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Patterns of fetal heart rate response at ~30 weeks gestation predict size at birth

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There is evidence that fetal exposure to maternal stress is associated with adverse birth outcomes. Less is known about the association between fetal responses to a stressor and indicators of fetal maturity and developmental outcomes. The purpose of the present study was to determine whether fetal heart rate (FHR) patterns in response to a startling stimulus at ~30 weeks of gestation were associated with gestational age at birth and birth weight. FHR was measured in 156 maternal–fetal dyads following a vibroacoustic stimulus. All pregnancies were singleton intrauterine pregnancies in English-speaking women who were primarily married, middle class, White and at least 18 years of age. Group-based trajectory modeling identified five groups of fetuses displaying distinctive longitudinal trajectories of FHR response to the startling stimulus. The FHR group trajectories were significantly associated with birth weight percentile (P < 0.01) even after controlling for estimated fetal weight at the time of assessment and parity, which are the known factors influencing birth weight (P < 0.01). Post hoc analyses indicated that two groups accounted for the association between FHR patterns and birth weight. The group (n = 23) with the lowest birth weight exhibited an immediate FHR deceleration followed by an immediate acceleration that does not recover. An FHR pattern characterized by immediate and fast acceleration to the peak and a slow discovery to baseline was associated with the highest birth weight. This is the first direct evidence showing that low birth weight and the resulting neurological consequences may have their origins in early fetal development.

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Key words: birth weight, fetal heart rate, fetal programming, group-based trajectory modeling

Introduction

The earliest and strongest evidence in support of the fetal programming of health and disease is from retrospective studies on birth outcomes. These pioneering studies indicated that increases in risk for numerous diseases were associated with being born small for gestational age (GA) or being born early.¹–⁵ Birth phenotype, itself, was not considered the only source of risk but instead reflected adverse in utero exposures that influenced fetal development and contributed to poor birth outcomes. Growing evidence from prospective longitudinal studies indicates that there is a link between prenatal adverse conditions and birth outcomes including reductions in birth weight.⁶–⁹ However, no studies have directly tested an association between measures of fetal well-being or maturation and birth weight.

Studies reporting continuity between fetal heart rate (FHR) and movement patterns and infant mental and motor development,¹⁰–¹⁵ infant temperament¹⁵–¹⁸ and infant autonomic function¹⁹,²⁰ suggest that fetal behavioral patterns may be useful predictors of developmental outcomes. There is compelling evidence that fetal responses to stimulation follow a developmental progression and recent evidence from our studies²¹ indicate that heart rate patterns in response to a simple startling stimulus reflect fetal neurological maturation.

Because of these developmental trends, a metric of central nervous system maturation is reflected in human fetal responses to external stimulation. This metric may reflect fetal health and may predict birth and developmental outcomes. Fetal maturation can be assessed by evoking FHR change in response to external stimulation. A variety of ex utero stimuli have been used to stimulate the human fetus including buzzers,²⁷–²⁹ clicks, tones and the human voice,²⁵,³¹,³², but the combined tactile and auditory stimulation of a vibroacoustic stimulus (VAS) elicits a more reliable response, earlier in gestation, than an auditory stimulus alone.²⁰

We have shown that the fetal response to the VAS at ~30 weeks of GA represents a transitional period in fetal maturation. By ~30 weeks of GA most fetuses exhibit a response to the VAS but the patterns vary widely in terms of the magnitude of response and the rate of recovery.³¹ The specific purpose of the present study was to determine whether FHR patterns in response to the VAS at ~30 weeks of GA predicted birth phenotype (GA at birth and birth weight). We will determine whether fetal responses to stimulation at a transitional period...
in fetal development are early indicators of birth outcomes that have long-term developmental consequences.

Methods

Study overview

All maternal–fetal dyads were recruited before the 16th week of gestation as part of a longitudinal study. Each dyad was assessed with measures of FHR following a VAS (startling) between 29 and 33 weeks of gestation (mean \( \pm 31.19, \) S.D. \( \pm 0.83 \)). All participants were followed up to delivery for assessment of GA and infant’s birth weight.

Participants

The sample comprised 174 maternal–fetal pairs who had complete FHR data at \( \sim 30 \) weeks of gestation. Women gave informed consent for all aspects of the protocol, which was approved by the Institutional Review Board for protection of human subjects. All pregnancies were singleton intrauterine pregnancies in English-speaking women of at least 18 years of age. Women were excluded if they had medical conditions potentially associated with risk for poor birth outcomes including uterine or cervical abnormalities, endocrine, hepatic or renal disorders, or if they used corticosteroid medications or recreational drugs during pregnancy. Maternal demographic information is summarized in Table 1. Four maternal–fetal dyads were excluded because women reported recreational drug use during their pregnancy.

Fetal assessment

The assessment of the human fetus followed procedures reported previously by our group. The vibroacoustic stimulator was placed on the mother’s abdomen above the fetal head, as determined by ultrasonography. During the assessment, mothers reclined in a semi-Fowler’s position (5–10° tilt) on a standard, padded examination table. Mothers listened to pure-tone music through headphones to mask extraneous noise and the auditory component of the VAS. Fetal assessment began with a 15-min baseline (resting) period, where FHR was recorded before 1-s administration of the VAS (72 dB, 75 Hz ± 10% harmonics ranging from 20 to 9000 Hz; EAL Model 146, Corometric Medical System, CT, USA) on the mother’s abdomen. The fetal assessment concluded with 60 s of FHR recording to assess the fetal response to VAS. Transabdominal transducers were attached to measure FHR. Transducers were positioned until a robust FHR signal was reliably detected. All fetal information and uterine contractions were quantified by a Toitu MT-430 ultrasound fetal monitor. The Toitu monitor measured Doppler frequency shifts in a weak ultrasound beam projected onto the fetus by an ultrasonic head and extrapolated the FHR from fetal movement and uterine contractions. Data from the fetal monitor were digitized at 2 kHz sampling rate with Active II (BioSemi Instrumentation, Amsterdam, The Netherlands) and automatically transferred to an off-line server for analysis. No uterine contractions occurred during the assessment period. Integrity of the FHR data was assured using customized software that included a viewer for examination of each tracing to scan for artifacts. An interpolation routine was applied for gaps or artifacts in the FHR record of no greater than 10 s. Each tracing was examined by a trained observer and a judgment was made about the validity of the interpolation. If a segment of the data resulted in unacceptable interpolations (the interval was \( >10 \) s or the estimate did not match the valid data points), that section of the data was omitted from the analyses. The change in FHR responses after stimulation (difference from baseline) was computed with a 10-s moving average filter. The first value after the VAS was the average change from baseline in FHR during the first 10 s, the second value was the average change of FHR from 2 to 11 s after the VAS, and this continued so that the FHR value at 30 s was the average FHR change from baseline for the interval between 30 and 40 s after stimulation.

Assessment of fetal growth and birth outcome

Maternal and infant medical records were reviewed by a research nurse to assess prenatal medical history and birth outcome. Birth weight percentiles (BWP’s), stratified by infant’s sex and GA at birth were assigned for each infant.

| Table 1. Demographic information for the 156 participants |
|----------------------------------------------------------|
| Average maternal age at delivery: 29.3 (s.d. = 5.0)      |
| Range of maternal age at delivery: 19–41                 |
| Marital status at assessment (%)                         |
| Legally married: 80.6                                    |
| Separated: 1.3                                           |
| Not married but living with father: 15.5                 |
| Not married/not living with father: 2.6                  |
| Primiparous (first child): 42.9                          |
| Fetal sex (%):                                           |
| Male: 51.9                                              |
| Female: 48.1                                            |
| Education (%):                                          |
| High school or equivalent: 98.7                         |
| College graduate: 42.9                                   |
| Annual household income (%)                              |
| $0–30,000: 17.5                                         |
| $30,001–$60,000: 25.3                                    |
| $60,001–$100,000: 34.4                                   |
| Over $100,000: 22.7                                     |
| Race/ethnicity (%):                                     |
| Latina: 32.1                                            |
| Non-Hispanic White: 50.0                                |
| Asian: 10.9                                             |
| Multi-ethnic, other: 5.8                                |
using published US norms. Pregnancies were dated according to current American College of Obstetricians and Gynecologists guidelines by comparison of last menstrual period to estimates based on early ultrasound measurements by the research nurse taken at 15 weeks of gestation. The mean GA at birth for the sample was 39.3 weeks. Ultrasound assessments were performed at each visit to collect biometric data and measures of fetal development (e.g. head circumference, biparietal diameter, abdominal circumference, length of femur). Estimated fetal weight at the time of assessment (~30 weeks of GA) was calculated using a regression equation proposed by Hadlock et al. with the fetal parameters of head circumference (HC), abdominal circumference (AC) and femur length (FL): \( \text{Log}_{10} \text{weight} = 1.326 - 0.00326 - 0.00326 \times \frac{\text{AC}}{\text{FL}} + 0.0107 \times \frac{\text{HC}}{0.0438} \times \frac{\text{AC}}{0.158} \times \text{FL}. \)

### Plan of analyses

All analyses were performed using FHR data at 1 s resolution. To rule out any impact of VAS preparation on resting FHR levels, the interval of seconds 180–60 (120 s total) preceding the VAS was applied as the baseline comparison. FHR data from the first 30 s after VAS were used for analyses because we have shown that this interval captures the FHR response and recovery at 30 gestational weeks. As described above, post-stimulus data were analyzed with a 10 s moving average of the change from baseline (delta averages).

Group-based trajectory modeling (GBTM) was used to categorize fetuses into groups based on unique patterns of FHR response to the VAS. Trajectory analysis, a semi-parametric group-based method, relies on finite mixture modeling to empirically identify groups of individuals displaying distinctive longitudinal trajectories of FHR response. GBTM was computed using the TRAJ procedure run under SAS. Equations were specified as cubic. The Bayesian information criterion was used to select the optimal number of trajectory groups among our sample \( (n = 7) \). Groups were added until the Bayes factor for the additional group was <10, at which point the last group was removed. The following criteria were used to determine the adequacy of the model: (i) The average posterior probability for each group was >0.70 (see Table 2); (ii) the odds of correct classification (model scheme vs. random assignment) was at least 5.0 for each group; and (iii) there was close correspondence between the probability of assignment and the proportion actually assigned to each group. Each mother–fetal pair was assigned to the GBTM FHR group for which they had the highest posterior probability of membership. Two subjects were excluded because their FHR profiles were not adequately fit for any of the group patterns (all posterior probabilities for each group <0.70 for each pair). In contrast with growth curve modeling, which assumes population homogeneity over time, GBTM empirically tests for heterogeneity in population change patterns and identifies both normative and atypical patterns.

Seven FHR groups were identified using GBTM. Two of the FHR groups were not included in analyses because they had fewer than 10 subjects in a group (12 subjects total – six per group). Thus, all analyses focused on the remaining five groups (156 subjects), which comprised 23–39 participants each (see Table 2). After group assignment, a between-subject analysis of variance assessed whether the empirically generated FHR groups significantly differed in BWP and length of gestation, with Bonferroni post hoc tests as needed. The possibility was assessed that race/ethnicity, socio-economic status, maternal age, obstetric risk factors, fetal sex, GA at assessment or parity might account for the observed links between FHR patterns and birth outcomes. Of these variables, only parity (primiparous  vs. multiparous) was associated significantly \( (P < 0.05) \) with BWP and was therefore included as a covariate.

### Results

#### FHR patterns

The FHR patterns that determined group membership are presented in Figure 1. Group 1 \( (n = 28) \) exhibits a small acceleration \( (1.62 \text{bpm at } 4 \text{s to the VAS}) \) and then a return to baseline indicating recovery \( (\text{maximum deceleration of } -1.43 \text{bpm at } 14 \text{s}) \). Group 2 \( (n = 23) \), exhibits an immediate FHR deceleration \( -8.55 \text{bpm and then an immediate acceleration with a peak of } 7.63 \text{bpm at } 16 \text{s after VAS} \). Group 3 \( (n = 38) \) exhibits an immediate acceleration reaching a peak of 9.08 bpm above baseline at 7 s after stimulation with a recovery to baseline at 17 s continuing to decelerate below baseline to ~3.81 bpm at 26 s. Group 4 \( (n = 39) \) immediately accelerates and reaches the peak FHR of 10.83 bpm above baseline at 10 s with a slow recovery to baseline \( (1.19 \text{bpm by } 30 \text{s after the stimulus}) \). Group 5 \( (n = 28) \) has a pattern of early FHR acceleration that does not recover throughout the 30 s after VAS period. The pattern for group 5 reaches a peak of 13.57 bpm above baseline at 12 s after the VAS and remains elevated at 10.18 bpm above the baseline at 30 s after the stimulus.

### Table 2. Fetal heart groups determined by GBTM

| FHR group | Posterior probability | GA at birth | BWP |
|-----------|-----------------------|-------------|-----|
| 1 \( (n = 28) \) | 0.987 ± 0.040 | 39.47 ± 1.16 | 50.11 ± 24.76 |
| 2 \( (n = 23) \) | 0.992 ± 0.037 | 39.36 ± 1.06 | 34.65 ± 21.33 \( ^* \) |
| 3 \( (n = 38) \) | 0.983 ± 0.039 | 39.42 ± 1.65 | 53.0 ± 29.42 |
| 4 \( (n = 39) \) | 0.987 ± 0.049 | 39.03 ± 1.37 | 60.13 ± 25.10 \( ^* \) |
| 5 \( (n = 28) \) | 0.998 ± 0.006 | 39.48 ± 1.21 | 42.25 ± 26.83 |

GBTM, group-based trajectory modeling; FHR, fetal heart rate; GA, gestational age; BWP, birth weight percentile.

Average probability of group membership, GA and BWP for each group.

All values are given as \( (\text{mean } ± \text{s.d.}) \).

\( ^* \) FHR groups 2 and 4 significantly differ in BWP; Bonferroni post hoc comparisons with parity and estimated fetal weight at time of assessment as covariates, \( P = 0.01 \).
The FHR group trajectories at approximately 30 weeks GA were significantly associated with BWP \( F(4, 150) = 3.35, P = 0.01 \). The overall difference between FHR groups remained significant \( F(4, 149) = 3.37, P = 0.01 \) when estimated fetal weight at the time of assessment was added to the model as a second covariate (with parity). 

Post hoc analyses with the Bonferroni adjustment indicated that groups 2 and 4 accounted for the significant differences in BWP. Group 2 included the infants with the lowest mean BWP (mean = 33.7, S.E. = 4.4), whereas group 4 included infants with the highest mean BWP (mean = 59.2, S.E. = 4.0; see Fig. 1 and Table 2). The difference between groups 2 and 4 remained significant (post hoc comparisons; \( P = 0.01 \)) when estimated fetal weight at the time of assessment was added to the model as a second covariate (with parity).

There were seven maternal/fetal dyads who participated in the study twice with two pregnancies separated by an average of 24.4 months. There were eight women who reported smoking cigarettes sometime during pregnancy, but smoking among our sample was not significantly associated with BWP \( t_{154} = 0.27, P = 0.79 \). The findings did not change when these women were excluded from the analyses.

FHR and BWP

The FHR group trajectories at approximately 30 weeks GA were significantly associated with BWP \( F(4, 150) = 3.35, P = 0.01 \). The overall difference between FHR groups remained significant \( F(4, 149) = 3.37, P = 0.01 \) when estimated fetal weight at the time of assessment was added to the model as a second covariate (with parity). 

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FHR and length of gestation

There was no difference between the FHR groups in GA at birth, \( F(4, 151) = 0.699, P = 0.594 \).

Discussion

Recent prospective studies, including the current study, support the proposal that fetal exposures, experience and perhaps behavior, contribute to birth phenotype\(^{9,40-42}\) in addition to developmental outcomes independent of birth outcome.\(^{16-18,43-46}\) This is the first direct evidence that fetal neurological maturation predicts birth outcome among healthy, normal subjects.

There are two primary findings from this large study of FHR response patterns to a startling stimulus. First, using a GBTM analysis, complex patterns of fetal heart responses to stimulation were identified. Each fetus has a probability of belonging to any of the groups; however, group assignment is based on the highest probability of membership. As presented in Figure 1, distinctive FHR patterns of response to the VAS were discovered at approximately 30 weeks of GA, a period of fetal maturational transition.\(^{34}\) This is the first use of this powerful analytic tool with FHR data and it provided a unique opportunity to group individual differences in FHR response to stimulation, perhaps reflecting neurological maturation.

Second, we found that FHR patterns at approximately 30 weeks of GA predicted birth outcomes nearly 2 months later. Fetuses exhibiting an immediate heart rate acceleration with a peak at \( 10 \) s after VAS and then a recovery to baseline (group 4) had the highest BWP, after accounting for sex, estimated fetal weight at approximately 30 weeks of GA and GA at birth. Fetuses with the lowest BWP (group 2) were the only group with an immediate deceleration in response to the VAS, followed by acceleration that did not recover. Previously we reported that these two patterns of FHR response to a VAS at approximately 30 weeks of GA were associated with a mature neurological pattern (group 4) and a delayed neurological pattern (group 2).\(^{31}\) The current findings suggest that prenatal markers of fetal neurological maturity are significantly associated with physical development at birth.

Assessment of fetal behavior, including FHR and movement in response to stimulation, has been associated with nervous system development,\(^{33,47-50}\) infant mental and motor development,\(^{10-15}\) infant temperament\(^{15-18}\) and infant autonomic function.\(^{19,20}\) The association reported here is the first of its kind between an elicited FHR and birth phenotype.
The findings that fetal response to a startling stimulus was significantly associated with birth weight after controlling for two established factors associated with size at birth, parity and estimated fetal weight provide support for the independent influences of fetal neurological maturation on birth outcome. It is not clear whether fetal neurological maturation itself exerts programming influences on development to influence size at birth or whether this association reflects a systemic or syndromic relationship between birth phenotype and fetal neurological maturation. For instance, other factors or a network of factors might influence both fetal and birth outcomes and account for this association. There are well-established neurological consequences associated with low birth weight and the current findings suggest that these consequences may have their origins in early fetal development.

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References

1. Barker DJP. Mothers, Babies and Health in Later Life, 1998. Churchill Livingston: Edinburgh.
2. Barker DJ, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. BMJ 1993; 306, 422–426.
3. McCormack VA, Silva I, De Stavola BL, et al. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. BMJ 2003; 326, 248.
4. Roseboom TJ, van der Meulen JHP, Osmond C, et al. Coronary heart disease after prenatal exposure to the Dutch famine, 1944–45. Heart 2000; 84, 595–598.
5. Richards M, Hardy R, Kuh D, Wadsworth ME. Birth weight and cognitive function in the British 1946 birth cohort: longitudinal population based study. BMJ 2001; 322, 199–203.
6. Sandman CA, Davis EP. Gestational stress influences cognition and behavior. Future Neurol 2010; 5, 675–690.
7. Glynn LM, Wadhwa PD, Dunkel-Schetter C, Chicz-Demet A, Sandman CA. When stress happens matters: effects of earthquake timing on stress responsivity in pregnancy. Am J Obstet Gynecol 2001; 184, 637–642.
8. Rini CK, Dunkel-Schetter C, Wadhwa PD, Sandman CA. Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. Health Psychol 1999; 18, 333–345.
9. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. Am J Obstet Gynecol 1993; 169, 858–865.
10. Vlastos EJ, Tomlinson TM, Bildirici I, et al. Fetal heart rate accelerations and the risk of cerebral lesions and poor neurodevelopmental outcome in very low birthweight neonates. Am J Perinatol. 2007; 24, 83–88.
11. Almli CR, Ball RH, Wheeler ME. Human fetal and neonatal movement patterns: gender differences and fetal-to-neonatal continuity. Dev Psychobiol 2001; 38, 252–273.
12. Groome LJ, Swiber MJ, Holland SB, et al. Spontaneous motor activity in the perinatal infant before and after birth: stability in individual differences. Dev Psychobiol 1999; 35, 15–24.
13. Leader LR, Baillie P, Martin B, Vermeulen E. The assessment and significance of habituation to a repeated stimulus by the human fetus. Early Hum Dev 1982; 7, 211–219.
14. DiPietro JA, Bornstein MH, Hahn CS, Costigan K, Achy-Brou A. Fetal heart rate and variability: stability and prediction to developmental outcomes in early childhood. Child Dev 2007; 78, 1788–1798.
15. Werner EA, Myers MM, Fifer WP, et al. Prenatal predictors of infant temperament. Dev Psychobiol 2007; 49, 474–484.
16. DiPietro JA, Hodgson DM, Costigan KA, Johnson TR. Fetal antecedents of infant temperament. Child Dev 1996; 67, 2568–2583.
17. DiPietro JA, Bornstein MH, Costigan KA, et al. What does fetal movement predict about behavior during the first two years of life? Dev Psychobiol 2002; 40, 358–371.
18. DiPietro JA, Costigan KA, Pressman EK. Fetal state concordance predicts infant state regulation. Early Hum Dev 2002; 68, 1–13.
19. DiPietro JA, Costigan KA, Pressman EK, Doussard-Roosevelt JA. Antenatal origins of individual differences in heart rate. Dev Psychobiol 2000; 37, 221–228.
20. Kisilevsky BS, Muir DW. Human fetal and subsequent newborn responses to sound and vibration. Infant Behav Dev 1991; 14, 1–26.
21. Gagnon R, Hunse C, Patrick J. Fetal responses to vibratory acoustic stimulation: influence of basal heart rate. Am J Obstet Gynecol 1988; 159, 835–839.
22. Gagnon R, Campbell K, Hunse C, Patrick J. Patterns of human fetal heart rate accelerations from 26 weeks to term. Am J Obstet Gynecol 1987; 157, 743–748.
23. Gagnon R, Hunse C, Fellows F, Carmichael L, Patrick J. Fetal heart rate and activity patterns in growth-retarded fetuses: changes after vibratory acoustic stimulation. Am J Obstet Gynecol 1988; 158, 265–271.
24. Gagnon R, Patrick J, Foreman J, West R. Stimulation of human fetuses with sound and vibration. Am J Obstet Gynecol 1986; 155, 848–851.
25. Lecanuet JP, Granier-Defere C, Busnel MC. Fetal cardiac and motor responses to octave-band noises as a function of central frequency, intensity and heart rate variability. Early Hum Dev 1988; 18, 81–93.
26. Pietrantoni M, Angel JL, Parsons MT, et al. Human fetal response to vibroacoustic stimulation as a function of stimulus duration. Obstet Gynecol 1991; 78, 807–811.
27. Leader LR, Baillie P, Martin B, Vermeulen E. Fetal habituation in high-risk pregnancies. Br J Obstet Gynaecol 1982; 89, 441–446.
28. Shaley E, Benett MJ, Megory E, Wallace RM, Zuckerman H. Fetal habituation to repeated sound stimulation. Isr J Med Sci 1989; 25, 77–80.
29. Zimmer EZ, Chao CR, Guy GP, Marks F, Fifer WP. Vibroacoustic stimulation evokes human fetal micturition. Obstet Gynecol 1993; 81, 178–180.
30. Grimwade JC, Walker DW, Bartlett M, Gordon S, Wood C. Human fetal heart rate change and movement in response to sound and vibration. *Am J Obstet Gynecol*. 1971; 109, 86–90.
31. DeCasper AJ, Fifer WP. Of human bonding: newborns prefer their mothers’ voices. *Science*. 1980; 208, 1174–1176.
32. Fifer WP, Moon C. Psychobiology of newborn auditory preferences. *Semin Perinatol*. 1989; 13, 430–433.
33. Sandman CA, Wadhwa P, Hetrick W, Porto M, Peeke HV. Human fetal heart rate dishabituation between thirty and thirty-two weeks gestation. *Child Dev*. 1997; 68, 1031–1040.
34. Buss C, Davis EP, Class QA, *et al*. Maturation of the human fetal startle response: evidence for sex-specific maturation of the human fetus. *Early Hum Dev*. 2009; 85, 633–638.
35. Class QA, Buss C, Davis EP, *et al*. Low levels of corticotropin-releasing hormone during early pregnancy are associated with precocious maturation of the human fetus. *Dev Neurosci*. 2008; 30, 419–426.
36. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr*. 2003; 3, 6.
37. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 101: Ultrasonography in pregnancy. *Obstet Gynecol*. 2009; 113, 451–461.
38. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. *Am J Obstet Gynecol*. 1985; 151, 333–337.
39. Nagin DS. *Group-based Modeling of Development*, 2005. Harvard University Press: Cambridge, MA.
40. Glynn LM, Schetter CD, Hobel CJ, Sandman CA. Pattern of perceived stress and anxiety in pregnancy predicts preterm birth. *Health Psychol*. 2008; 27, 43–51.
41. Dunkel Schetter C. Stress processes in pregnancy and preterm birth. *Curr Dir Psychol Sci*. 2009; 18, 204–209.
42. Dunkel Schetter C, Glynn LM. Stress in pregnancy: empirical evidence and theoretical issues to guide interdisciplinary research. In *Handbook of Stress* (eds. Contrada R, Baum A), 2010, pp. 321–343. Springer: New York.
43. Van den Bergh B. The influence of maternal emotions during pregnancy on fetal and neonatal behavior. *Pre-Peri-Nat Psychol J*. 1990; 5, 119–130.
44. Davis EP, Sandman CA. The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Dev*. 2010; 81, 131–148.
45. Buss C, Davis EP, Muftuler LT, Head K, Sandman CA. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9-year-old children. *Psychoneuroendocrinology*. 2010; 35, 141–153.
46. Ellman LM, Dunkel Schetter C, Hobel CJ, *et al*. Timing of fetal exposure to stress hormones: effects on newborn physical and neuromuscular maturation. *Dev Psychobiol*. 2008; 50, 232–241.
47. Dipietro JA, Irizarry RA, Hawkins M, Costigan KA, Pressman EK. Cross-correlation of fetal cardiac and somatic activity as an indicator of antenatal neural development. *Am J Obstet Gynecol*. 2001; 185, 1421–1428.
48. Hepper PG. The behavior of the fetus as an indicator of neural functioning. In *Fetal Development: A Psychobiological Perspective* (eds. Lecanuet J-P, Fifer WP, Krasnegor NA, Smotherman WP), 1995, pp. 405–417. Lawrence Erlbaum Associates: Hillsdale.
49. Nijhuis IJ, ten Hof J, Nijhuis JG, *et al*. Temporal organization of fetal behavior from 24-weeks gestation onwards in normal and complicated pregnancies. *Dev Psychobiol*. 1999; 34, 257–268.
50. Nijhuis JG. Fetal behavior. *Neurobiol Aging*. 2003; 24 (Suppl 1), S41–S46.
51. Lundgren EMT, Tuveo T. Effects of being born small for gestational age on long-term intellectual performance. *Best Pract Res Clin Endocrinol Metab*. 2008; 22, 477–488.