Maternal Cigarette-Smoking During Pregnancy Disrupts Rhythms in Fetal Heart Rate

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Objective  To examine the effects of maternal cigarette smoking during pregnancy on the developing infant’s autonomic regulation before the possible effects of parturition and neonatal withdrawal could alter outcome measures.  Methods  Heart rate variability (HRV) was assessed for 10 min during late gestation for 21 cigarette-exposed (CE) and 22 nonexposed (NE) fetuses.  Results  HRV was significantly lower in fetuses whose mothers smoked cigarettes during pregnancy. Spectrum analysis of that variability showed temporally organized rhythms at a frequency similar to rhythms previously found in fetal cyclic motility (approximately .3 cycles per min). Lower powered rhythms—associated with poorer development—at the first, second, and dominant rhythms, as well as lower overall power of the power spectrum, were found for CE fetuses. Pearson correlations showed significant negative correlations between the amount of maternal cigarette smoking during the first trimester of pregnancy and measures of fetal HRV and power of spectral peaks.  Conclusions  Results show that CE fetuses have lower HRV and disrupted temporal organization of autonomic regulation before effects of parturition, postnatal adaptation, and possible nicotine withdrawal contributes to differences in infant neurobehavioral function.

Key words  fetus, heart rate, prenatal environment, prenatal drug exposure, cigarette smoking.

Maternal cigarette smoking during pregnancy remains a significant concern for the health, behavior, and development of infants and children. Estimates suggest that approximately 12.3% of all mothers report cigarette smoking during pregnancy (Matthews, 2001), affecting 20–25% of pregnancies in the United States (NIDA, 1996). Tobacco smoke contains nicotine and carbon monoxide, both of which are neurotoxins (Slotkin, 1998), and at least 2000 other chemical constituents (Longo, 1977) that readily gain access to the fetal compartment via the placenta (Lambers & Clark, 1996). Metabolites of cigarette smoke that pass through the placenta act as vasoconstrictors that reduce blood flow (Suzuki, Minei, & Johnson, 1980) and result in episodic fetal hypoxia-ischemia, altered brain development, and malnutrition (Slotkin, 1998). These and other effects of prenatal cigarette-exposure may contribute to consistent dose–response associations with lower birthweight, shorter gestational ages, and increased prenatal and early postnatal mortality (Lambers & Clark, 1996; Windham, Von Behren, Waller, & Fenster, 1999), including sudden infant death syndrome (SIDS; Lewis & Bosque, 1995; Mitchell et al., 1993).

Although these studies have established a strong link between maternal cigarette smoking during pregnancy and adverse neonatal outcome, the focus on such measures as birth weight and/or gestational age has often resulted in the mistaken assumption that, in the absence of low birthweight or gestational age, infants with prenatal cigarette exposure have escaped detrimental
effects. A wide range of studies have shown neurobehavioral effects of prenatal cigarette exposure on seemingly healthy infants with measures that consistently implicate disruption of neonatal autonomic nervous system (ANS) function. In studies using standard neurobehavioral assessment scales, cigarette-exposed (CE) newborns show poorer habituation, state regulation, and autonomic regulation, as well as heightened irritability, increased numbers of tremors and startles (Fried & Makin, 1987; Fried, Watkinson, Dillon, & Dulberg, 1987; Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984; Picone, Allen, Olsen, & Ferris, 1982), and dose-response relationships with neonatal signs of visual stress, excitability and degree of stress/abstinence, or withdrawal (Law et al., 2003). Spectrum analysis of cries of infants with prenatal cigarette exposure shows higher-pitched fundamental and second formant frequencies (Nugent, Lester, Greene, Wieczorek-Deering, & O’Mahony, 1996)—spectral features characteristic of disruptions to central and ANS organization (Zeskind & Lester, 2001). More recent work has also found that prenatal cigarette exposure is predictive of a higher neonatal mean heart rate, lower heart rate variability (HRV), and increased tremulousness, even after the effects of alcohol, caffeine, and maternal demographic variables are statistically controlled (Schuetze & Zeskind, 2001).

One purpose of this study was to further explore the relationship between prenatal cigarette exposure and ANS regulation via spectrum analysis of HRV. Imbedded in the variability of heart rate over time is a rhythmic rise and fall in activity that reflects the combined effects of sensory experiences, including physiological and behavioral systems oscillating at specific frequencies (Porges, 1983; Zeskind & Marshall, 1991). In essence, spectrum analysis uncovers the frequency of the rhythm at which these systems oscillate and how their strength (power) is affected by disruptive conditions. For example, power of the cycle in heart period at the frequency of respiratory sinus arrhythmia (20 cycles per min or cpm) is significantly lower in a wide range of conditions where the health and/or development of the infant has been compromised (for a review, see Porter, 2001). A lower power of the spectral peak at the frequency of the basic rest activity (1.5 cycles per hour) has been found in newborn infants with atypical fetal growth (Zeskind, Goff, & Marshall, 1991) and other signs of disrupted autonomic regulation (Zeskind, Marshall, & Goff, 1992, 1996). Lower power rhythms averaging .3 cpm have been also found in the spontaneous movement of fetuses of diabetic mothers at 36 weeks’ gestation (Robertson & Dierker, 1986), rhythms that should have corresponding changes in fetal heart rate (Junge & Walter, 1981; Marsal, 1982).

To the extent that prenatal cigarette exposure disrupts autonomic regulation, we hypothesized that the power of spectral peaks would be reliably lower in infants whose mothers smoked cigarettes during pregnancy.

A second purpose of this study was to explore the relationship between prenatal cigarette exposure and autonomic regulation during late gestation. Recent evidence suggests that the effects of maternal cigarette smoking found in studies of newborn neurobehavioral organization may partially reflect the effects of the neonate’s withdrawal from the nicotine-rich prenatal environment (Law et al., 2003; Schuetze & Zeskind, 2001; Stephens, Zeskind, O’Grady, & Tremblay, 2002). Clinical studies suggest that fetuses also show reduced fetal HRV and reactivity, as well as reduced fetal movement, during episodes of maternal cigarette smoking during pregnancy (Graca, Cardoso, Clode, & Calhaz-Jorge, 1991; Oncken, Kranzler, O’Malley, Gendreau, & Campbell, 2002). As such, we were interested in analyzing the effects of prenatal cigarette exposure on the possible rhythms underlying fetal HRV before possible nicotine withdrawal may contribute to differences in neurobehavioral outcome.

**Methods**

**Participants**

As part of a larger study of the effects of prenatal nicotine and cocaine exposure on early infant development, women and their unborn infants were recruited for study from local obstetric clinics between their 20 and 27th weeks of pregnancy based on a review of the mothers’ medical records with results of drug screens. Clear fetal heart rate data were available from a subset of women who reported no cocaine use during pregnancy and showed negative screens for cocaine. Participants in this study included 21 CE fetuses whose mothers reported smoking cigarettes during pregnancy and 22 nonexposed (NE) comparison fetuses whose mothers reported no cigarette use during pregnancy. All fetuses were subsequently born full birthweight (≥2500 g) and full term (≥37 weeks), except for one CE infant who was born at 36.3 weeks’ gestation. Infants were healthy by standard neurological and physical examination. Table I summarizes some of the demographic and birth characteristics of the CE and NE infants and their mothers.

Results of t tests showed that CE and NE groups did not reliably differ in the mothers’ mean age or number of pregnancies, or in the infants’ mean eventual gestational age at birth, birthweight, birth length, head circumference, and Apgar scores at both 1 and 5 min. Chi-square
analyses also showed that the two groups of mothers did not reliably differ in the distributions of their marital status (NE: single = 16, married = 5, divorced = 1; CE: single = 18, married = 3), $\chi^2(2) = 1.59, p < .45$. Maternal education level was scored as 1, “high-school graduation”; 2, “high-school graduation”; and 3, “>high-school graduation.” As frequently found in the literature (Olds, Henderson, & Tatelbaum, 1994), mothers who smoked cigarettes during pregnancy tended to have fewer years of education (see Table I). Further, cigarette-using mothers were more often of Anglo-American ethnic background (14 of 21) than comparison mothers who were more often of African-American descent (19 of 22), $\chi^2(1) = 12.6, p < .001$. No direct measures of socioeconomic status were obtained in the larger study.

### Prenatal Cigarette Exposure

Standard interviews, conducted regularly after enrollment in the study, were used to obtain a history of the amount of cigarette and alcohol use, as well as whether illegal drugs were used. Amount of cigarette smoking per day was scored as none (0 cigarettes/day), mild (1–10 cigarettes/day), moderate (11–20 cigarettes/day), and strong (>20 cigarettes/day). Table II summarizes that the reported level of cigarette smoking/day by trimester was mostly mild to moderate throughout pregnancy. Pearson product–moment correlations showed higher associations between the amount of cigarettes mothers smoked in the first and second trimesters ($r = .73, p < .001$), and second and third trimesters ($r = .84, p < .001$), and a more moderate association between first and third trimesters ($r = .47, p < .02$). Mothers who smoked cigarettes during pregnancy also reported using alcohol ($n = 3$) or marijuana ($n = 7$) or both ($n = 2$) during pregnancy, but no reliable information regarding the amount of these substances was available. One mother in the comparison group admitted to drinking alcohol during pregnancy, but no other alcohol or marijuana use was reported by any mothers in that group. No other illicit drugs were reported as having been used by mothers in either group. In addition to the self-report data, drug tests were conducted on mothers twice during pregnancy (urine tests) and at birth on the newborns (urine and meconium) and mothers (urine). No evidence of drugs of abuse (cocaine, barbiturate, and cannabinoid) was found in the urine of mothers and infants in this study by fluorescence polarization immunoassay (Abbott AXSYM) or in meconium by homogeneous enzyme assay (Beckman CX). Mothers were instructed not to smoke for at least 1 hour before the ultrasound, but no reliable data were available to indicate exactly when mothers had their last cigarette before testing nor for the amount of cigarettes smoked per day. Based on the mild to moderate levels of cigarette smoking, it is likely that mothers smoked at least one cigarette earlier in the day before testing.

### Heart Rate

Fetal heart rate was measured during a late-gestation ($M = 37.1$ weeks, $SD = 0.79$) ultrasound examination by continuous-wave Doppler and was continuously recorded via a Corometrics fetal monitor and dual-channel strip chart recorder. Time samples of fetal heart rate were
determined from the charts at five-section intervals for 10 contiguous min by an assistant who was blind to group membership and provided accurate measures with a resolution of ±1 bpm. The resulting 120 time-sampled measures of fetal heart rate were subjected to spectrum analytic techniques previously used to study oscillations in neonatal heart rate among high risk infants (Zeskind et al., 1996). By using these methods, linear, quadratic, and cubic trends in the data were removed before heart rate spectra were computed to improve the stationarity of the time series. The residual variance of each time series was then spectrum analyzed by using a Blackman–Tukey window. Finally, a Kolmogorov–Smirnov test was calculated for each power spectrum to determine the signal to noise ratio and significance of spectral peaks by using a 95% confidence interval (Jenkins & Watts, 1968). This analysis detected cycles in HRV ranging from .1 to 6 cpm with a resolution of .1 cpm.

Measures determined from the power spectra included the power of the (a) basic spectral peak (BSP)—the first significant spectral peak, (b) second spectral peak (SSP)—the second significant spectral peak, (c) dominant spectral peak (DSP)—the spectral peak with the highest power, and (d) sum of the spectral density values (SSDV)—the sum of the power at all frequencies throughout the power spectrum. Figure 1 shows a power spectrum for a NE infant with the Kolmogorov–Smirnov criterion level superimposed. In this power spectrum, the BSP was also the DSP at approximately .9 cpm; the SSP was not significant. In addition to these measures of the power spectrum, we were interested in measures of the statistical variance of the 120 data points of fetal heart rate or HRV and the residual variance after the regressions were conducted or variance of the time series (VTS).

Results
Spectral analysis of HRV showed that the cumulative variance distribution departed significantly from that of white noise for 42 of the 43 infants in this study (all p’s < .05). That is, for all but one of the infants in the NE group, heart rates showed reliable oscillations. Reliable power spectra showed from 1 to 3 significant spectral peaks: 27 showed one reliable cycle (15 NE, 12 CE), 13 showed two reliable cycles (6 NE, 7 CE), and one showed three reliable cycles (1 CE). The first significant cycle or BSP was evident at .3 cpm for 25 infants (12 NE, 13 CE), .6 cpm for 13 infants (8 NE, 5 CE), and .9 cpm for 2 infants (1 NE, 1 CE). The one remaining infant (CE) had its first reliable cycle in the power spectrum at 4.2 cpm. Thus, all but one of the power spectra that contained significant cycles in fetal heart rate showed their BSP at .3 cpm or its multiples in the known range of frequencies of cyclic motility (.2–.9 cpm).

Group comparisons of the measures of the power spectra were made via t tests (see Table III). Comparisons
of measures of HRV were based on log_{10} transformations of
the data to normalize the distributions (Porges, Arnold, &
Forbes, 1973). Results showed that CE fetuses showed
reliably lower HRV and VTS than NE fetuses. Analyses of
the power spectra of this variability showed that CE
fetuses showed also reliably lower power in the BSP, DSP,
and SSP than NE infants. CE fetuses also showed a reli-
ably lower SSDV, a measure of the overall power of all the
spectral values, not just identifiable peaks.

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<th>Table III. Outcome Measures in Cigarette Exposed and Nonexposed Groups</th>
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Figures 2 and 3 show three-dimensional landscapes of the power spectra for NE and CE groups, respectively. The generally lower power of spectral peaks in HRV of CE fetuses is evidenced by the “flatter” spectral land-
scape. The above group differences were found in the
absence of differences in mean heart rate (CE: M = 138.6,
SD = 6.1; NE: M = 139.0, SD = 8.5), t(41) = .18, p < .86, or
the number of reliable peaks in the power spectra (CE:
M = 1.38, SD = .67; NE: M = 1.23, SD = .53), t(41) = .84,
Further, there was no difference in the distribution of the frequencies at which the DSP occurred, $\chi^2(3) = .64, p < .89$. Pearson product–moment correlations showed also no reliable associations between gestational age at time of testing and all outcome measures (all $p$'s > .48).

Figure 4 shows results of Pearson product–moment correlations among the amount of reported maternal cigarette use in each trimester with the measures of HRV and spectral analyses. Correlations between the amounts of reported maternal cigarette smoking and measures of HRV and power spectra were progressively smaller with each succeeding trimester. Significant negative correlations were found between the amount of maternal cigarette smoking in the first trimester of pregnancy and each outcome measure. Correlations were marginal ($p$'s > .05 and < .10) with reported second trimester exposure and nonsignificant ($p$'s > .10) with third trimester exposure, except with PDP at $p < .07$. No reliable relation was found between the infant's gestational age at testing and any of the outcome measures (all $p$'s > .48). Correlations between the infant's eventual birthweight and the amount of maternal cigarette smoking during each trimester were all low ($r$'s < .06) and nonsignificant ($p$'s > .81). The infant's eventual gestational age was negatively correlated with the amount of maternal cigarette smoking during the third trimester ($r = -.41, p < .045$), but not with the amount smoked during the first ($r = .13, p > .60$) or second ($r = .037, p > .88$) trimesters.

Spearman correlations were also conducted within the CE group for associations between measures of fetal heart rate and alcohol and marijuana use. Correlations between marijuana use and all measures of heart rate and power spectra were low (all $r$'s < .04) and nonsignificant (all $p$'s > .69). Similarly, correlations between alcohol use and measures of heart rate were also low ($r$'s < .16) and nonsignificant ($p > .55$), except for a negative correlation with heart rate mean, $r = -.60, p < .01$. Group comparisons of mean heart rate were repeated without the four fetuses (NE = 1, CE = 3) exposed to maternal alcohol use during pregnancy. Results continued to show no differences between the mean heart rates of CE ($M = 139.9, SD = 5.5$) and NE ($M = 139.4, SD = 8.5$) fetuses, $t(37) = .237, p < .81$. Further, $t$-test comparisons between marijuana-exposed and NE infants in the CE group showed no differences in any of the measures based on HRV (all $p$'s > .52) or heart rate mean ($p > .25$). Thus, although cigarette-using mothers also more often reported using other legal and illegal drugs during pregnancy, no reliable effects of these drugs were found on measures of HRV or its temporal organization in this sample.

**Discussion**

Maternal cigarette smoking during pregnancy has been associated with a wide range of adverse biochemical and physiological effects, including reducing oxygen to the
developing fetus, creating episodic fetal hypoxia-ischemia, and disrupting central cardiac regulation (Slotkin, 1998). Comparative studies indicate that adverse effects on fetal brain development may occur at doses that do not result in low birthweight (Luck, Nau, Hansen, & Steldinger, 1985). Studies of full term, full birthweight newborns have shown adverse effects of prenatal cigarette exposure on neurobehavioral measures, including withdrawal symptoms (Law et al., 2003) and HRV (Schuetze & Zeskind, 2001), at levels as low as less than 10 cigarettes (half pack) per day. Results of this study of fetuses who would subsequently be born full term and full birthweight showed that prenatal cigarette exposure was associated with lower fetal HRV, and lower overall power and power of spectral peaks in the power spectrum of that HRV. These results were found before the effects of parturition, adaptation to the postnatal environment, and/or total withdrawal from nicotine contributed to differences in autonomic regulation.

First, finding lower HRV in CE fetuses is similar to findings of previous studies in which CE fetuses (Graca et al., 1991; Oncken et al., 2002) and newborn infants showed lower HRV (Schuetze & Zeskind, 2001). Heart rates of CE fetuses were relatively flat and unchanging over time. These results add to our evidence that HRV is sensitive to the effects of prenatal CE and that prenatal cigarette exposure may disrupt ANS regulation. Unlike the previous study in which higher mean heart rates were found in CE newborns, no differences in mean heart rate were found in this study, either before or after effects of prenatal alcohol were removed. Although statistical and methodological differences between the two studies could account for this difference in findings, the higher mean heart rates found in newborns may also reflect the effects of neonatal withdrawal from prenatal nicotine exposure. Nicotine concentrations may reach 15% higher in the fetus than in the mother (Lambers & Clark, 1996; Luck et al., 1985) and even low levels of prenatal cigarette exposure may create agitation, tremors, and increased numbers of state changes (Schuetze & Zeskind, 2001) and specific measures of withdrawal in the newborn (Law et al., 2003). Results of this study indicate that lower HRV, but not necessarily mean heart rate, occurs in utero.

Second, an important distinction from the previous work on HRV is that this study showed that this HRV was temporally organized. Although spectrum analysis of short-term variability sampled at higher rates are hypothesized to reflect neural control of the heart by the vagus (Porges, McCabe, & Yongue, 1982; Porter, 2001), analysis of long-term variability sampled at slower rates is used to detect the effects of relatively stable timing mechanism underlying behavior (Robertson, 1982; Zeskind & Marshall, 1991). Spectrum analysis of fetal heart rate showed reliable cycles with a basic rhythm at .3 cpm or its multiples for all but one of the infants. Previous work has indicated that fetuses show cycles in spontaneous movement at these frequencies (Robertson & Dierker, 1986) and that burst in motor activity are evident in changes in heart rate (Junge & Walter, 1981; Marsal, 1982). Thus, results of this study indicate that the cyclic nature of spontaneous movements may result in comparable cycles in fetal heart rate. The presence of additional significant spectral peaks at higher frequencies in the heart rate power spectrum may reflect the tendency for movement to occur in short bursts during the slower rhythmic processes oscillating at the basic frequency (Thelen, Bradshaw, & Ward, 1981).

Third, the power of these spectral peaks differentiated CE and comparison fetuses. Power spectra of CE fetuses were characterized by lower overall power (SSDVs) and lower power of the DSP, BSP, and secondary spectral peaks than those of NE fetuses. Statistically, reduced power of the spectral peaks may indicate that there was less HRV at the respective frequencies. These findings indicate that the CE fetus shows less variability in heart rate associated with motility than NE infants during gestation. This finding is similar to the findings of Robertson and Dierker (1986) in which poor metabolic conditions in the prenatal environment resulted in fetuses during late gestation having lower powered spectral peaks at the frequency of cyclic motility. Other work has also indicated that less amplitude in the oscillation of physiological systems, within normal parameters, is associated with poorer health (Porjes & Byrne, 1992). Results of this study provide evidence that the power of spectral peaks at rhythms associated with spontaneous fetal motility is sensitive to the effects of prenatal cigarette exposure. To the extent that newborn infants show neurobehavioral indices of nicotine withdrawal, an important question for future work is how and whether the effects of prenatal cigarette exposure would be evident in the temporal organization of neonatal HRV in the postnatal context.

Fourth, correlations within the CE group showed that greater amounts of reported maternal cigarette use during the first trimester of pregnancy were reliably associated with lower HRV and lower powered measures of the power spectrum. The strengths of associations were progressively smaller with each succeeding trimester of pregnancy until associations with third trimester cigarette use were small and nonsignificant. Although
the effects of nicotine are seen in every trimester of pregnancy (Lambers & Clark, 1996), results of this study suggest that maternal cigarette smoking during the first trimester of pregnancy may have a particularly strong impact on fetal autonomic regulation associated with cyclic motility. This may be because spontaneous cyclic motility is a system undergoing rapid development during the first trimester. Spontaneous movement appears in the human fetus as early as 7.5 weeks’ gestation and peaks in incidence by mid gestation (Hooker, 1952; Patrick, Campbell, Carmichael, Natale, & Richardson, 1982). Cyclic patterns in fetal motility emerge by mid gestation and remain relatively unchanged throughout the second half of gestation (Robertson, 1985) and thus would be more susceptible to a first trimester insult. Others suggest that cigarette smoking during early gestation may have primary effects on brain stem sites (Olds et al., 1994) and that brain stem activity may be part of the supraspinal system that modulates spinal motor circuits generating cyclic motility (Robertson, 1987; Vertes, 1984; Visser, Bekedam, Mulder, & van Ballegooie, 1985).

In conclusion, this study provides evidence that disruptions in autonomic regulation associated with maternal cigarette smoking are evident in late gestation before the effects of parturition, postnatal adaptation, and possible nicotine withdrawal contributes to neurobehavioral outcome. Importantly, differences in autonomic regulation were found in fetuses who would eventually become full birthweight, full term infants who were otherwise unremarkable in the newborn nursery. The often reported relationship between infant birthweight and the amount of maternal cigarette smoking during pregnancy was not found in this sample. Although the reasons for not finding this often-found relationship are not clear, many factors, including overall nutrition, presence of infection, and metabolic activity, may contribute to the development of birthweight. In any case, in the absence of these routine physical signs of risk, it could be inaccurately concluded by health care professionals and/or caregivers that the maternal cigarette smoking that occurred during pregnancy had no significant effects on the infant’s health and development.

Another important conclusion is that disruptions in autonomic regulation were highly correlated with the amount of cigarette smoking during the first trimester of pregnancy. Professional advice that cigarette smoking has its detrimental effects mostly during the third trimester of pregnancy may provide an unwarranted assumption of safety. This conclusion may be based on findings of studies using birthweight—which mostly accumulates during the third trimester—as the primary outcome measure. That is, the seemingly apparent effects of prenatal cigarette exposure may be based on when during development the outcome measure develops. Maternal smoking during the first trimester of pregnancy may impact the development of cyclic motility, but may not be evident in a lower birthweight. Finding significant effects of first trimester cigarette use on fetal development underscores the importance of prevention and smoking cessation before conception.

The differences in HRV found in this study have been previously discussed as the foundation of, or contribution to, a wide range of poor cognitive and social–behavioral outcomes in subsequent development (Zeskind & Marshall, 1991). In particular, we can speculate that these findings may contribute to our understanding of some of the possible mechanisms underlying the development of SIDS. Maternal cigarette smoking during pregnancy is one of the highest risk factors for SIDS with a linear relationship between the number of cigarettes smoked and SIDS risk (Golding, 1997; MacDorman, Cnattingius, Hoffman, Kramer, & Haglund, 1997). One of the most significant hypotheses is that autonomic dysfunction or autonomic maturational delay is a feature of some infants who succumb to SIDS (Fox & Matthews, 1989; Harper, 2000; Harrington, Kirjavainen, Teng, & Sullivan, 2002; Matthews, 1992; Schechtman et al., 1992; Schwartz et al., 1997). Results from this study suggest that maternal cigarette smoking during pregnancy, as early as the first trimester, may contribute to problems in the temporal organization of autonomic regulation.

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