 27:586–598

Biederman J, Hirshfeld-Becker DR, Rosenbaum JF et al. (2001), Further evidence of association between behavioral inhibition and social anxiety in children. *Am J Psychiatry* 158:1673–1679

Dawson G, Ashman SB, Hessl D et al. (2001), Autonomic and brain electrical activity in securely- and insecurely-attached infants of depressed mothers. *Infant Behav Dev* 24:135–149

DiPietro JA, Costigan KA, Pressman EK, Doussard-Roosevelt JA (2000), Antenatal origins of individual differences in heart rate. *Dev Psychobiol* 37:221–228

DiPietro JA, Hilton SC, Hawkins M, Costigan KA, Pressman EK (2002), Maternal stress and affect influence fetal neurobehavioral development. *Dev Psychol* 38:659–668

DiPietro JA, Hodgson DM, Costigan KA, Hilton SC, Johnson TR (1996a), Fetal neurobehavioral development. *Child Dev* 67:2553–2567

DiPietro JA, Hodgson DM, Costigan KA, Hilton SC, Johnson TR (1996b), Development of fetal movement–fetal heart rate coupling from 20 weeks through term. *Early Hum Dev* 44:139–151

Field T, Sandberg D, Quetel TA, Garcia R, Rosario M (1985), Effects of ultrasound feedback on pregnancy anxiety, fetal activity, and neonatal outcome. *Obstet Gynecol* 66:525–528

First MB, Spitzer RL, Gibson M et al. (1997), *Structured Clinical Interview for DSM-IV Axis I Disorders-Non-Patient Edition*. Biometrics Research Department, New York State Psychiatric Institute

Groome LJ, Swiber MJ, Bentz LS, Holland SB, Atterbury JL (1995), Maternal anxiety during pregnancy: effect on fetal behavior at 38 to 40 weeks of gestation. *J Dev Behav Pediatr* 16:391–396

Heim C, Nemeroff CB (1999), The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biol Psychiatry* 46:1509–1522

Heim C, Newport DJ, Heit S et al. (2000), Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* 284:592–597

Kagan J, Snidman N (1991), Infant predictors of inhibited and uninhibited profiles. *Psychol Sci* 2:40–44

Kofman O (2002), The role of prenatal stress in the etiology of developmental behavioural disorders. *Neurosci Biobehav Rev* 26:457–470

Llewellyn AM, Stowe ZN, Nemeroff CB (1997), Depression during pregnancy and the puerperium. *J Clin Psychiatry* 58(suppl 15):26–32

Lundy B, Jones N, Field T et al. (1999), Prenatal depression affects neonates. *Infant Behav Dev* 22:119–129

Monk C, Fifer WP, Myers MM, Sloan RP, Trien L, Hurtado A (2000), Maternal stress responses and anxiety during pregnancy: effects on fetal heart rate. *Dev Psychobiol* 36:67–77

Monk C, Myers MM, Sloan RP et al. (2003), The effects of women's stress-elicited psychological activity and chronic anxiety on fetal heart rate. *J Dev Behav Pediatr* 24:32–38

Nomura Y, Wickramaratne PJ, Warner V, Mufson L, Weissman MM (2002), Family discord, parental depression, and psychopathology in offspring: ten-year follow-up. *J Am Acad Child Adolesc Psychiatry* 41:402–409

Pressman EK, DiPietro JA, Costigan KA, Shupe AK, Johnson TRB (1998), Fetal neurobehavioral development: Associations with socioeconomic class and fetal sex. *Dev Psychobiol* 34:79–91

Rosenbaum JF, Biederman J, Gersten M et al. (1988), Behavioral inhibition in children of parents with panic disorder and agoraphobia: a controlled study. *Arch Gen Psychiatry* 45:463–470

Sjostrom K, Valentin L, Thelin T, Marsal K (2002), Maternal anxiety in late pregnancy: effect on fetal movements and fetal heart rate. *Early Hum Dev* 67:87–100

Sloan RP, Shapiro PA, Bigger JT Jr, Bagiella E, Steinman RC, Gorman JM (1994), Cardiac autonomic control and hostility in healthy subjects. *Am J Cardiol* 74:298–300

Snidman N, Kagan J, Riordan L, Shannon DC (1995), Cardiac function and behavioral reactivity during infancy. *Psychophysiology* 32:199–207

Spielberger CD (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press

Spielberger CD, Sydeman SJ (1994), State-Trait Anxiety Inventory and State-Trait Anger Expression Inventory. In: *The Use of Psychological Tests for Treatment Planning and Outcome Assessment*, Maruish ME, ed. Hillsdale, NJ: LEA, pp 292–321

Teixeira J, Fisk N, Glover V (1999), Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. *Br Med J* 318:153–157

Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Porto M, Sandman CA (1996), Prenatal psychosocial factors and the neuroendocrine axis in human pregnancy. *Psychosom Med* 58:432–446

Zuckerman B, Bauchner H, Parker S, Cabral H (1990), Maternal depressive symptoms during pregnancy and newborn irritability. *J Dev Behav Pediatr* 11:190–194