Fetal Neurobehavioral Development: A Tale of Two Cities

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Longitudinal neurobehavioral development was examined in 237 fetuses of low-risk pregnancies from 2 distinct populations—Baltimore, Maryland, and Lima, Peru—at 20, 24, 28, 32, 36, and 38 weeks gestation. Data were based on digitized Doppler-based fetal heart rate (FHR) and fetal movement (FM). In both groups, FHR declined while variability, episodic accelerations, and FM–FHR coupling increased, with discontinuities evident between 28 and 32 weeks gestation. Fetuses in Lima had higher FHR and lower variability, accelerations, and FM–FHR coupling. Declines in trajectories were typically observed 1 month sooner in Lima, which magnified these disparities. Motor activity differences were less consistent. No sex differences in fetal neurobehaviors were detected. It is concluded that population factors can influence the developmental niche of the fetus.

Most of the vast amount of study on the physical and mental development of children has begun with birth, more or less completely neglecting the possible influence of environment during the period of intra-uterine development. (Sontag & Wallace, 1934, p. 1050)

Consideration of the environmental context provided by the pregnant woman to her developing fetus remains as vanguard a concept today as it was in the 1930s for the investigators in the Fels Longitudinal Study. Well-established models of child development after birth include both proximal and distal influences on developmental processes, ranging from biological factors to parental caregiving to the social and political environment (Pachtier & Harwood, 1996). The developmental niche of a given child reflects the particular setting for development within these multiple levels of influence (Super & Harkness, 1986). Cross-cultural research has been used to distinguish biological, maturative processes from those that are guided by environmental influences. Such studies typically compare cultures that broadly differ on many dimensions, including ethnicity, socioeconomic status, and general living conditions (Freedman & DeBoer, 1979). Cross-cultural differences in neonatal neurobehaviors have been observed (Choi & Hamilton, 1986; Coll, Spekoski, & Lester, 1981; Eishima, 1992; Keef, Tronick, Dixon, & Brazelton, 1982)—as have differences in the rate and proficiency of motor development in the first few years of life—between, for example, infants in the United States and Brazil (Santos, Gabbard, & Goncalves, 2001), Paraguay (Kaplan & Dove, 1987), and the Yucatan (Solomons & Solomons, 1975). Although some variation in motor development has been attributed to variations in aspects of the physical or social environment, in general, the sources of these differences are poorly understood.

The uterus is the developmental niche of the fetus. In contrast to other periods of development, there has been little coherent conceptualization of the environmental factors that may influence fetal neurobehavioral development as it unfolds. Despite the acknowledgment that both environmental and biological processes serve as sources of variation in postnatal development, there is a tendency to regard differences that are apparent at birth, or before, as reflecting genetic influences alone. However, there is increasing recognition of the influence of the maternal womb environment on...
constitutional factors (Devlin, Daniels, & Roeder, 1997). The perspective that the sequence and timing of prenatal development are universal phenomena is reflected in the small sample sizes (i.e., often 20 or fewer participants) of most studies of fetal neurobehavioral development. Few studies consider the sociodemographic characteristics of participants despite evidence for social class effects on fetal neurobehavioral development at-risk (M. Johnson et al., 1992) and normal (DiPietro, Costigan, Shupe, Pressman, & Johnson, 1998) pregnancies in the United States. Knowledge about fetal development has been generated predominantly from samples of pregnant middle-class women from developed countries with the assumption that these findings reflect universal antenatal processes.

Interest in antenatal development has burgeoned with the knowledge that processes beginning before birth contribute to later health in general (Barker, 1995; Gillman & Rich-Edwards, 2000; Phillips, 2001) and to neurological disorders such as cerebral palsy in particular (Lamb & Lang, 1992; Nelson & Ellenberg, 1986). The view that fetal neurobehaviors reflect the developing nervous system within normal populations has received support from many sources (DiPietro, Irizarry, Hawkins, Costigan, & Pressman, 2001; Hepper, 1995; I. Nijhuis & ten Hof, 1999; J. G. Nijhuis, 1986; Sandman, Wadhwa, Hetrick, Porto, & Pecce, 1997). In addition, neurobehavioral development is affected in fetuses with congenital anomalies (Hepper & Shahidullah, 1992; Horimoto et al., 1993; Romanini & Rizzo, 1995; Vindla, Sahota, Coppens, & James, 1997) and in fetuses exposed to other deleterious antenatal conditions including growth restriction (Bekedam, Visser, de Vries, & Prechtl, 1985; I. Nijhuis et al., 2000; Vindla, James, & Sahota, 1999), maternal diabetes (Kainer, Prechtl, Engele, & Einspieler, 1997; Mulder, 1993), and substance exposure (Gingras & O’Donnell, 1998; Mulder, Morssink, van der Schee, & Visser, 1998; Szeto, 1983).

Understanding of the developmental trajectories of normative fetal neurobehavior has emerged over time through synthesis of findings obtained with the more common cross-sectional approach and findings from longitudinal studies. The general pattern of decline in fetal heart rate (FHR) accompanied by an increase in time-dependent (G. S. Dawes, Moulden, Sheil, & Redman, 1992; Fleisher, DiPietro, Johnson, & Pincus, 1997) or time-independent (G. S. Dawes, Houghton, Redman, & Visser, 1982; van Leeuwen, Lange, Bettermann, Gronemeyer, & Hatzmann, 1999) variability is well known. Accelerations, defined as episodic excursions in FHR, form the cornerstone of antepartum clinical monitoring (Ware & Devoe, 1994). Reports of developmental trends in fetal motor activity are less consistent. Some report that the fetus becomes less active as term approaches (DiPietro, Hodgson, Costigan, Hilton, & Johnson, 1996b; Roedenburg, Wladimiroff, van Es, & Prechtl, 1991; ten Hof et al., 2002), but others fail to show changes during the third trimester (Manning, Platt, & Sipos, 1979; Patrick, Campbell, Carmichael, & Probert, 1982). Differences in how fetal movement (FM) is defined across studies make comparisons difficult (ten Hof et al., 1999), and this inconsistency may partially explain discrepancies. For example, fetuses may make fewer individual movements over time without a corresponding change in the proportion of the time they spend moving (DiPietro et al., 1998; Roberts, Griffin, Mooney, Cooper, & Campbell, 1980). Therefore, inclusion of both types of measures provides a more comprehensive characterization of movement.

A third feature of fetal neurobehavioral development that has received attention is the relationship between heart rate and motor activity. As gestation advances, fetal motor activity becomes increasingly associated with transient accelerations of FHR. The strength of this relationship indicates general fetal well-being (Baser, Johnson, & Paine, 1992), and its developmental nature has been interpreted as a sign of progressive integration between sympathetic and parasympathetic innervation of the autonomic nervous system (DiPietro et al., 1996b; T. R. B. Johnson, Besinger, Thomas, Strobino, & Niebyl, 1992; Timor-Tritsch, Dierker, Zador, Hertz, & Rosen, 1978; Vintzileos, Campbell, & Nochinson, 1986). The linkage between somatic and cardiac functioning is also at the basis of the emergence of fetal behavioral states as gestation progresses (Groome & Watson, 1992; I. J. M. Nijhuis et al., 1999; J. G. Nijhuis, Prechtl, Martin, & Bots, 1982; van Vliet, Martin, Nijhuis, & Prechtl, 1985).

Consistent with the long-standing interest and well-developed literature on sex differences in infants and children in general, the most frequently investigated moderator of development before birth has been fetal sex. Despite persistent clinical conviction, antenatal differences in mean heart rate between male and female fetuses have not been documented (G. S. Dawes et al., 1982; DiPietro et al., 1996b; Druzin, Hutson, & Edersehns, 1986). Heart rate during labor was found to be significantly higher in female fetuses in one study (N. Dawes, Dawes, Moulden, & Redman, 1999) but not in another (Petrie & Segalowitz, 1980) that explicitly tested for sex differences. Similarly, variability in FHR was reported as greater in male fetuses in one study (DiPietro et al., 1998) but not in another (I. Nijhuis et al., 2000). The most consistently documented postnatal sex difference is that boys are more physically active than girls. Male fetuses are reported to make more frequent leg movements (Almli, Ball, & Wheeler, 2001); female fetuses, more frequent mouthing movements (Hepper, Shannon, & Dorman, 1998). However, a meta-analysis of six studies concluded that there are no antenatal sex differences in activity level (Eaton & Enns, 1986). Conflicting results have been generated within our own work, with male fetuses being active for more of the observation time in one sample (DiPietro et al., 1996b) but not in another (DiPietro et al., 1998).

Two investigative groups, our own (DiPietro et al., 1996a, 1996b) and a team in the Netherlands (I. Nijhuis et al., 1998; ten Hof et al., 2002), have modeled normative fetal neurobehavioral development using statistical techniques that are becoming more commonly applied in developmental science. Results generated by these projects, which measured antenatal neurobehavior at either monthly or bimonthly intervals, have provided perhaps the most comprehensive information regarding development during the second half of gestation. However, both are limited in sample size (Ns = 31 and 29, respectively) and are based on relatively homogeneous groups of women in the United States and England. No study to date has either explicitly compared development before birth cross-culturally or comprehensively evaluated fetal neurobehavioral development in a developing country.

We had two primary goals for this project. The first was to examine the levels and trajectories of development in two different cultures: one marked by the degree of affluence typical in the
developed world; the other, by the pervasive disadvantages encountered in developing countries. To this end, we implemented parallel longitudinal data collection at two sites: Baltimore, Maryland, in the United States and Lima, Peru. By recruiting only low-risk women with normally progressing pregnancies who gave birth to healthy offspring, we were able to focus on normative development in both locations. If antenatal development is driven primarily by intrinsic maturative processes, one would not expect fetal development to differ in these two locales. If, however, the environmental milieu of the pregnancy affects antenatal development, significant variation both in the level and trajectories of fetal neurobehavior would be expected between Baltimore and Lima.

Our second goal was to confirm preliminary findings regarding the trajectory of fetal neurobehavioral development from our earlier, small sample. In particular, we focused on those findings suggestive of a period of discontinuity at the beginning of the third trimester, which has implications for the understanding of the neuromaturational processes of preterm infants delivered at this time. In previous reports, discontinuities were detected in five of eight aspects of fetal neurobehavioral development, clustering around the 28th to 32nd weeks of gestation (DiPietro et al., 1996a, 1996b). In each instance, the slope of the trajectory of neurobehavioral development slowed after this gestational period. Thus, we sought to replicate this finding with a larger U.S. sample and to establish whether it is a universal phenomenon by applying the same statistical analysis to a group of fetuses drawn from an entirely different population. A secondary goal, afforded by the larger sample sizes, was to reconcile the discrepancies in the literature regarding whether sex differences in fetal neurodevelopment exist.

Method

Participants

Eligibility for enrollment in Baltimore and Lima was restricted to nonsmoking women with uncomplicated pregnancies carrying singleton fetuses. Accurate dating of the pregnancy, based on early first trimester pregnancy testing or examination and/or confirmation by ultrasound, was required. Gestational age was ultimately established by using the best clinical estimate that was based on all available dating information (DiPietro & Allen, 1991). Fifty percent of each sample consisted of primiparous women.

A total of 185 self-referred pregnant women were enrolled in Baltimore at Johns Hopkins Hospital. Women learned of the project through advertisements placed in local university publications and by word of mouth. Women resided either in Baltimore or the surrounding suburbs and did not necessarily receive prenatal care or deliver their infants at the recruiting hospital. Forty-eight participants were either prospectively or retrospectively excluded for the following reasons: preterm labor, preterm delivery, or both (21; 11%); gestational diabetes (6; 3%); congenital malformation (2; 1%); fetal death in utero or nonviable delivery (2; 1%); growth retardation or other condition of antepartum origin detected in the newborn (6; 3%); and lack of continued participation because of scheduling difficulties, moving, etc. (12; 6%).

Participants in Lima were part of a randomized controlled trial investigating the role of prenatal zinc supplementation in fetal growth and development. In order to approximate comparison with the population norms in Lima, the current analysis was based on women who made up the control arm of the larger study and thus did not receive zinc supplementation. However, as is consistent with the recommendation of the Peruvian Ministry of Health, women in this group received daily supplementation of iron and folic acid. There were no sociodemographic differences between women in the control and the experimental arms of the study. Recruitment proceeded at the Materno Infantil San Jose in Villa El Salvador, an impoverished district at the periphery of the city. Women who are served by this hospital are considered to be at low risk for poor pregnancy outcomes, and those in the study enrolled in prenatal care prior to 16 weeks gestation. Lima, like Baltimore, is at sea level.

The same exclusionary criteria for developing pregnancy complications and infant conditions as in Baltimore were applied. Of the 117 women who began fetal testing, 16 were excluded for the following reasons: preterm delivery (3; 2.6%); congenital malformation (3; 2.5%); fetal death in utero or nonviable delivery (2; 5%); condition of antepartum origin detected in the newborn (1; 1%); and lack of continued participation because of scheduling difficulties, moving, etc. (7; 7%).

The final samples comprised 137 Baltimore and 101 Lima participants. Although a range of socioeconomic levels was represented in the U.S. sample, as a group they represented a well-nourished, middle-to-upper-class population receiving a high standard of prenatal care. The Peruvian sample represented a much less affluent population that was disadvantaged in terms of income, status, and all that these entail. However, the health care system provides a relatively high level of prenatal care, including early detection, monthly prenatal visits, screening, and referral services.

Design and Procedure

In both locations, fetal monitoring commenced at 20 weeks gestation and was repeated at 24, 28, 32, 36, and 38 weeks gestation. In Baltimore, women were assessed at the same time of day during each visit (either 1:00 p.m. or 3:00 p.m.), but testing conditions in Lima made this degree of control impossible. Testing in Lima took place between 9 a.m. and 6 p.m. However, no systematic diurnal effects for FHR or FM parameters have been found when testing is done within daytime hours (I. Nijhuis et al., 2000; ten Hof et al., 2002). All women were instructed to eat 1/2 hr prior to testing but not thereafter. A member of the Baltimore investigative team supervised implementation of the study in Lima to ensure fidelity in data collection procedures. A brief real-time ultrasound scan was conducted to determine fetal position and provide photographs to parents. Fetal monitoring proceeded for 50 min, with the mother resting comfortably in a semirecumbent, left-lateral position. This duration was consistent with that chosen in our prior studies and exceeds the 30 to 40 min of recording time established for intrafetal stability (I. Nijhuis et al., 1998; Ribbert, Fidler, & Visser, 1991). The standards and methods of data collection and analysis at both sites were identical with one exception: Data collection at 32 weeks in Baltimore was shortened to 30 min to facilitate an experimental manipulation following the undisturbed recording.

Fetal data were collected using a Toitu MT320 fetal actocardiograph (Toitu Co., Ltd., Tokyo, Japan). This monitor detects FM and FHR through the use of a single, wide array transabdominal Doppler transducer and processes signals via a series of filters. The actograph detects FM by preserving the remaining signal after bandpassing frequency components of the Doppler signal that are associated with FHR and maternal somatic activity. Reliability studies comparing actograph-based versus ultrasound-visualized FM have found the performance of this monitor to be highly accurate in detecting both fetal motor activity and quiescence (Bensing & Johnson, 1989; DiPietro, Costigan, & Pressman, 1999; Maeda, Tatsumura, & Utsu, 1999).

Fetal data in both sites were collected from the output port of the monitor and digitized at 1000 Hz through an internal A/D (analog/digital) board using streaming software. Data were analyzed offline with software developed for this project. Digitized FHR data underwent error rejection procedures based on moving averages of acceptable values as needed. Fetal
Variables included three cardiac measures: FHR, variability (the standard deviation of each 1-min epoch aggregated over time), and accelerations. Based on standard clinical definitions, accelerations were defined as occurring when FHR values attained 10 beats per minute (bpm) above baseline for 15 s or longer. FM measures were based on the actograph signal, which ranges from 0 to 100 in arbitrary units. A movement bout was considered to begin when the first spike of the actograph attained amplitude of 15 units and to end when there was a cessation of 15 unit signals for at least 10 s. The number of movements was counted, and the duration of each movement was measured. Total motor activity was computed as the number of movement bouts multiplied by the mean movement duration (in seconds) divided by 3,000 (the number of seconds per 50 min of recording). This variable represents the proportion of time the fetus spent moving during the observation period. FHR-FM coupling was calculated as the proportion of fetal movements associated with excursions in FHR > 5 bpm over baseline within 5 s before the start of a movement or within 15 s after the start of a movement, consistent with previously developed criteria (Baser et al., 1992; DiPietro et al., 1996a).

**Data Analysis**

All fetal and maternal measures were examined for normality; two FM outliers were found, one in Baltimore and one in Lima. Because two variables (accelerations and movement bouts) at 32 weeks required weighting relative to the shortened recording length, care was taken to detect instances in which the 32-week data did not conform to expectations based on patterns of earlier and later data. Weighted least squares analysis was used to model the developmental trends of the FHR, FM, and FHR-FM coupling measures over time separately for each sample. This method estimates the correlation structure generated by the repeated measurements on the same fetus and uses the estimate to weight the observations in the regression analysis. The robustness of the estimated unstructured correlation matrix was assessed using generalized estimating equations methodology (GEE; Zeger & Liang, 1986). This technique produces appropriate estimates of regression parameters and their variances (Diggle, Liang, & Zeger, 1994). Moreover, unlike repeated measures analysis of variance procedures, GEE does not exclude subjects with missing data from the final model. There were few instances of missing data that were due to either noncompliance or technical problems at any visit prior to the final one (2 cases at 28 weeks in Baltimore; 1 to 2 cases at each gestational age in Lima). However, a substantial number of women who delivered at term (i.e., 37 to 41 weeks) delivered before their scheduled 38-week visit (33% in Baltimore; 9% in Lima), usually because they delivered earlier during that week.

To model nonlinear trends, we included knotted splines in each model at 24, 28, 32, and 36 weeks gestation, and thus there were at least two contiguous data points before a deviation was established. Knotted splines allow nonlinear trends to be modeled by permitting the slope to change at the “knot”; consideration of significance reflects the degree to which the slopes prior to and following this point diverge. In the event that changes in slope were significant at more than one point, the placement of the spline knot was determined by the magnitude of the deviation from the saturated model. Terms for fetal sex were added to each linear model. Comparisons between the general developmental trends in Baltimore and Lima were conducted by modeling slopes by location.

**Results**

**Maternal and Infant Characteristics**

Table 1 presents maternal and infant characteristics. There were clear differences in maternal sociodemographic characteristics between the Baltimore and Lima samples. The level of maternal education diverged greatly, with some degree of graduate training (43%) being the modal value in the U.S. sample compared with a high school education (49.5%) in Peru. Almost a third of the Lima sample did not have a high school diploma. Explicit comparisons of income and occupation were not possible because of differences in monetary value and the low levels of maternal employment during childbearing in Lima. Peruvian women were of Mestizo descent. The U.S. sample was 85% White, 12% African American, and 3% Hispanic or Asian. The Baltimore women were about 8 years older than the Lima women.

Anthropometric measures can provide indicators of nutritional status in mothers and fetal growth in infants. Peruvian women were shorter and lighter, but the difference in body mass index (BMI) between groups was only marginally significant. Similarly, although Peruvian infants were smaller at birth, the ponderal index, which reflects the relationship between weight and length, was not lower, nor was head circumference. Despite the Peruvian infants’ lower birth weight, the average gestational age at delivery was 3 days later in Lima than in Baltimore.

**Developmental Trends**

Table 2 presents the results of the linear and spline-based GEE analyses for the Baltimore and Lima samples over gestation. Results include the coefficients (estimates), the standard errors, and the Z scores for significance testing. Each estimate indicates the magnitude of weekly change for each variable in its unit of measurement. For example, from 20 weeks to 38 weeks, FHR declined at a rate of 0.41 bpm per week. Mean raw data values are plotted in Figures 1 through 7. Highly significant positive linear
trends over gestation were detected for all three FHR measures (mean, variability, and accelerations) at both sites, with declining mean FHR but increasing variability and accelerations. Coupling between FHR and FM increased significantly over time at both sites. The number of fetal movements declined over time in both sites, but the total amount of activity and mean FM duration declined significantly in Peru only.

Values listed in Table 2 under “Discontinuity (spline)” indicate the gestational period (if any) at which a significant change in slope was detected. Discontinuities in development were evident for FHR variability, accelerations, and coupling with FM in both Baltimore and Lima, clustering between 28 and 32 weeks gestation. FHR showed a change in trajectory in Lima only, at 28 weeks. Examination of the data plotted in the figures reveals that the slope of the trajectory following each spline is reduced relative to the trajectory to that point. Inspection of Figure 1 indicates an apparent change in slope for FHR in Baltimore at 32 weeks. Examination of the data revealed substantial interfetal variability in the 36-week FHR, which thus suppressed detection of a change in slope (Z = −1.48, p = .14). Exclusion of a single case of unusually high FHR (170 bpm) resulted in a marginally significant discontinuity at 32 weeks (estimate = −.223, SE = .125, Z = −1.78, p = .07). There were two significant spline terms with similar deviance values for FHR variability (at 24 and 28 weeks) in the Baltimore sample. After visual inspection of the plots, the 28-week point was selected as the more conservative estimate because it included three, instead of two, data points in the initial trajectory.

Trajectories for FM were less consistent. No significant splines were detected in Baltimore for the number of movements, which was the only FM measure to display a gestational trend. In Peru, the number of movements and total motor activity declined most precipitously after 28 and 36 weeks, respectively.

**Table 2**

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<th>Fetal Neurobehavioral Development: Results of Generalized Estimating Equations Analysis Showing Trends in Development Over Gestation</th>
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**Note.** GA = gestational age at which a significant change in slope was detected; FM = fetal movement; FHR = fetal heart rate.

* See text for additional description of discontinuity.

* p ≤ .01.
Baltimore–Lima Comparisons

Results of the comparisons in overall levels of fetal neurobehaviors between Baltimore and Lima are provided in the upper corners of Figures 1 through 7. The coefficients reflect the adjusted mean difference over gestation; the Z scores are used to determine significance levels of the comparison between groups across gestation. There were large, significant mean differences in the three FHR measures and FM–FHR coupling. Fetuses in Baltimore had slower FHR, greater FHR variability, more accelerations, and higher levels of FM–FHR coupling. Information concerning the nature of these differences as they relate to developmental trajectories is provided by comparisons of the onsets of the discontinuities. For three of these four measures (FHR, FHR variability, and FM–FHR coupling), the change in slope signifying the onset of the deceleration in development occurred 1 month earlier in Peru than in the United States. Moreover, after the initial decline in the rate of increase in FHR variability, FHR variability plateaued with a slight decline with advancing gestation (see Figure 2). This process began at 32 weeks in Lima (estimate = .247, SE = .042, Z = 5.87, p < .01) but at 36 weeks in Baltimore (estimate = .301, SE = .095, Z = 3.19, p < .01). With respect to accelerations, a discontinuity was detected in both groups at 32 weeks, but inspection of Figure 3 reveals a very different pattern of development beyond this point. In Baltimore, accelerations continued to increase but at a slower rate; fetuses in Lima showed little continued development on this measure and then declined at 36 weeks (Z = 3.97, p < .01). Trajectories for FM–FHR coupling were similar between groups (see Figure 4), but levels of coupling were consistently lower in Lima than in Baltimore.

The plotted values and trajectories for the number of fetal movements (see Figure 5) are remarkably similar between groups, although the Baltimore sample made significantly more movements. Across gestation, Baltimore fetuses made between 3.6 and 9.1 more movements per 50-min recording period than did fetuses in Lima. In contrast, fetuses in Lima spent significantly more of the observation period in motor activity (see Figure 6) driven by the longer mean duration of each movement (see Figure 7). This difference was more pronounced earlier in gestation than as term neared. Discontinuities had relatively little impact on differences between fetal motor activity between study locations.

Fetal Sex

No sex differences in fetal neurobehaviors in either the Baltimore or Lima samples were detected, and there were no interactions between fetal sex and gestational age. To determine whether potential fetal sex effects might be masked by within-location analyses, we conducted an additional series of analyses in which

Figure 3. Episodic accelerations in fetal heart rate per 50-min recording were more frequent in Baltimore than in Lima. Significant discontinuity existed at 32 weeks in both locations (see Table 2) followed by a continuing increase in incidence in Baltimore but a decline in Lima. *p < .01.

Figure 2. Fetal heart rate variability during gestation was significantly higher in Baltimore than in Lima. As indicated in Table 2, variability increased over time in both populations, but the change in slope was significant at 24 weeks in Lima and at 28 weeks in Baltimore. *p < .01.

Figure 4. Fetal movement (FM) – fetal heart rate (FHR) coupling was higher in Baltimore than in Lima. From Table 2, note the increase over gestation with deceleration at 32 weeks in Baltimore and at 28 weeks in Lima. *p < .01.
both location and sex were entered into the same model. Inspections of plots revealed that male and female values within each location were, for the most part, overlapping or closely parallel, while the disparities between Baltimore and Lima were preserved. The addition of fetal sex did not result in a better fit for the model for any neurobehavioral measure. Moreover, the coefficients for both gestational age and location remained relatively unchanged in the presence of fetal sex, further confirming that male and female fetuses in each locale were more similar to each other than to their counterparts in the other city.

Supplemental Analysis

In an effort to determine whether the sociodemographic variables in Table 1 that differed between groups contributed to the observed differences in fetal development, we conducted a series of within-group analyses. Maternal age, education, and size (weight, height, and BMI) and infant size at birth (weight, length, and ponderal index) were analyzed as covariates for Baltimore and Lima in separate GEE equations. Maternal education was not significantly related to any fetal measure. No maternal or infant characteristic was related to FHR, variability, or accelerations in either group. Several significant but inconsistent relations emerged between various indicators of maternal or infant size and infant measures. In Baltimore, larger women and bigger infant size at birth (an imprecise indicator of relative fetal size) tended to be associated with fetal motor behavior marked by greater activity, frequency, or duration, although associations were not consistently found for each indicator of size or measure of FM. In contrast, when significant or near-significant relations between maternal or infant size and FM measures were detected in Lima, they were negative in direction. Thus, while maternal and infant size may represent population-specific pregnancy characteristics that moderate fetal motor activity, these analyses do not reveal any systematic biases that can explain the observed group differences.

Discussion

Fetuses of pregnant women in two cultures develop in strikingly similar and dissimilar ways. We consider the similarities first. FHR, measured in terms of mean rate and both continuous and episodic measures of variability, changed over the course of gestation in expected ways. The decline in FHR and the concomitant increase in features of variability during gestation are attributed, in part, to maturation of parasympathetic processes (Dalton, Dawes, & Patrick, 1983; Freeman, Garite, & Nageotte, 1991; Martin, 1978) and advancing cortical control (Yoshizato et al., 1994). Similarly, the strengthening of the relationship between FHR and FM, reflected in our measure of coupling, is representative of the neural integration between somatic and cardiac processes within the central nervous system.
With respect to FM, given the potential range in the number of movements a fetus could make in 50 min, the mean values and trajectories for this measure were surprisingly consistent between groups. The average number of fetal movements across gestation and study site ranged from 48 to 66, or between 0.96 and 1.32 per minute. Observations that the fetus moves, on average, once per minute have been reported from studies that rely on various methods of identifying FM (DiPietro et al., 1998; Manning et al., 1979; Nasello-Paterson, Natale, & Connors, 1988; Roberts et al., 1980; Roodenburg et al., 1991). There was convergence in fetal activity level at term such that both groups of fetuses spent approximately 25% of the observation time moving. The trajectories of development for mean movement duration were also quite similar, again showing convergence at term. Investigations of periodicity in motility in animal and human fetuses provide strong evidence for endogenously generated cyclic motor activity (Roberson, 1985), and the similarity observed between samples supports this phenomenon.

Results from the current study confirm earlier observations that a developmental transition occurs between the 28th and 32nd gestational weeks (DiPietro et al., 1996a, 1996b). Fetuses in both Lima and Baltimore exhibited developmental discontinuities in all measures that involved FHR, including its relation to FM, within this period. Fetal motor measures were much less consistent in this regard, but when discontinuities were detected, they clustered within this period. Others have also reported transitions in fetal functions during this period. The inspiratory component of fetal breathing movements peaks between 28 and 32 weeks (Kozuma, Nemoto, Okai, & Mizuno, 1991), and fetal breathing rates plateau during this time (Pillai & James, 1990; Roodenburg et al., 1991). The fetus attains mature levels and patterns of responsiveness to vibroacoustic stimuli between 29 and 32 weeks (Kisilevsky, Muir, & Low, 1992; Kuhlman, Burns, Depp, & Sabbaghia, 1988), and there is a concomitant increase in habituation (Groome, Gotlieb, Neely, & Waters, 1993). The onset of these neurobehavioral changes coincides with a period of rapid increase in neural development and myelination, including cortical and vagal processes (Kinney, Karthigason, Boenshteyn, Flax, & Kirschner, 1994; Sachs, Armstrong, Becker, & Bryan, 1982). In a study of the development of neural control of the heart, measures of FHR variability were compared between anencephalic and normal fetuses at varying gestational ages (Yoshizato et al., 1994). A critical transition period during which higher cortical control was exerted was documented between 27 and 30 weeks gestation.

On the basis of the existing literature and the current findings, we propose that the deceleration in neurobehavioral maturation after 32 weeks suggests that antenatal neural development through term is somewhat overdetermined. Ancillary support for this position is provided by the ultimate developmental and cognitive success of preterm infants who are born after this gestational period, despite immaturity in other organ systems. This is not to imply that development ceases after this period or that certain aspects of fetal neurobehavior do not continue to develop in a linear fashion. For example, there is a linear increase in periods of wakefulness as fetuses progress through postterm pregnancies (Junge, 1979; van de Pas, Nijhuis, & Jongsma, 1994). At the very least, the consistently decelerative trajectories observed in these two samples of fetuses indicate that the rate of development begins to taper off well before term.

Despite the overall similarities in trends between the Baltimore and Lima samples, the disparities are equally revealing. These results make clear that there is population-based variation both in the level and the trajectories of fetal neurobehavior. The Lima sample failed to attain the same level of decline in FHR and was consistently lower in both FHR variability and FM–FHR coupling throughout gestation. Moreover, after 24 weeks gestation, this group displayed approximately 50% of the number of accelerations in FHR, the primary clinical indicator of fetal well-being. Differences in level were exacerbated by variation in developmental trajectories. For three of these measures, the deceleration in development that is denoted by the significant spline term occurred at least 4 weeks before the corresponding change was evident in the Baltimore sample. For FHR and FM–FHR coupling, this was expressed as lack of further significant change beginning as early as 28 weeks gestation, compared with 32 weeks in Baltimore. With respect to FHR variability, not only did the decline in slope begin 1 month earlier in Peru (at 24 vs. 28 weeks), but the decline in level expressed in both samples as gestation progressed was initiated a month earlier in Peru (at 32 vs. 36 weeks). The most striking contrast in trajectory was displayed for accelerations. The discontinuity observed in both samples at 32 weeks preceded a continuing increase at a reduced rate in Baltimore but a collapse of subsequent development in Peru. Thus, on the measures most clearly affiliated with neural development, the Peruvian fetuses lagged significantly behind their Baltimore counterparts.

What is the source of these disparities? Women at each site reflected widely different populations of affluence and disadvantage, yet all had good prenatal care, uneventful pregnancies, and healthy newborns. Recruitment techniques were somewhat different for the two populations, but participation was ultimately dependent on volunteerism in both groups. Post hoc analyses failed to show that the differences in measured sociodemographic characteristics of the sample contributed to FHR measures within each group, making it difficult to conclude that they generated between-groups differences. Although fetal motor activity showed some relations with maternal and infant size, the directions of these associations varied within each group and did not parallel the between-groups differences. More surprisingly, maternal education, an important proxy that confers a wide sphere of influence on a woman’s life, failed to differentiate fetal neurobehavior within either sample.

The potentially important genetic influence of ethnicity cannot be ascertained by this study, nor could a targeted study be easily mounted because of corresponding social class differences within Peru. However, we have been unable to identify published reports that show an effect of maternal ethnicity per se on any aspect of fetal development. Racial differences in fetal heart rate patterns have been observed (Ogueh & Steer, 1998) but are typically confounded with socioeconomic status (M. Johnson et al., 1992). Similarly, an effort to match on sociodemographic characteristics between locales would have created a new set of potential confounds. Finally, numerous unmeasured characteristics of the maternal–fetal intrauterine milieu exist that may have contributed to these results, including hemoglobin levels, uteroplacental sufficiency, by-products of maternal psychosocial stress, and nutri-
Fetal neurobehavioral development

Among developmentalists, there is long-standing acceptance of the notion that continuity exists among processes that span the prenatal and postnatal periods (Als, 1982; Prechtl, 1984). More recently, Barker (1995) and colleagues have reinvigorated interest in this construct with their proposal that fetal programming provides a substrate for subsequent health and well-being in a variety of domains throughout life. An adverse prenatal environment has been linked with hypertension and cardiovascular disease (Barker, 2002; Szitani, Janda, & Polendne, 2003), insulin resistance and diabetes (Hales & Ozanne, 2003; Phillips & Barker, 1997), and a number of other undesirable health outcomes, although detection of these associations has not been universal across studies (Lauren et al., 2003). The failure of this construct to similarly ignite the developmental community may be a result of the existing acceptance of the importance of the fetal period but also may be due to the fact that the original literature focused almost exclusively on weight at birth as an indicator of the prenatal environment. More recent discourse in this arena has acknowledged that birth weight is an imperfect proxy for mechanisms through which antenatal factors challenge growth and development, and attention has been reoriented to the intrauterine processes that may link fetal growth to outcomes. These processes, which include aberrations in fetal nutrient or oxygen delivery (Godfrey, 2002; Harding, 2001) and metabolic or endocrinological consequences, such as hypothalamic–pituitary–adrenal (Betram & Hanson, 2002; Matthews, 2002) and sympathetic–adrenal (Young, 2002) activation, likely have direct application to fetal development as well as growth and have been implicated in an array of postnatal developmental processes.

The results from the current study indicate that fetal neurobehavioral development represents a confluence of epigenetic, environmental, and maturative processes. The processes brought to bear on shaping fetal neurobehavioral development within groups and individuals are probably not unlike those that influence development after birth but are mediated through the direct biological and physiological constraints imposed by the maternal uterine environment. Although there are many consistencies in the nature and trajectories of fetal neurobehavioral development in the two samples studied, there were unattributable but unquestionable cross-cultural discrepancies. These results suggest that different developmental trajectories expressed in the fetal period underlie existing observations of cross-cultural differences on neonatal neurobehavioral assessments (Choi & Hamilton, 1986; Coll et al., 1981; Eishima, 1992; Keefer et al., 1982). The task of identifying potential mechanisms while adequately controlling for other relevant factors will be a complex one but one that serves as an impetus for future research. Efforts to determine whether fetal neurobehaviors will predict either different developmental trajectories or variations in temperament between cultures in the postnatal period are under way in both cities. Despite the current ambiguity in understanding the mechanisms through which the intrauterine milieu engages the developing fetal nervous system, these findings indicate that the broader context of the antenatal environment must be considered in the putative role of the fetus as the precursor to the child.

References


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