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Early rapid growth, early birth: Accelerated fetal growth and spontaneous late preterm birth

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Abstract

The past two decades in the United States have seen a 24 % rise in spontaneous late preterm delivery (34 to 36 weeks) of unknown etiology. This study tested the hypothesis that fetal growth was identical prior to spontaneous preterm (n=221, median gestational age at birth 35.6 weeks) and term (n=3706) birth among pregnancies followed longitudinally in Santiago, Chile. The hypothesis was not supported: Preterm-delivered fetuses were significantly larger than their term-delivered peers by mid-second trimester in estimated fetal weight, head, limb and abdominal dimensions, and they followed different growth trajectories. Piecewise regression assessed time-specific differences in growth rates at 4-week intervals from 16 weeks. Estimated fetal weight and abdominal circumference growth rates faltered at 20 weeks among the preterm-delivered, only to match and/or exceed their term-delivered peers at 24–28 weeks. After an abrupt decline at 28 weeks attenuating growth rates in all dimensions, fetuses delivered preterm did so at greater population-specific sex and age-adjusted weight than their peers from uncomplicated pregnancies ($p<0.01$). Growth rates predicted birth timing: one standard score of estimated fetal weight increased the odds ratio for preterm birth from 2.8 prior to 23 weeks, to 3.6 (95% confidence interval, 1.82–7.11, $p<0.05$) between 23 and 27 weeks. After 27 weeks, increasing size was protective (OR: 0.56, 95% confidence interval, 0.38–0.82, $p=0.003$).

These data document, for the first time, a distinctive fetal growth pattern across gestation preceding spontaneous late preterm birth, identify the importance of mid-gestation for alterations in fetal growth, and add perspective on human fetal biological variability.

Keywords

growth rate; fetal growth patterns; large offspring

INTRODUCTION

Preterm labor is one of the “great obstetrical syndromes” (Romero et al, 2006b) with multifactorial etiology and heterogeneity in perinatal outcome (Villar et al., 2004). The most recent national statistics identified that, as of 2004, one in eight infants in the US was born preterm, a 30% increase across two decades (Mathews et al., 2007). Seventy-one percent of these were “late preterm” births (34–36 gestational weeks), the group contributing most significantly to the rising rates, and together with those born at the youngest gestational ages, accounting disproportionately for infant morbidity and mortality (Davidoff et al., 2006). As 36% of infant deaths in the United States are preterm-related, with considerable disparity among subpopulations, there is a critical need to increase our understanding of developmental biology during the fetal period, and clarify growth patterns of fetuses in various growth categories (Behrman et al., 2007).

Birth outcome studies have noted heterogeneity in etiology and timing of preterm labor and delivery, with reports identifying aberrant growth outcomes, defined as neonatal sizes that deviate from the population means for gestational age (Lackman et al., 2001). These observations include the often investigated small-for-gestational-age infants, but less well appreciated are reports of neonates who are larger than expected. A hospital-based cohort study of more than 37,000 consecutive births conducted in Ontario, Canada identified increased size at birth as a significant risk factor for spontaneous preterm birth after spontaneous onset of labor (controlling for maternal age, parity, maternal hypertension and gender) (Lackman et al., 2001). Similar observations were reported from the more than one million births recorded in the Swedish Medical Birth Register, in which an association between larger-than-population-mean birth weight and spontaneous preterm birth was found among infants nearest term (34–36 weeks) (Morken et al 2006). While it may be obvious that if the neonates were larger at birth, they must have grown more rapidly, neither of these previous studies had serial ultrasound data. Thus, the proposition remains undocumented. Further, the important question of *when* during gestation the rapid growth occurs in this group is not known.

The present study aimed to investigate fetal growth patterns among pregnancies with spontaneous preterm labor and delivery and to compare these with fetal growth patterns among uncomplicated pregnancies delivered at term. With no a priori assumptions regarding the growth curves for the two groups, the data were first examined for best-fit polynomial descriptors of the growth trajectories. This was followed by a comparison of growth rates across age. The null hypotheses tested were that (1) growth trajectories and (2) age-based patterns of growth among preterm and term delivered fetuses were identical; and (3) the study asked, can earlier fetal size predict preterm birth?

MATERIAL AND METHODS

Study design

This is a longitudinal, retrospective, nested cohort study.

Study population

The study sample is part of a longitudinal cohort of 4115 healthy women with a singleton pregnancy who presented for obstetrical care at the Center for Perinatal Diagnosis and Research (Sotero del Rio Hospital in Santiago, Chile) and agreed to participate in a longitudinal study with repeated fetal ultrasound measures of biparietal diameter, head circumference, femur diaphyseal length, and abdominal circumference at each prenatal visit. Exclusion criteria included maternal chronic disease (e.g., diabetes, chronic hypertension, cardiac insufficiency, and asthma), evident fetal anomalies, and fetal demise at the time of enrollment. All patients provided written informed consent for the collection of data under protocols approved by the Institutional Review Boards of the Sotero del Rio Hospital, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Services (NIH/DHHS).

Clinical definitions

Uncomplicated pregnancies in this sample were those without medical, obstetrical, or surgical complications ending in a term labor and delivered neonate (≥ 37 gestational weeks). Preterm labor was defined as the presence of at least two regular uterine contractions and progressive cervical change (dilation of ≥ 1 cm with observed cervical effacement of $\geq 50\%$) that required hospitalization prior to 37 weeks of gestation. Preterm delivery was defined as birth prior to 37 weeks; late-preterm delivery was defined as birth at greater than 34 and less than 37 gestational weeks (Engle et al., 2007).

Fetal biometry

Serial ultrasound measurements of the biparietal diameter, head circumference, abdominal circumference, and femur diaphyseal length were made at each visit. The median age at first ultrasound was 13 weeks (interquartile range, 6–16 weeks; all subjects were measured on two or more occasions (75% ≥ 3 repeated measures). Fetal weight was estimated according to the formula of Hadlock et al., (1985). Fetal gestational ages reflect pregnancies dated according to the last menstrual period (LMP) or sonographic criteria if there was a discrepancy greater than one week between the LMP and fetal biometry before 20 weeks of gestation.

Statistical analysis

The null hypotheses in this study, that identical (1) growth trajectories and (2) age-based growth patterns characterized both term and preterm delivered fetuses, involved two approaches: curve-fitting and piecewise regression analyses. To facilitate comparisons, all fetal biometric parameters were transformed to internal standard scores (or z -scores, the difference between actual measures and the sample mean, divided by the sample standard deviation, $(x - \bar{x})/sd$) for ages < 37 gestational weeks. Box-Cox regression identified if a power transformation of the biometric parameters (Y^{λ}) improved heteroscedasticity and/or skewness of residuals; a transformation was used for fetal weight (log) and abdominal circumference (0.7 power).

Growth trajectories—The goal of comparing fetal growth patterns between groups required that no a priori assumptions be made regarding the shapes of growth trajectories. Therefore, fractional polynomials of increasing powers (up to fourth degree) were compared to identify the best-fit descriptor of the longitudinal data for each measured dimension (Royston and Altman, 1995, 1997). The simplest polynomial function that fit both groups was then used to test the hypothesis that fetal growth trajectories of the groups were homogeneous in a mixed-effects, multilevel model for cross-sectional time series data (Stata 9 *xtreg, re*; StataCorp, 2005). This approach considers the variation within fetuses by age

(i.e., the repeated-measures longitudinal data, information regarding individual patterns across time) as well as the variation among fetuses (i.e., cross-sectional information comprising both genetic and environmental components) in a simultaneous estimation of error due to factors such as measurement, sampling bias, gender, and other unknown individual-level factors by a random effects matrix with weighted average of within and between subject effects. Potentially significant covariates (i.e., fetal gender, tertiles of maternal height, maternal weight and body mass index, parity [0=primipares, 1=multipares], age, smoking and maternal gestational diabetes) were simultaneously considered and appropriately retained in the final model. As y-intercept corresponding to age=0 was time of conception with no measurable size, the growth trajectory analyses were centered at the gestational age of 18 weeks.

The polynomial approach merely characterizes trends in longitudinal data. Any differences in the timing of growth that may be present between groups are smoothed and contribute to the magnitude of coefficients.

Fetal growth timing—With no previous descriptions of divergent longitudinal growth patterns across gestation among term and preterm delivered fetuses, a systematic approach further evaluated patterns at arbitrarily-defined four-week intervals across the data set from 16 weeks. This analysis investigated both the slopes across the intervals, and the significance of changes in slope at these nodal points. The latter was generated from the marginal option in *mkspline* (Stata 9; StataCorp 2005). The slopes of fetal size for age were then compared in random effects multilevel models (Stata 9 *xtreg, re*; StataCorp 2005), specifically testing for the interaction effects of group and age. Covariates in these analyses included dichotomous variables for fetal sex, maternal gestational diabetes (presence/absence), and age at preterm delivery (late preterm/other). This served as both a confirmatory step to the curve-fitting approach, and a further exploration comparing time-specific patterns between groups.

The shape and equality of distributions for continuous variables were investigated by Shapiro-Francia and Kolmogorov-Smirnov, respectively. Non-Gaussian variables were compared between groups with Kruskal-Wallis and were transformed to categorical variables for parametric analyses. Chi-square tested proportionality between groups in categorical variables. Logistic regression quantified the odds ratios of preterm birth from standard scores of fetal size at three time intervals: prior to 23 gestational weeks of age, at mid-gestation (>23 and <28 gestational weeks of age), and between 28 and 34 weeks of age. A two-sided *p*-value less than 0.05 is reported as significant in all analyses.

RESULTS

Uncomplicated pregnancies occurred in 90% (3706/4115) of the individuals in the sample. The rate of spontaneous preterm labor and delivery among live-born neonates was 5.3% (221/4111); 77% (170/221) were late preterm deliveries at a median gestational age of 36 weeks (interquartile range, 35–36.4); and 51 individuals were born at a median age of 32.6 weeks (interquartile range, 28.9–33.7). No significant differences were found in the distribution of gestational ages contributing to the analysis between the term and preterm birth groups (Kolmogorov-Smirnov, *p*=0.47).

Sample characteristics

Maternal and fetal continuous variables were non-Gaussian. The only maternal characteristic differentiating the study groups was smoking, with a greater proportion of women among the preterm delivery pregnancies (Table 1). No substance abuse was self-reported among the

women in this study sample and no significant differences were found for maternal alcohol consumption (3% of women reported one or less drink per day).

Among the preterm pregnancies, 24 women (11%) developed gestational diabetes. Fifteen of these delivered late preterm. As gestational diabetes is documented to effect fetal growth rates (Keller et al., 1990; Lampl and Jeanty, 2004), these pregnancies were considered in stratified analyses as appropriate. Amniocentesis was performed on 59 of the women who delivered preterm; intra-amniotic infection/inflammation was identified among seven by positive culture ($n=3$) or white blood cell count >50 cells/mm³. All term pregnancies in this analysis were free of complications; this included the absence of gestational diabetes.

Pregnancies that ended preterm resulted in delivered fetuses at greater birth weight percentiles, adjusted for sex and age according to the Chilean national reference (González et al., 2004), in both univariate and multiple regression analyses (with fetal sex, maternal age, parity, smoking or size [height, weight or body mass index (BMI), entered separately due to inter-correlation] as covariates). Maternal gestational diabetes was a significant covariate (standardized $\beta=0.06$), ($p=0.001$); history of infection was not.

Fetal Growth

Growth Trajectories

The null hypothesis of identical growth trajectories was not supported (Table 2):

Compared to their peers from uncomplicated term pregnancies, fetuses delivered preterm were significantly larger by 18 weeks (greater intercepts). Their growth rates then declined relative to their peers for all dimensions except the femur. Slower growth of abdominal circumference tracked from the mid-trimester (reduced linear trends, the first coefficient), and a decline in head size growth rates followed (reduced curvature, the second coefficient, Table 2, Figure 1).

Males were larger than females in both groups, while maternal variables (height, weight, BMI, multiparity) had significant (positive) effects on size among fetuses delivered at term only. No significant differences in growth trends accompanied exposure to maternal gestational diabetes among the preterm delivered group in this analysis (Table 2).

Fetal growth timing

Fetal growth was not identical between groups across gestational ages: Compared to their term delivered peers, fetuses delivered preterm experienced more rapid growth in biparietal diameter and abdominal circumference from 16 to 20 weeks. A perturbation across mid-gestation followed, with a phase of slower growth (20–24 weeks), followed by a rebound (24–28), prior to an abrupt decline in growth rates for all dimensions at 28 weeks (Table 3, Figures 2–4). Notably, head circumference and limb growth rates did not share in the slowing of growth from 20 to 24 weeks. The preterm delivered fetuses not only maintained larger head dimensions than the term delivered fetuses across this time period, but larger head sizes relative to abdominal circumference (see Fig. 5).

In a stratified analysis, maternal gestational diabetes was associated with an increased growth rate between 24 and 28 weeks in abdominal circumference, and from 32 weeks in biparietal diameter and abdominal circumference (data not shown). In contrast, term delivered fetuses experienced steady growth across mid-gestation with no comparable declines at 28 weeks (Table 3).

Fetal size and preterm birth

Preterm birth was predicted by size until mid-gestation: The logistic regression results quantified the relationship between the early rapid growth pattern and birth timing (Table 4). Larger size increased the odds ratio of preterm birth through mid-gestation: Prior to 23 weeks, one standard score of estimated fetal weight had an odds ratio for preterm birth of 2.8, increasing to 3.6 by mid-gestation (23–28 weeks). The individually assessed parameters shared an approximate 50% increased likelihood of preterm birth per standard score prior to 23 weeks. By 23 – 28 weeks, the odds ratios for preterm birth from head and limb dimensions doubled, surpassing those for abdominal circumference nearly two-fold (OR, 4.2 vs 2.5, respectively).

From 28 weeks, these relationships had reversed and larger fetal dimensions were associated with odds ratios less than one for preterm birth. Larger head circumference and femur length were most protective, with the likelihood of preterm birth decreasing to 70 and 60 percent, respectively. Likewise, each standard score of abdominal circumference and estimated fetal weight decreased the likelihood of preterm birth by 54% and 44%, respectively. Maternal gestational diabetes did not alter these relationships.

DISCUSSION

These data document for the first time a distinctive growth pattern across gestation among fetuses subsequently delivered after idiopathic, spontaneous preterm labor (median age at birth, 35.6 weeks). A model of faster fetal overgrowth followed by decline emerges as a phenotypic precursor to late preterm birth. This phenotype is characterized by three phases: First, fetuses delivered preterm grew faster and were larger than their peers of similar gestational age in the mid-trimester. Second, a growth perturbation subsequently occurred at mid-gestation: slower growth at 20 weeks was followed by a transient recovery at 24 weeks. Third, a general decline in growth rates occurred from 28 weeks and ended in preterm birth.

A rapid growth and decline phenotype

The sequence found in these data highlights mid-gestation as a transitional time between an early accelerated phase and a waning in growth rates. The notable distinction in head circumference and limb growth rates compared with abdominal circumference growth prior to mid-gestation suggests that this period of preferential growth was a precursor to the more general slow-down to follow. This change in body proportionality may have indicated altered energetics at this time (Kramer et al., 1989), or other unknown sources of growth perturbation may have been operational. No such differences were found after 28 weeks, when the growth rates of all fetal dimensions declined compared to their peers delivered at term.

A specific strength of the present investigation was the attention to detail in data collection of both maternal clinical histories and fetal biometric parameters in a study of this sample size. The natural history, longitudinal design permitted investigation of the various dimensions of fetal size over time, and provided the opportunity to identify the exceptional growth pattern phenotype.

The present results raise the question of how the growth pattern observed here is to be understood within the tradition of long-reported associations between preterm delivery and intrauterine growth restriction (e.g., Ott et al. 1993). The interpretations from earlier investigations aiming to describe fetal growth and the etiology of preterm delivery have often been based on ultrasounds from smaller samples focused later in gestation. For example, if the present study were confined to data at 32 weeks (Hediger et al., 1995), a

comparison of size between the present study groups would provide no hint of their dynamic developmental history.

In a study seeking to “confirm the relationship between small fetal size and prematurity,” Doubilet and colleagues used sonograms taken at 24–29.9 weeks and 30–36.9 weeks to compare sizes among fetuses who would deliver at term and those who delivered very prematurely, or prior to 30 weeks gestation, and moderately prematurely, or between 30 and 36 weeks (Doubilet et al., 2003, p. 360). They identified reduced size in all dimensions (biparietal diameter, abdominal circumference and femur diaphyseal length) among the very premature fetuses in the first interval, while a decline characterized the later-delivering preterm fetuses. Abdominal circumference and femur length were reduced during the first interval, joined by biparietal diameter after 30 weeks.

Thus, the data collection protocol in the present sample enabled identification of the overall growth pattern. In general, it is likely that both small fetal size and large fetal size are precursors of preterm delivery, as both are relatively aberrant patterns. This idea is compatible with previous observations of both under- and over-growth among samples of pregnancies ending in spontaneous preterm labor and birth (Lackman et al., 2001; Morken et al., 2006). The present data are unique in illustrating the less appreciated influence of the large fetal size.

Early rapid growth, early birth

The early rapid growth phenotype in the present analysis provides evidence of greater variability in fetal growth rates than has been previously appreciated and identifies the importance of further investigating how fetal growth dynamics influence reproductive outcome. The present observations suggest unrecognized mechanisms linking early size, growth rates and gestation length, not found in studies that have focused on fetal growth rates later in gestation among uncomplicated term pregnancies (Zhang et al., 2008). The early rapid growth, early birth association found in the present study is a reversal of the observed longer duration of pregnancy following smaller fetal size at second trimester (Johnsen et al., 2008). The odds ratios found in the present study for preterm birth from size at mid-gestation are in line with those from the Copenhagen First Trimester study in which fetuses with growth rates for biparietal diameters >97.5th percentile between the first and second trimester were found to have an odds ratio of 2.7 (95% CI, 1.44–5.1) for delivery in weeks 34–36 (Pederson et al., 2007). The processes responsible for these observations are not known.

Human biological variability in fetal growth and gestation length—The present results should be considered with the caveat that they may reflect human biological variation that is unique to this population. The relatively high rate of late preterm births in the present sample fits the demographic profile for Latin America as reported by the Pan American Health Organization based on data from 1.7 million births that occurred between 1985 and 2003 in more than 50 maternity hospitals (Barros and Velez, 2006). The mean birth weight among spontaneous preterm birth in this larger sample was 2541 grams (sd, 741) at an average gestational age of 33.9 weeks (sd, 2.9), very close to the present study outcome.

Indeed, the specific patterns in the present data may be relevant to previous reports of rapid fetal growth rates and greater birth size for gestational age associated with Hispanic ethnicity among both singletons and twins (Alexander et al., 1999; Chung et al., 2003; Luke et al., 2005). The paradoxical observations that heavier infants are born to Mexican Americans between 30 and 37 gestational weeks, contrasted with those delivered at 37–42 weeks (Overpeck et al., 1999) led some researchers to conclude that these results were most likely due to errors in gestational aging (Buekens et al., 2000).

As the present study data represent novel observations, it is essential to consider potential sources of error or bias in the study. The mean neonatal birth weight of the pregnancy cohort is close to the Chilean national reference population (Gonzalez et al., 2004), suggesting no identifiable source of bias among the enrolled pregnancies. The present study was designed to follow the natural history of unselected pregnancies, but for the self-selection bias of the mother to participate. There was no known source of bias in pregnancy dating in the present study sample that would generalize to the subsequent timing of preterm vs. term labor and delivery. As the results identify larger sizes at earlier ages among fetuses from pregnancies with episodes of spontaneous preterm labor and delivery, it could be suggested that the results are merely an artifact of the misattribution of gestational ages at enrollment. This implies consistent under-aging at study admission, selectively by group. As the preterm fetuses were actually relatively large, this is not likely. All pregnancies were dated by both LMP and ultrasonography; it is doubtful that aging inconsistencies underlie the preterm delivery category results (Dietz et al., 2007) as it is a statistically unlikely bias to have occurred across the entire cohort of fetuses destined for preterm labor.

The data do raise the question of how accurately reference data reflect gestational age among fetuses with early rapid growth. Theoretically, there is a possibility that fetuses from such pregnancies will be assumed to be older than they really are. This has implications for what may be unappreciated sources of variability in maturational status at birth.

Understanding gestation length and growth rate: Two aberrant features compared to the normal pregnancy are presented in these data: altered gestation length and altered growth pattern. A challenge is to posit a mechanism that would explain the co-occurrence of early faster fetal growth followed by decline, yet a relatively robust birth weight, after preterm gestation duration.

Previously published work on the non-infectious etiology of preterm labor and birth among animal models has highlighted maternal nutrition both prior to, and at the time of, conception. For example, early increased fetal cortisol levels followed by preterm delivery were the outcome in an ovine model that reduced caloric intake to produce a 10–15% reduction in ewe body weight prior to conception. This undernutrition-induced stress model saw no differences in offspring weight at birth, only attenuated gestation time (Bloomfield et al., 2003). From the perspective of initial maternal weight, the study actually documented relatively greater growth among the fetuses from undernourished ewes by comparison with their peers.

Faster fetal overgrowth: The phenotype of relatively greater birth weight found among the preterm fetuses in the present study sample may be a natural variant of the “large offspring syndrome”, first identified from studies based on in vitro fertilization (IVF) procedures among cattle and sheep (Walker et al., 1996). Although the present sample is not a precise analogue of these earlier reports, the IVF work has contributed insight into determinants of fetal growth rates and offspring size from factors acting prior to, during, and shortly after conception (Koo et al., 2002). At the present time, considerable evidence supports epigenetic mechanisms and altered expression of imprinted genes (reviewed in Ferin et al., 2004).

The large offspring syndrome is associated with fetal overgrowth from early ages, unassociated with increased placental weight (Young et al., 1998), suggesting that there are sources for perturbed growth intrinsic to the fetus. Investigation to date has focused on the identification of exposures that may alter the cell cycle and differentiation processes from the oocyte through the blastocyst and embryonic period. For example, in a murine model, a low protein diet prior to implantation resulted in both an increased conceptus weight from

the blastocyst stage, and increased weight at birth. This was shown to be independent of maternal environment, and linked to adaptive responses in the yolk sac (Watkins et al., 2008). There were no associated differences in gestation length.

Animal models have identified the significant effects of periconceptual nutrition on both fetal and placental growth (reviewed in Fowden et al., 2006). It has been suggested that at the earliest stages of development, when the cells that will become the fetus (the inner cell mass) differentiate from those that will form placental tissues (trophectoderm), variability in apportionment can have profound effects (Walker et al., 1996). For example, metabolic influences favoring allocation of cells to the inner cell mass in lieu of the trophectoderm (Adjaye et al., 2005), or selective loss of trophectoderm (Banwell et al., 2007), would favor more fetal tissue at the expense of the placenta. In this scenario, the potential for rapid early fetal growth would be set, as would a limitation on growth maintenance, as functional placenta became limiting. This would be a set-up in which a fetus could quite literally both out-grow their nourishment, and provoke parturition as they outgrew the placenta itself.

A close relationship between growth of trophoblast-derived structures and gain in fetal mass has been described from 10 weeks (Jackson et al., 1992), with the diffusive conductance of normal placental tissue capable of matching fetal mass from the second trimester, albeit with a lag-time behind fetal mass (Mayhew, 2006). In the present study, relatively larger than their peers by mid-gestation, the declining growth velocities in the third trimester among the preterm group only attenuated their size relative to their peers, but did not result in a relative diminution. It is possible that they reached a maximal capacity state (Ehrhardt and Bell, 1995), limiting further placental expansion at the same rate as their peers. It appears that fetal/placental interactions at this time are an important indicator of fetal growth (Thame et al., 2004), and it is evident that further research is needed to clarify second trimester placental growth patterns as they mediate fetal outcome (Salafia et al., 2007).

Whether the present data reflect a fetal contribution to gestation length as the rapidly growing fetus stretches the placental limits, activating a parturition cascade (Challis et al., 2000; Lee et al., 2008), or it is another mechanism that is associated with the rapid grower phenotype underlying gestational length curtailment, remains to be identified. There is no doubt that altered fetal growth rates and trajectories from early ages likely have numerous etiologies, associated with multiple windows of opportunity for perturbations, including epigenetic effects (Allegrucci et al., 2005; Duranthon et al., 2008; Kaku et al., 2007; Ohlsson et al., 1993; Osada et al., 2007). The timing of the surge and decline growth patterns among the preterm group found here may well reflect perturbations that accompany the mid-gestation transition (Knox and Baker, 2008), with effects that are yet to be elucidated.

Present study strengths and short-falls: A specific strength of the present investigation was the sample size, and providing a group of uncomplicated pregnancies to be used as a comparative frame of reference. This mitigated the need for an external growth reference and the attendant confounding from the use of postnatal weights to interpret prenatal size (Ehrenkranz, 2007). A short-coming was the lack of consistently-timed measurements. The unbalanced design limited analyses of greater temporal precision. The results point to the need for further study of mid-gestation fetal growth patterns through protocols with more frequent ultrasound assessments, coupled with investigation of placental factors that may relate to these observations. This may lead to more specific hypotheses regarding the etiology and mechanisms underlying preterm labor and birth. In addition, the collection of paternal anthropometric information in future studies may broaden understanding of fetal growth patterns described here.

The lack of significant findings associated with maternal gestational diabetes in the growth trajectory analysis was notable. This likely reflected the small sample size of these individuals (24 of the affected women who delivered preterm). Preliminary stratified analyses identified a late accelerated growth pattern (from 30 gestational weeks) in all dimensions among fetuses exposed to maternal gestational diabetes (data not shown), as has been previously reported (e.g., Bochner et al., 1987; Kehl et al., 1996). As an aspect of the random effects associated with individuals, it appears that the few exposed individuals did not alter the downward trend in growth rates across gestation among the preterm group by comparison with their term-delivered peers.

Further research: The identification of distinctive growth patterns across biometric variables that consistently differentiated the fetuses delivered of pregnancies with spontaneous preterm labor and birth supports the proposition of differences in developmental biology associated with this outcome in this sample. These observations draw attention to the importance of further understanding the interplay between genetically-based growth programs (e.g., Knight et al., 2005) and reproductive biology on pregnancy outcome. Relationships between parental birth weights and offspring size and delivery age have been interpreted as suggesting heritable growth rate influences on earlier gestational age at delivery (Lie et al., 2006). Evidence for this theoretical relationship is scant to date among humans.

Research identifying biomarkers of fetal growth is critical to elucidate the mechanisms by which the fetal growth program interacts with maternal physiology (Romero et al., 2006a). The limited nature of an evidentiary base at present challenges articulation of pathways by which early growth proceeds, and restricts the ability to track the growing fetus physiologically across gestation, although interesting approaches have been initiated (Leung et al., 2006). Evidence for biological marker differences among preterm delivery categories (McGrath et al., 2002) and delivery timing after spontaneous preterm labor (Grisaru-Granovsky et al., 2007) encourage further investigation into the specific etiologies of preterm birth. Moreover, the identification of an association between preterm birth and polymorphisms in the K121Q genotype of the maternal ENPP1 gene among Hispanics (Norwitz et al., 2007) is particularly intriguing as the variant has been linked to a propensity towards insulin resistance, diabetes, and obesity among children (Bottcher et al., 2006). The present data suggest that clarifying the biology of the rapid grower phenotype may be important in understanding causal pathways of spontaneous preterm labor.

It is notable that the increasing rates of late spontaneous preterm birth reported at the national level (Engle et al., 2007) parallel demographic shifts found across the same time frame. The first is the shift in population demographics, consistent with a rise in what may be population-specific growth patterns (US Census Bureau 2005). The second is the increase in weight of the American population more generally (CDC, 2005). It is important to consider the effects that the changes in adult body size may be having on early developmental biology through the reproductive interface.

In summary, the present study identified a unique fetal growth phenotype preceding idiopathic late preterm delivery. These fetuses experienced faster growth and were of larger size in the mid-trimester, compared to their peers from uncomplicated pregnancies. They subsequently experienced slower growth from 28 weeks, and were, nonetheless, born at greater population-specific sex and age-adjusted birth weight percentiles, compared to their peers. The mechanisms underlying the early rapid growth phenotype found in the present analysis are unknown. Further research is needed to explore factors acting prior to, during, and shortly after conception, implicated in animal studies of the large offspring syndrome. These may include, but are not limited to nutritional and metabolic signals, epigenetic

mechanisms and altered expression of imprinted genes, and population-specific polymorphisms. Mechanisms underlying the slower growth in the early third trimester, likewise, await further clarification; fetal/placental relationships are suggested by the present observations.

Variability in fetal growth rate timing is likely to be greater than presently appreciated. The discovery of an early rapid growth phenotype as a precursor to late preterm labor and delivery invites further clarification of fetal growth pattern diversity.

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Literature Cited

- Adjaye J, Huntriss J, Herwig R, BenKahla A, Brink TC, Wierling C, Hultschig C, Groth D, Yaspo ML, Picton HM, Gosden RG, Lehrach H. Primary differentiation in the human blastocyst: comparative molecular portraits of inner cell mass and trophoctoderm cells. *Stem Cells*. 2005; 23:1514–1525. [PubMed: 16081659]
- Alexander GR, Kogan MD, Himes JH. 1994–1996 US singleton birth weight percentiles for gestational age by race, Hispanic origin, and gender. *Maternal and Child Health Journal*. 1999; 3:225–231. [PubMed: 10791363]
- Allegretti C, Thurston A, Lucas E, Young L. Epigenetics and the germline. *Reproduction*. 2005; 129:137–149. [PubMed: 15695608]
- Banwell KM, Lane M, Russell DL, Kind KL, Thompson JG. Oxygen concentration during mouse oocyte in vitro maturation affects embryo and fetal development. *Human Reprod*. 2007; 22:2768–2775.
- Barros FC, del Pilar Velez M. Temporal trends of preterm birth subtypes and neonatal outcomes. *Obstet Gynecol*. 2006; 107:1035–1041. [PubMed: 16648408]
- Behrman, RE.; Stith Butler, A., editors. *Preterm Birth: Causes, Consequences, and Prevention*. National Academies Press; Washington D.C: 2007.
- Bloomfield FH, Oliver MH, Hawkins P, Campbell M, Phillips DJ, Gluckman PD, Challis JRG, Harding JE. A periconceptional nutritional origin for noninfectious preterm birth. *Science*. 2003; 300:606. [PubMed: 12714735]
- Bochner CJ, Medearis AL, William J, Castro L, Hobel CJ, Wade ME. Early third-trimester ultrasound screening in gestational diabetes to determine the risk of macrosomia and labor dystocia at term. *Am J Obstet Gynecol*. 1987; 157:703–708. [PubMed: 3307427]
- Bottcher Y, Korner A, Reinehr T, Enigk B, Kiess W, Stumvoll M, Kovacs P. ENPP1 variants and haplotypes predispose to early onset obesity and impaired glucose and insulin metabolism in German obese children. *J Clin Endocrinol Metab*. 2006; 91:4948–4952. [PubMed: 16968801]
- Buekens P, Notzon F, Kotelchuck M, Wilcox A. Why do Mexican Americans give birth to few low-birth-weight infants? *Am J Epidemiol*. 2000; 152:347–351. [PubMed: 10968379]
- Centers for Disease Control and Prevention, Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion. *Obesity trends among US adults 1991, 1996, 2004: Obesity Trends: US Obesity Trends 1985–2004*. 2005.
- Challis JRG, Matthews SG, Gibb W, Lye SJ. Endocrine and paracrine regulation of birth at term and preterm. *Endo Rev*. 2000; 21:514–550.
- Chung JH, Boscardin WJ, Garite TJ, Lagrew DC, Porto M. Ethnic differences in birth weight by gestational age: At least a partial explanation for the Hispanic epidemiologic paradox? *Am J Obstet Gynecol*. 2003; 189:1058–1062. [PubMed: 14586355]
- Davidoff MH, Dias T, Damus K, Russell R, Bettgowda VR, Dolan S, Schwarz RH, Green NS, Petrini J. Changes in the gestational age distribution among U.S. singleton births: Impact on rates of late preterm birth, 1992–2002. *Semin Perinatol*. 2006; 30:8–15. [PubMed: 16549207]

- Dietz PM, England LJ, Callaghan WM, Pearl M, Wier ML, Kharrazi M. A comparison of LMP-based and ultrasound-based estimates of gestational age using linked California livebirth and prenatal screening records. *Paed Perinatal Epidemiol.* 2007; 21(Suppl 2):62–71.
- Doubilet PM, Benson CB, Wilkins-Haug L, Ringer S. Fetuses subsequently born premature are smaller than gestational age-matched fetuses not born premature. *J Ultrasound Med.* 2003; 22:359–363. [PubMed: 12693619]
- Duranthon V, Watson AJ, Lonergan P. Preimplantation embryo programming: transcription, epigenetics, and culture environment. *Reproduction.* 2008; 135:141–150. [PubMed: 18239045]
- Ehrenkranz RA. Estimated fetal weights versus birth weights: should the reference intrauterine growth curves based on birth weights be retired? *Arch Dis Child Fetal Neonatal Ed.* 2007; 92:F161–2. [PubMed: 17449851]
- Engle WA, Tomashek KM, Wallman C. the Committee on Fetus and Newborn. “Late-preterm” infants: A population at risk. *Peds.* 2007; 120:1390–1401.
- González R, Gomez R, Castro R, Nien JK, Merino P, Etchegaray A, Carstens M, Medina L, Viviana P, Rojas I. Curva nacional de distribución de peso al nacer según edad gestacional. Chile, 1993a 2000. *Rev Med Chile.* 2004; 132:1155–1165. [PubMed: 15631202]
- Grisaru-Granovsky S, Halevy T, Planer D, Elstein D, Eidelman A, Samueloff A. PAPP-A levels as an early marker of idiopathic preterm birth: a pilot study. *J of Perinatol.* 2007; 27:681–686. [PubMed: 17703186]
- 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. [PubMed: 3881966]
- Hediger ML, Scholl TO, Schall JI, Miller LW, Fischer RL. Fetal growth and the etiology of preterm delivery. *Obstet Gynecol.* 1995; 85:175–182. [PubMed: 7824227]
- Jackson MR, Mayhew TM, Boyd PA. Quantitative description of the elaboration and maturation of villi from 10 weeks gestation to term. *Placenta.* 1992; 13:357–370. [PubMed: 1438084]
- Kehl R, Drew M, Thomas A, Catalano P. Fetal growth and body composition in infants of women with diabetes mellitus during pregnancy. *Matern Fetal Med.* 1996; 5:273–280.
- Keller J, Metzger B, Dooley SL, Tamura RK, Sabbagha RE, Freinkel N. Infants of diabetic mothers with accelerated fetal growth by ultrasonography. *Am J Obstet Gynecol.* 1990; 163:893–897. [PubMed: 2206077]
- Knight B, Shields BM, Turner M, Powell RJ, Yajnik CS, Hattersley AT. Evidence of genetic regulation of fetal longitudinal growth. *Early Hum Dev.* 2005; 81:823–831. [PubMed: 16085375]
- Knox K, Baker JC. Genomic evolution of the placenta using co-option and duplication and divergence. *Genome Research.* 2008; 18:695–705. [PubMed: 18340042]
- Koo D-B, Kang Y-K, Choi Y-H, Park JS, Kim H-N, Oh KB, Son D-S, Park H, Lee K-K, Han Y-M. Aberrant allocations of inner cell mass and trophoblast cells in bovine nuclear transfer blastocysts. *Biol Reprod.* 2002; 67:487–492. [PubMed: 12135886]
- Kramer MS, McLean FH, Olivier M, Willis DM, Usher RH. Body proportionality and head and length ‘sparing’ in growth-retarded neonates: a critical reappraisal. *Ped.* 1989; 84:717–723.
- Lackman F, Capewell V, Richardson B, daSilva O, Gagnon R. The risks of spontaneous preterm delivery and perinatal mortality in relation to size at birth according to fetal versus neonatal growth standards. *Am J Obstet Gynecol.* 2001; 184:946–953. [PubMed: 11303203]
- Lampl M, Jeanty P. Exposure to maternal diabetes is associated with altered fetal growth patterns: A hypothesis regarding metabolic allocation to growth under hyperglycemic-hypoxemic conditions. *Am J Hum Biol.* 2004; 16:237–263. [PubMed: 15101051]
- Lee SE, Romero R, Park IS, Seong HS, Park CW, Yoon BH. Amniotic fluid prostaglandin concentrations increase before the onset of spontaneous labor at term. *J Matern Fetal Neonatal Med.* 2008; 21:89–94. [PubMed: 18240075]
- Leung TY, Chan LW, Leung TN, Fung TY, Sahota S, Lau TK. First-trimester maternal serum levels of placental hormones are independent predictors of second-trimester fetal growth parameters. *Ultrasound Obstet Gynecol.* 2006; 27:156–161. [PubMed: 16435317]
- Lie RT, Wilcox AJ, Skjoerven R. Maternal and paternal influences on length of pregnancy. *Obstet Gynecol.* 2006; 107:880–5. [PubMed: 16582127]

- Luke B, Brown MB, Misiunas RB, Gonzalez-Quintero VH, Nugent C, van de Ben C, Witter FR, Newman RB, D'Alton M, Hankins GDV, Grainger DA, Macones GA. The Hispanic Paradox in twin pregnancies. *Twin Research and Human Genetics*. 2005; 8:532–537. [PubMed: 16212843]
- Mathews, TJ.; MacDorman, MF. Infant mortality statistics from the 2004 period linked birth/infant death data set. *National vital statistics reports*. Vol. 55. Hyattsville, MD: National Center for Health Statistics; 2007.
- Mayhew TM. Allometric studies on growth and development of the human placenta: growth of tissue compartments and diffusive conductances in relation to placental volume and fetal mass. *J Anat*. 2006; 208:785–794. [PubMed: 16761978]
- McGrath S, McLean M, Smith D, Bisitis A, Giles W, Smith R. Maternal plasma corticotropin-releasing hormone trajectories vary depending on the cause of preterm delivery. *Am J Obstet Gynecol*. 2002; 186:257–260. [PubMed: 11854646]
- Molteni RA, Stys SJ, Battaglia FC. Relationship of fetal and placental weight in human beings: fetal/placental weight ratios at various gestational ages and birth weight distributions. *J Reprod Med*. 1978; 21:327–334. [PubMed: 731626]
- Morken N-H, Kallen K, Jacobsson B. Fetal growth and onset of delivery: A nationwide population-based study of preterm infants. *Am J Obstet Gynecol*. 2006; 195:154–161. [PubMed: 16813752]
- Norwitz E, Snegovskikh V, Lockwood C, Kuczynski E, Muglia L, Tilden D, Kozel B, Funai E, Bahtiyar MO, Luo G, Thung S, Morgan T. Maternal carriage of the K121Q single nucleotide polymorphism (SNP) in the ENPP (PC-1) gene is associated with preterm birth and diminished birthweight in a Hispanic population. *Am J Obstet Gynecol*. 2007; 197:S132. [PubMed: 17825644]
- Ott WJ. Intrauterine growth retardation and preterm delivery. *Am J Obstet Gynecol*. 1993; 168(6 Pt1): 1710–1715. [PubMed: 8317512]
- Overpeck MD, Hediger ML, Zhang J, Trumble AC, Klebanoff A. Birth weight for gestational age of Mexican American infants born in the United States. *Obstet Gynecol*. 1999; 93:943–947. [PubMed: 10362159]
- Pederson NG, Wojdemann KR, Scheike T, Tabor A. Growth rate between first and second trimester and the risk of adverse pregnancy outcome. *Ultrasound Obstet Gynecol*. 2007; 30:367. [PubMed: 17886921]
- Reynolds LP, Redmer DA. Utero-placental development and placental function. *J Anim Sci*. 1995; 73:1839–1851. [PubMed: 7545661]
- Romero R, Espinoza J, Gotsch F, Kusanovic JP, Friel LA, Erez O, Mazaki-Tovi S, Than NG, Hassan S, Tromp G. The use of high-dimensional biology (genomics, transcriptomics, proteomics, and metabolomics) to understand the preterm parturition syndrome. *BJOG*. 2006a; 113:118–135. [PubMed: 17206980]
- Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, Chaiworapongsa T, Mazor M. The preterm parturition syndrome. *Am J Obstet Gynecol*. 2006b; 113(Supp 3):17–42.
- Royston P, Altman PG. Design and analysis of longitudinal studies of fetal size. *Ultrasound Obstet Gynecol*. 1995; 6:307–312. [PubMed: 8590199]
- Royston P, Altman PG. Approximating statistical functions by using fractional polynomial regression. *The Statistician*. 1997; 46:411–422.
- Salafia CM, Zhang J, Miller RK, Charles AD, Shrout P, Sun W. Placental growth patterns affect birth weight for given placental weight. *Birth Defects Research (Part A)*. 2007; 79:281–288.
- StataCorp. *Stata Statistical Software: Release 9*. College Station, TX: StataCorp LP; 2005.
- Thame M, Osmond C, Bennett F, Wilks R, Forrester T. Fetal growth is directly related to maternal anthropometry and placental volume. *Eur J Clin Nutr*. 2004; 58:894–900. [PubMed: 15164110]
- U.S. Census Bureau. Cumulative estimates of the components of population change by race and Hispanic or Latino origin for the United States: April 1, 2000 to July 1, 2004 (NC-EST2004–05). 2005. www.census.gov
- Valenzuela C, Rothhammer F, Chakraborty R. Sex dimorphism in adult stature in four Chilean populations. *Ann Hum Biol*. 1978; 5:533–538. [PubMed: 742841]
- Villar J, Abalos E, Carroli G, Giordano D, Wojdyla D, Piaggio G, Campodonico L, Gulmezoglu M, Lumbiganon P, Bergsjö P, Ba'aqeel H, Farnot U, Bakketeig L, Al-Mazrou Y, Kramer M. for the

- World Health Organization Antenatal Care Trial Research Group. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. *Obstet Gynecol.* 2004; 104:78–87. [PubMed: 15229004]
- Walker SK, Hartwich KM, Seamark RF. The production of unusually large offspring following embryo manipulation: concepts and challenges. *Theriogenology.* 1996; 45:111–120.
- Young LE, Sinclair KD, Wilmut I. Large offspring syndrome in cattle and sheep. *Rev Reprod.* 1998; 3:155–163. [PubMed: 9829550]
- Watkins AJ, Ursell E, Panton R, Papenbrock T, Hollis L, Cunningham C, Wilkins A, Hugh Perry V, Sheth B, Kwong WY, Eckert JJ, Wild AE, Hanson MA, Osmond C, Fleming TP. Adaptive responses by mouse early embryos to maternal diet protect fetal growth but predispose to adult onset disease. *Biol Reprod.* 2008; 78:299–306. [PubMed: 17989357]
- Zhang J, Sundaram R, Sun W, Troendle J. Fetal growth and timing of parturition in humans: A prospective study. *Am J Obstet Gynecol.* 2007; 197:S201.

Figure 1. Best-fit fractional polynomial for head circumference growth, ($HC=y+gestational\ age-gestational\ age^3$)

Fetuses delivered preterm were larger by mid-second trimester, followed parallel linear trajectories until about 28 weeks, when their growth began to decline compared with their term-delivered peers. These patterns are statistically different, as indicated by a greater y-intercept, similar coefficients for gestational age (the first coefficient) and significantly more negative values for the second coefficient (gestational age³) (Table 2).

Figure 2.

Estimated fetal weight growth fit by piecewise regression with nodes at 4-week intervals from 16 weeks. The preterm group experienced significant declines in growth rate at 20, 28, and 32 weeks by comparison with their term-delivered peers, while relatively more robust between 24 and 28 weeks. Abdominal circumference patterns were similar (Table 3).

Figure 3. Biparietal diameter growth. Piecewise regression with nodes at 4-week intervals from 16 weeks identified significantly greater growth among the preterm group from 16 weeks until 28 weeks, when they experienced a significant decline (Table 3).

Figure 4. Femur diaphyseal length growth. Piecewise regression with nodes at 4-week intervals from 16 weeks identified parallel growth trajectories for the preterm group and their term-delivered peers until 28 weeks, when the preterm group experienced a significant decline. Their growth trajectory then remained steady, compared to a progressive decline among the term-delivered (Table 3).

Figure 5. Fetal head and limb dimensions regressed on abdominal circumference between 20 and 28 gestational weeks of age

Head dimensions among preterm-delivered fetuses were significantly larger than their peers from term pregnancies in absolute terms (top panel), and larger relative to their abdominal circumferences (bottom panel, p -values = 0.097, 0.056 biparietal diameter and head circumference, respectively). Analyses were based on sex-corrected z -scores for fetal variables in multilevel models with an interaction term between group and abdominal circumference (*xtreg*, *re* STATA 9, Statacorp, 2005).

Table 1

Maternal and fetal characteristics of the study sample

	Term	Preterm	<i>p</i> -value
Maternal Characteristics			
Maternal height (m)	1.56 (1.52–1.60) ¹ [3691] ²	1.56 (1.52–1.6) [219]	0.31
Maternal weight (kg)	59 (52–66) [3582]	58 (52–65) [214]	0.34
Maternal BMI (kg/m²)	23.9 (21.8–26.7) [3573]	23.9 (21.5–26.9) [213]	0.46
Maternal age (yrs)	25 (21–30) [3627]	25 (20–32) [214]	0.87
Primiparity	1295/3704 (35%)	85/221 (38.5%)	0.30
Smoking	411/3705 (11.1%)	34/221 (15.4%)	0.05
Cesarean section	664/3703 (18%)	44/221 (21.2%)	0.44
Fetal Characteristics			
Sex (male)	1925/3703 (52%)	124/221 (56.1%)	0.24
Birth GA³ (wk)	39.7 (38.9–40.4) [3706]	35.6 (34.1–36.4) [219]	<0.001
Birthweight percentile⁴	47 (23–71)	55 (31–77)	0.002
Males	53 (29–76)	60 (33.5–79.5)	0.06
Females	41 (19–66) (0.000) ⁵	47 (25–75) (0.06) ⁵	0.02

¹ median (interquartile range);² [n] for available data;³ GA, gestational age;⁴ sex and age-adjusted birth weight percentiles according to the population-based reference (González et al., 2004);⁵ *p*-value comparing birth weight percentile by sex within each group.

Table 2Fetal growth trajectories for best-fit second degree polynomials¹.

	Size at 18 weeks (Y-intercept)	Linear component (1 st coefficient)	Curvature (2 nd coefficient)	Sex
Estimated fetal weight²				
Term	−0.90	0.136	-3.8×10^{-3}	−0.02(0.00)
Preterm	−0.75 (0.000) ⁵	0.131 (0.000)	-3.6×10^{-3} (0.17)	−0.04 (0.01)
Preterm GD³	−0.83 (0.39) ⁵	0.136 (0.88)	-3.6×10^{-3} (0.65)	−0.04 (0.39)
R² 0.99, 0.95, 0.98				
Abdominal circumference²				
Term	−1.05	0.147	-2.25×10^{-3}	−0.03 (0.000)
Preterm	−0.91 (0.000)	0.142 (0.001)	-2.36×10^{-3} (0.44)	−0.04 (0.08)
Preterm GD	−1.01 (0.56)	0.152 (0.22)	-2.24×10^{-3} (0.95)	−0.05 (0.43)
R² 0.99, 0.95, 0.98				
Head circumference²				
Term	−1.29	0.189	-1.3×10^{-4}	−0.05 (0.000)
Preterm	−1.16 (0.000)	0.188 (0.56)	-1.58×10^{-4} (0.003)	−0.05 (0.01)
Preterm GD	−1.06 (0.06)	0.186 (0.65)	-1.49×10^{-4} (0.54)	−0.03 (0.63)
R² 0.99, 0.93, 0.97				
Biparietal diameter²				
Term	−1.27	0.182	-9.76×10^{-5}	−0.06 (0.00)
Preterm	−1.10 (0.000)	0.182 (0.91)	-12.4×10^{-5} (0.001)	−0.04 (0.04)
Preterm GD	−1.13 (0.28)	0.177 (0.43)	-9.73×10^{-5} (0.88)	−0.01 (0.87)
R² 0.99, 0.92, 0.97				
Femur diaphyseal length⁴				
Term	−1.36	0.187	-1.21×10^{-4}	0.01 (0.05)
Preterm	−1.25 (0.000)	0.184 (0.21)	-1.21×10^{-4} (0.41)	−0.04 (0.02)
Preterm GD	−1.25 (0.29)	0.186 (0.39)	-1.21×10^{-4} (0.39)	−0.04 (0.45)
R² 0.99, 0.94, 0.97				

¹ $\ln EFW$ and $AC^{0.7} = y + GA - GA^2$; all other variables = $y + GA - GA^3$; ² Covariates: maternal BMI, parity, maternal height, maternal weight and the interaction between them; ³ GD, gestational diabetes.

Coefficients for fetal biometric parameter z-scores as a function of gestational age from a multilevel random effects model (*xtreg, re*, Stata 9, StataCorp 2005). In a two parameter model, the coefficients describe a linear trend (first parameter) and the shape, or curvature of the trajectory (second parameter). The group interaction effects for the constants and coefficients were investigated and the *p*-values for fetuses delivered preterm⁴ clarified for the effects of gestational diabetes⁵. All models were significant at $p < 0.001$. The R^2 values represent the within individuals, between individuals and overall effects.

Table 3

Fetal growth timing for term and preterm-delivered fetuses compared.

Ages	Term	Preterm	<i>p</i> -value slope ¹	<i>p</i> -value change in slope ²
Estimated fetal weight³				
16–20	0.21	0.221	0.19	0.11
20–24	0.179	0.167	<i>0.04</i>	0.07
24–28	0.147	0.156	0.19	<i>0.04</i>
28–32	0.127	0.107	<i>0.002</i>	<i>0.02</i>
32–36	0.081	0.072	0.33	<i>0.03</i>
Abdominal circumference⁴				
16–20	0.191	0.215	0.13	0.17
20–24	0.169	0.155	<i>0.05</i>	0.07
24–28	0.146	0.158	0.18	0.05
28–32	0.151*ns	0.131	<i>0.02</i>	0.06
32–36	0.104	0.111	0.57	0.12
Head circumference				
16–20	0.190	0.192	0.81	0.35
20–24	0.177	0.175	0.74	0.77
24–28	0.164	0.174	0.27	0.35
28–32	0.135	0.099	<i>0.00</i>	0.006
32–36	0.082	0.098	0.21	0.003
Biparietal Diameter				
16–20	0.178	0.191	0.13	<i>0.04</i>
20–24	0.170	0.157	0.06	0.07
24–28	0.170*ns	0.184	0.12	<i>0.04</i>
28–32	0.140	0.110	<i>0.001</i>	<i>0.01</i>
32–36	0.093	0.089	0.74	0.14
Femur diaphyseal length				
16–20	0.193	0.199	0.51	0.49
20–24	0.173	0.164	0.19	0.31
24–28	0.151	0.157	0.47	0.23
28–32	0.147*ns	0.128	<i>0.03</i>	0.14
32–36	0.098	0.126	<i>0.02</i>	<i>0.01</i>

Coefficients for the slopes of size for age are given with *p*-values¹ comparing the respective four-week intervals between the study groups. Significant values are in bold italics. Among the term-delivered fetuses, the significance of a change in slope across gestational ages was confirmed for all dimensions with three exceptions, as noted (*). An interaction between change in slope and group investigated differences in the timing of growth between groups². The analyses were a random-effects multilevel model (*xtreg, re*) with piecewise regression intervals generated by *mkspline* and the *marginal* option from Stata 9 (StataCorp, 2005).

Table 4

Odds ratios of preterm delivery by standard score for each fetal parameter at three gestational age ranges.

	<23 weeks ¹	p-value	>=23 & <28 ¹	p-value	>=28 & <34 ¹	p-value
EFW²	2.84(1.09–7.41) ^{3,4}	0.03	3.59(1.82–7.11)	0.001	0.56 (0.38–0.82)	0.003
	2.93 (1.08–8.04) ⁵	0.04	3.59 (1.75–7.39)	0.001	0.52 (0.35–0.78)	0.002
AC	1.49(1.03–2.14)	0.03	2.49(1.30–4.77)	0.01	0.46 (0.27–0.81)	0.007
	1.46 (0.99–2.15)	0.06	2.41 (1.21–4.8)	0.01	0.42 (0.23–0.75)	0.003
BP	1.55(1.10–2.18)	0.01	4.18(2.29–7.64)	0.001	0.40(0.21–0.77)	0.01
	1.50 (1.04–2.15)	0.03	4.49 (2.38–8.47)	0.001	0.42 (0.21–0.84)	0.014
HC	1.48(1.06–2.07)	0.02	4.14(2.22–7.74)	0.001	0.24(0.13–0.43)	0.000
	1.44 (1.01–2.05)	0.04	4.14 (2.15–7.98)	0.000	0.25 (0.13–0.47)	0.000
FDL	1.43(1.04–1.98)	0.03	3.50 (1.76–6.98)	0.001	0.33(0.17–0.66)	0.002
	1.39 (0.99–1.96)	0.06	3.83 (1.85–7.92)	0.001	0.31 (0.15–0.63)	0.001

¹ Gestational age, weeks ² EFW, estimated fetal weight; AC, abdominal circumference; BP, biparietal diameter; HC, head circumference; FDL, femur diaphyseal length. ³Odds ratio (95% confidence interval); ⁴ pregnancies uncompromised by maternal gestational diabetes; ⁵ analyses controlling for maternal gestational diabetes.

Analyses excluding pregnancies complicated by maternal gestational diabetes (top line for each parameter) compared to analyses controlling for maternal gestational diabetes (second line for each parameter). Covariates included fetal sex, maternal BMI, parity, and smoking.