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Growth perturbations in a phenotype with rapid fetal growth preceding preterm labor and term birth

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Abstract

The variability in fetal growth rates and gestation duration in humans is not well understood. Of interest are women presenting with an episode of preterm labor and subsequently delivering a term neonate, who is small relative to peers of similar gestational age.

To further understand these relationships, fetal growth patterns predating an episode of preterm labor were investigated. Retrospective analysis of fetal biometry assessed by serial ultrasound in a prospectively studied sample of pregnancies in Santiago, Chile tested the hypothesis that fetal growth patterns among uncomplicated pregnancies ($n=3706$) and those with an episode of preterm labor followed by term delivery ($n=184$) were identical across the time intervals 16–22 weeks, 22–28 weeks and 28 to 34 weeks in a multilevel mixed-effects regression.

The hypothesis was not supported. Fetal weight growth rate was faster from 16 weeks among pregnancies with an episode of preterm labor ($p<0.05$), declined across mid-gestation (22 to 28 weeks, $p<0.05$), and rebounded between 28 and 34 weeks ($p=0.06$). This was associated with perturbations in abdominal circumference growth and proportionately larger biparietal diameter from 22 gestational weeks ($p=0.03$), greater femur ($p=0.01$), biparietal diameter ($p=0.001$) and head circumference ($p=0.02$) dimensions relative to abdominal circumference across mid-gestation

(22–28 weeks), followed by proportionately smaller femur diaphyseal length ($p=0.02$) and biparietal diameter ($p=0.03$) subsequently.

A distinctive rapid growth phenotype characterized fetal growth preceding an episode of preterm labor among this sample of term-delivered neonates. Perturbations in abdominal circumference growth and patterns of proportionality suggest an altered growth strategy pre-dating the preterm labor episode.

Keywords

growth rate; growth patterns; rapid growth phenotype

Fetal size has been associated with altered length of gestation in a variety of species (Challis et al., 2001; Challis and Smith, 2001; Johnsen et al., 2008) and animal models have identified specific interactions between genetics and environmental conditions that influence these processes (Asher, 2007). Complex connections are involved in fetal growth and gestational duration, with consequences that challenge neonatal survival. Unraveling the mechanisms through which maternal and fetal genotypes interact within the prenatal environment is essential for understanding the heterogeneity of birth outcome (Deter and Spence, 2004; Menon, 2008). The pathways by which environmental influences act on genetically based growth programs in humans are not well understood.

A phenotype of rapid growth prior to the occurrence of preterm labor and delivery has been described recently (Lampl et al., 2009). These observations raise questions about the variability in fetal growth patterns in general, and growth patterns that portend variability in gestational timing, specifically. The clinical phenotype of preterm labor that resolves in a term birth provides a naturally-occurring variant offering the opportunity to further investigate variability in fetal growth patterns associated with altered gestation length.

Fetuses delivered at term after an episode of preterm labor have been found to be smaller than their peers of similar gestational age at birth (Espinoza et al., 2007), following a decline in size relative to their peers across the third trimester by comparison with the second trimester (Lampl et al., 2008). It is unknown if an altered fetal growth pattern was a consequence of the preterm labor episode, predated the event, and/or was associated with one of the underlying causes of preterm labor. Documentation of the growth patterns of neonates who are relatively smaller for gestational age than they would have been in the absence of prenatal challenges is important to better understand the mechanisms underlying the long-term associations between size at birth and subsequent health (Barker et al., 2006; Gluckman et al., 2008).

Labor commencing prior to term (defined as <37 gestational weeks) complicates approximately 10% of pregnancies in the United States. In about half of these cases, however, contractions subside and pregnancy results in term delivery (≥ 37 weeks) (Grover et al., 1998; Goldenberg et al., 2008). Preterm labor is one of the great obstetrical syndromes, with largely idiopathic, if multifactorial etiology (Romero et al., 2006). Considering the lifelong consequences of preterm birth (Moster et al., 2008), clarification of

fetal growth patterns that pre-date threatened preterm delivery are central to expanding our strategies for predicting preterm birth, and intervening to promote health among an increasing number of women and children encountering preterm pregnancies globally (Goldenberg et al., 2008).

To further clarify whether perturbed growth antedated or followed the preterm labor episode, the present study compared fetal growth patterns among term-delivered neonates from pregnancies complicated by an episode of preterm labor and those from uncomplicated pregnancies. As there is no empirical basis identifying the timing of the growth perturbations associated with an episode of preterm labor, the study hypotheses posited that the fetuses from both groups exhibited (1) identical growth patterns across gestational age in fetal biometric dimensions and (2) identical growth patterns among dimensions (i.e, identical allometry) as overall size increased across age.

METHODS

Study design and population

This was a retrospective, nested cohort study. The sample was composed of 4115 healthy women who presented for obstetrical care at the Center for Perinatal Diagnosis and Research (Sotero del Rio Hospital in Santiago, Chile) by the second trimester of pregnancy and agreed to participate in a longitudinal study of fetal growth. The women were of lower middle class background, lived in the city of Santiago at an altitude of approximately 500 meters, and were an ethnic mixture of Spanish and Araucanian. Exclusion criteria for study participation included multiple pregnancy, major fetal anomalies, and fetal demise at the time of enrollment, as well as any maternal health conditions requiring treatment (e.g., asthma treated with steroids), and a history of previous chronic diseases (e.g., diabetes, chronic hypertension, cardiac insufficiency). All participants provided written informed consent for the collection of data under protocols approved by the Institutional Review Boards of the Sotero del Rio Hospital in Santiago, Chile and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Services (NIH/DHHS).

Clinical definitions

The study requirement for a pregnancy to be defined as uncomplicated included no medical, obstetrical, or surgical complications during the course of the pregnancy, and the delivery of a term neonate (≥ 37 gestational weeks). This study sample included women who experienced an episode of preterm labor (PTL), defined as the occurrence of at least two regular uterine contractions in ten minutes, and a progressive cervical change (dilation of ≥ 1 cm with observed cervical effacement of $\geq 50\%$) requiring hospitalization prior to 37 weeks of gestation.

Fetal growth assessment

The median gestational age at enrollment was 13 weeks (interquartile range, 6–16 weeks) with measurements of the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur diaphyseal length (FDL) repeated on two or more subsequent occasions. No significant differences were found in the distribution of

gestational ages at measurement between the groups and there were no significant differences in the proportion of fetuses by gender. Fetal weight was estimated according to the formula of Hadlock et al., (1985). Pregnancies were dated according to the last menstrual period (LMP), confirmed by an ultrasound during the second trimester.

Study aims and statistical analysis

Exploratory analyses were undertaken with locally weighted polynomial graphical procedures (STATA 10, StataCorp. 2007) to compare growth trajectories of the fetuses from uncompromised pregnancies with those from pregnancies complicated by an episode of preterm labor. This approach generated empirically the hypothesis that 22 and 28 weeks of gestational age were the inflection points of interest.

The *hypothesis of identical growth patterns between groups* was tested by piecewise regression across three time intervals (16–22 weeks, 22–28 weeks, and 28 to 34 weeks) generated by the *mkspline* procedure, with the *marginal* option (Stata 10, StataCorp. 2007). This analysis was implemented in a two-way multilevel mixed model that permitted random intercepts and slopes at the group level, and random intercepts at the individual level (*xtmixed*, STATA 10, StataCorp. 2007). This approach allowed groups to differ in sample size, repeated measurement intervals, and growth rates, with an interaction between randomness in slopes from the unbalanced occasions, and the individual subject's variability in growth. Statistical significance was estimated after adjusting for the nested-level error structure (individuals within groups) with maximum likelihood estimation (Rabe-Hesketh and Skrondal, 2008). Maternal size and parity were investigated as covariates.

The *hypothesis of identical growth patterns among fetal parameters across age between groups* was also investigated by mixed-effects regression. Interaction terms for group and abdominal circumference and growth rate for abdominal circumference were included in the analysis.

All fetal growth parameters were transformed to within-sample, sex-specific z-scores (or standard scores) prior to analysis. That is, the difference between each individual's measurement and the sex-stratified sample mean for that variable was divided by the sample standard deviation. Fetuses from the uncomplicated pregnancies served as the comparison for the fetuses from pregnancies complicated by an episode of preterm labor. Box-Cox regression identified that a transformation for fetal weight (ln) and abdominal circumference (0.7 power) reduced heteroscedasticity and/or skewness of the residuals for analysis. Maternal size was investigated as a binary categorical covariate, above and below the sample median.

The distributions of continuous variables were tested by Shapiro-Francia and Kolmogorov–Smirnov. With non-Gaussian variables, medians for each group were compared by median regression (*qreg*, STATA 10). Chi-square test of randomness of distribution investigated proportionality between groups in categorical variables. A two-sided *p*-value less than 0.05 was considered as significant.

RESULTS

Pregnancy history and sample characteristics

Ninety percent of the participants in the study sample experienced an uncomplicated pregnancy (3706/4115 individuals). An episode of spontaneous preterm labor occurred in 9.9% (407/4115) of the pregnancies, of which 45.2% (184/407) delivered at term.

Pregnancies with complications.—At the time of the preterm labor episode, amniocentesis was performed on 44 participants at a median gestational age of 32.4 weeks (interquartile range, 29.7–33.9 weeks). There was no evidence of intra-amniotic infection among the women undergoing amniocentesis (absence of white blood cell count >100 cells/ml). Among the participants who experienced an episode of preterm labor, forty-three were diagnosed with medical conditions that have been previously associated with aberrant fetal growth, in terms of both over- and under-growth (gestational diabetes, $n=8$; chronic and gestational hypertension, pre-eclampsia, hemorrhage, placental abruption, placenta previa, and cholestasis of pregnancy, $n=35$) (Das and Sysyn, 2004; Vega et al., 1993). The eight individuals exposed to gestational diabetes were removed from further analyses, but the others were kept in the analysis to maintain sample size. The PTL group was stratified by presence/absence of diagnosed medical complications in subsequent analyses to investigate the potential effects. Within the sample of women who experienced an episode of preterm labor, the subset who experienced diagnosed medical complications were distinguished only by greater BMI ($p=0.04$) from those who did not. All analyses employing maternal BMI subsequently considered maternal medical complications as a covariate within the PTL group.

The median age at the time of the preterm labor episode was 32.5 weeks (interquartile range, 29.2–34.6). To further explore the effects of the timing of the preterm labor episode, the sample was stratified by pregnancies experiencing an episode of preterm labor before ($n=71$), and ≥ 32 weeks ($n=113$). No significant differences were identified between these sub-groups in either the proportion of diagnosed medical conditions or the maternal and fetal characteristics, and the PTL group was not further stratified. The presence of maternal medical complications and the timing of PTL were investigated as dichotomous covariates in the growth analyses.

Maternal characteristics

Pregnancies with and without an episode of preterm labor compared.—The demographic characteristics of the sample are shown in Table 1. There were no significant differences in maternal size between women who experienced pregnancies complicated by an episode of preterm labor and those with uncomplicated pregnancies. Of note, there were also no significant differences between groups in either the proportions of primiparous individuals, those who delivered by cesarean section, or those who self-reported smoking or consumption of alcohol.

Fetal characteristics and maternal/fetal relationships

While all of the pregnancies in this investigation were delivered at term, the fetuses from pregnancies complicated by an episode of preterm labor experienced birth at an earlier median gestational age, and delivered at lower median birth weight (sex- and age-adjusted for the population, González et al., 2004). Significant sex differences in median birth weight percentiles were evident only for neonates delivered after uncomplicated pregnancies (Table 2).

Among the uncomplicated pregnancies, maternal height, weight, BMI and multiparity were positively associated with neonatal birth weight percentiles (population-specific, age and sex-adjusted, Gonzalez et al., 2004). By contrast, neonatal birth weight percentiles were negatively associated with maternal weight and body mass index among the fetuses that experienced an episode of preterm labor (Table 3).

Fetal growth

Growth patterns across gestational age—*The hypothesis of identical fetal growth patterns between the study groups was not supported.* Fetuses from pregnancies with an episode of preterm labor and who delivered at term experienced three phases of perturbed growth compared to their peers from uncomplicated pregnancies: an augmentation in growth rate from mid-trimester to 22 weeks, a slowing across mid-gestation to a nadir at 28 weeks, and a subsequent rebound, followed by attenuation after 34 weeks (Figure 1). No significant effects of maternal medical complications or timing of PTL were identified.

Specifically, fetuses from mothers who experienced an episode of preterm labor grew faster than their peers from 16 weeks, and were larger in all measured dimensions by 22 gestational weeks (Table 4, Figure 2). Their abdominal circumference and biparietal diameter growth rates then dropped significantly across mid-gestation (22 to 28 weeks, Figure 3), although never lower than those of their peers from uncomplicated pregnancies. Concomitantly, femur and head circumference growth rates were maintained, and femur length remained comparatively greater than their peers by 28 weeks. A boost in abdominal circumference growth between 28 and 34 weeks resulted in significantly greater estimated fetal weight at 34 weeks (Figure 4). A relative decline in their growth rates followed (Table 2).

Altered proportionality and disturbed allometry.—Perturbations in abdominal circumference growth among the fetuses that experienced an episode of preterm labor suggested that they may be characterized by an atypical within-body growth pattern when compared to fetuses from uncomplicated pregnancies. Further analysis confirmed this.

Relative growth rates of the abdomen, head, and limb differentiated the study groups. Regression of head and limb size on abdominal circumference identified that prior to 28 weeks, as abdominal circumference increased, so did other dimensions for both groups. Among uncomplicated pregnancies, one z-score increment in abdominal circumference predicted larger head dimensions compared to femur diaphyseal length, both prior to 22 gestational weeks and across mid-gestation. This pattern was shared by fetuses from

pregnancies with an episode of preterm labor prior to 22 weeks only. Across mid-gestation, abdominal circumference was associated with larger biparietal diameter and femur diaphyseal length among the fetuses that experienced an episode of preterm labor compared to their peers (Figure 5).

Body proportionality was different between the study groups, as the differential growth rates implied. Controlling for abdominal circumference, by mid-gestation (22–28 weeks) fetuses that experienced an episode of preterm labor had significantly longer femur diaphyseal length and larger biparietal diameter, relative to their abdominal circumference. From 28 weeks, however, this was reversed and their abdominal circumferences were relatively larger than head and limb dimensions, by comparison with their peers from uncomplicated pregnancies (Table 5, Figure 6, top panel).

Allometric relationships were different between the study groups. Fetuses from uncomplicated pregnancies maintained greater concordance among body dimensions: One *z*-score increase in abdominal circumference predicted proportionally similar increases for both biparietal diameter and head circumference (0.72 *z*-score), closely followed by femur length (0.63 *z*-score) during mid-gestation (Table 5). A consistent relationship was established by the third trimester, such that one *z*-score increase in abdominal circumference predicted a 0.46 *z*-score increment in each of the head and limb dimensions (Figure 6, bottom panel).

This did not occur among the fetuses that experienced an episode of preterm labor; they had preferential growth of the biparietal diameter: Across mid-gestation, each *z*-score increase in abdominal circumference predicted 0.89 *z*-score increase in biparietal diameter, followed by limb and head circumference (0.82, 0.79 *z*-score, respectively). This pattern was subsequently maintained, albeit at decreasing magnitude, and no consistent allometry was achieved.

In summary, *differential growth patterns among the abdominal circumference, head, and limb dimensions characterized the study groups*. From the mid-trimester, the fetuses that experienced an episode of PTL had a 25–30% larger abdominal circumference for each *z*-score of biparietal diameter and femur diaphyseal length, compared to their peers from uncomplicated pregnancies (Table 5). At the same time, each *z*-score of abdominal circumference was associated with relatively larger biparietal diameters and longer limbs prior to 28 gestational weeks, and relatively smaller biparietal diameter and femur length after 28 gestational weeks (Table 5, Figure 7). Thus, while the fetuses from pregnancies complicated by an episode of preterm labor had relatively larger abdominal circumferences, they were also proportionally distinctive. Relative to abdominal circumference, they had bigger biparietal diameters and femur lengths prior to 28 gestational weeks, and relatively smaller biparietal diameters and shorter femur diaphyseal lengths subsequently.

Maternal effects across gestation—*The study samples were not equivalent in the effects of maternal size on fetal growth*. No significant effects were found among the pregnancies complicated by an episode of preterm labor (data not shown). The uncomplicated pregnancies were limited to third trimester (28–34 weeks) effects, with equal

positive associations between maternal weight and BMI, and abdominal circumference ($p<0.001$) and biparietal diameter ($p=0.02$).

Discussion

The present study broadens the perspective on fetal growth patterns associated with atypical patterns of labor. This analysis identified an aberrant fetal growth pattern from the mid-trimester among fetuses from pregnancies complicated by an episode of preterm labor that subsequently delivered earlier and lighter than their peers at term. In this sample, these fetuses were robust growers during both mid-trimester (16 to 22 gestational weeks) and third trimester (28 to 34 weeks) intervals. The coincidence between these findings and the timing of the preterm labor episodes, at a median age of 32.5 gestational weeks (interquartile range, 29.2–34.6 weeks), implicates rapid fetal growth rates as contributory. This is a novel observation, provoking consideration of fetal contributions to the mechanisms and biological cascade underlying the onset of labor (Challis et al., 2002; Lee et al., 2008).

Two findings emerged in this study that differentiated the growth patterns of these fetuses: (1) A three-phase growth phenotype characterized by two times of faster growth separated by an interval of slow-down in abdominal circumference growth; and (2) an abdominal growth perturbation that accompanied differences in proportionality and allometry. Maternal size was unrelated to fetal growth rates among these fetuses.

Augmentation, Perturbation, Rebound

The three-phase growth phenotype that distinguished the fetuses who experienced an episode of preterm labor and delivered at term from their peers unfolded across gestational age.

Augmented growth at the midtrimester.—By 22 gestational weeks, the fetuses who would be exposed to an episode of preterm labor were both larger than their peers from uncomplicated pregnancies and had relatively greater biparietal diameters relative to abdominal circumference. The etiology of this early faster growth is not known.

Mid-gestation perturbations in abdominal circumference.—Mid-gestation saw a deceleration in abdominal circumference growth in both absolute terms, and relative to other body dimensions. Thus, they were distinctive from their peers, with proportionately long femurs and large biparietal diameters relative to abdominal circumference.

The rebound.—From 28 weeks, a rebound in abdominal circumference growth occurred, driving a burst in estimated fetal weight. This was accompanied by greater growth rates for all measured parameters except head circumference, by comparison with uncomplicated pregnancies. Their body proportions were different from their peers, with relatively large abdominal circumference dimensions for their femur length and biparietal diameter. No maternal size effects were associated with these growth rate changes.

Understanding fetal growth phenotypes

As novel findings, the sequence of altered fetal growth rates and perturbations in body proportionality are challenging to explain.

Faster midtrimester fetal growth.—In vitro fertilization studies have identified an array of peri-conceptual conditions that accelerate early fetal growth rates (reviewed in Farin et al., 2004). These range from energy signals, influencing cell lineage commitments determining the size of the fetus and placenta (inner cell mass vs trophoctoderm, respectively), with subsequent developmental effects, including alterations of epigenetic programming (Young and Beaujean 2004), and associated metabolic sequelae (Tamashiro et al., 2002). For example, animal studies have identified genomic imprinting effects in the insulin growth factor 2 pathway (IGF-2) (Shao et al., 2007) and early fetal overgrowth (Ohlsson et al., 1993; Jiang et al., 2007). The mid-trimester accelerated growth pattern in the present study is similar to these observations, as well as those reported for the IGF-independent effects of the Grb10 gene (Charalambous et al., 2003).

Mid-gestation abdominal circumference growth attenuation.—Likewise, early nutritional conditions have been related to alterations in placental growth and morphology (Sjoblom et al. 2005; Wallace et al., 2006; Fowden et al., 2006), with effects on hormonal pathways at mid-gestation (Gallaher et al., 1998), and repercussions that include slower growth in mid- to late gestation (Harding, 1997; Oliver et al., 2001).

As the decline in abdominal growth rate was concomitant with unflinching skeletal growth at mid-gestation in the present study, it is reasonable to question whether this was an energetically-based process, with skeletal growth advancing at “the expense” of other tissues. Such growth exchanges have been previously described as “organ sparing” (e.g., Desai et al., 1996). Moreover, the relatively large biparietal diameter for abdominal circumference found already in the mid-trimester suggests that preferential growth was initiated at earlier ages. Evidence linking fetal abdominal circumference decline with energetic challenge at mid-gestation includes studies of human pregnancies complicated by placental vascular damage, with biochemical profiles reflecting low partial pressure of oxygen and low glucose, together with increasing maternal triglycerides, implicating compensatory, altered fat metabolism (Roberts et al., 1999). The lack of data on nutritional status and weight gain across gestation limit interpretation in the present study, and transient alterations in energetic distribution cannot be confirmed or excluded.

Third trimester rebound.—Mechanistically, the timing of the burst in growth at 28 weeks may have reflected placental expansion, following the skeletal growth thrust of the preceding interval (e.g., Coan et al., 2008). Perhaps this represented an attempt to recalibrate allometric growth and establish a more normative proportionality among abdominal, limb and head sizes. This was not, however, the result. These fetuses did not attain an allometry similar to their peers.

Several lines of reasoning suggest potential hormonal correlates of the observed pattern. One possibility is a contribution from placental growth hormone (pGH), a variant of pituitary hormone, produced by placental trophoblasts (Zeck et al., 2008; Mittal et al., 2008). A

prospective, longitudinal study of fetal growth and maternal hormone levels among 103 pregnant women in Copenhagen (Chellakooty et al., 2004) identified a rapid rise phase in serum pGH from 26 weeks, reaching peak concentrations between 34 and 37 weeks, after which pGH levels dropped with decreasing tertiles of birth weight. The pGH rise was significantly positively associated with fetal growth rate, assessed from biparietal diameter and abdominal circumference measurements between 27 and 35 weeks.

Of further interest for this line of reasoning, the ages at peak pGH concentrations were reported to predict pregnancy duration, with earlier births accompanying earlier pGH peaks among the Chellakootey et al. (2004) sample; and a 3.4 ± 2.7 week time from pGH peak to parturition has been separately reported by Wu and colleagues (Wu et al., 2003). Both of these investigations identified negative relationships between maternal pre-pregnancy BMI and pGH levels, and higher levels of pGH were found among underweight women in the latter sample. Finally, peak pGH concentrations were found to correlate with birth length (Wu et al., 2003). Taken together, these observations support a hypothetical relationship between pGH and the growth patterns in the present data.

Abdominal circumference: Anatomical dimension, functional perspective

As the greater part of the fetal abdominal circumference dimension comprises the liver (e.g., Boito et al., 2002), the present observations implicate differences in fetal liver growth and/or blood flow patterns (Bellotti et al., 2000). The perturbations in abdominal circumference found in the present sample may have signaled alterations in fetal liver perfusion (Kessler et al., 2007, 2008). Animal models have observed an allometric preference augmenting liver growth during early fetal development under conditions of limited uterine and placental resources (Vallet and Freking, 2006). It has been suggested that in the face of energetic challenge, this may provide a selective survival advantage by capitalizing on the erythropoietic and/or metabolic functions of the liver (Nicolini et al., 1991). The increasing abdominal circumference relative to other body dimensions across the third trimester found in the present sample may be an analogue, supplementing placental expansion (Battaglia, 2007; Mayhew 2006).

As greater liver blood flow has been reported among fetuses of mothers who are slim, have low body fat and/or poor diet (Haugen et al., 2005), the present results provoke consideration that even the modestly reduced maternal pre-pregnancy BMI of the women free from medical conditions who experienced an episode of preterm labor (Table 1) may have been contributory. Animal models of maternal dietary protein compromise during pregnancy have identified a doubling of hepatic lobular volume (the functional units of the liver organ) among offspring who were small at birth, with changes suggesting that the fetal liver adopted the role of energy production in lieu of maternal resources (Burns et al., 1997).

While the importance of the postnatal liver's contribution to compensatory mechanisms in response to energy depletion has been long appreciated (Truswell et al., 1969; Cahill, 1970), less is known about how the fetal liver meets prenatal energetic challenge (Shimano et al., 1996; Strauss 2005). To date, attention has focused primarily on the association between fetal growth compromise and a *reduction* in fetal liver volume, following the observations that (1) a small abdominal circumference at birth predicted raised serum concentrations of

total and low density lipoprotein cholesterol in adulthood (Barker et al., 1993), and (2) the interaction between abdominal circumference and birth weight predicted increased risk of death from coronary heart disease (Barker et al., 1995). A predominant explanatory framework following these observations has stressed depleted hepatic glycogen stores (Evans et al., 1983), and blood flow redistribution (Economides et al., 1990), for example. The lack of a consistent finding of reduced liver dimensions among small for gestational age fetuses (Roberts et al., 1999; Senoh et al., 1994), however, may point to the larger scope of adaptive responses that are ongoing in the liver. Further clarification of alternative pathways, involving compensatory liver strategies, may be useful to consider in future research aiming to understand how the fetus confronts energetically challenging circumstances.

Considering Fetal Growth Variability

Implications of fetal growth pattern variability and gestational duration.—The present observations connect altered fetal growth patterns with attenuated gestation duration, and emphasize the need for further basic research. The rapid growth phases among the present sample link phenotypic variability in growth patterns and variability in gestation duration that have been rarely considered (Johnsen et al., 2008; Zhang et al., 2008).

Maternal size effects.—It is notable that the fetuses who experienced an episode of preterm labor received no positive effects of maternal size on body dimensions evident among their peers from uncomplicated pregnancies. One sign that a complicated relationship was ongoing between fetal growth and maternal energy resources is that fetuses delivered after an episode of preterm labor had the paradoxical finding of negative effects from maternal weight/BMI on birth weight. This was specifically investigated as an interaction term between group and maternal size, and is a result contrary to the circumstances among the uncomplicated group. The mechanisms for these findings are not known.

Reflections on the present study.—The patterns of growth across gestational age rely on the accuracy of aging among the sample pregnancies. The LMP was used in this study, confirmed by an ultrasound before 22 weeks of gestation. The margin of error for ultrasound at that gestational age is approximately 1.5 weeks (+/–10 days). If dating was not correct, the error was smaller than the linear regression assessment interval and will be one aspect of the random error component of the individual nested within the group, accommodated by the multi-level model approach used for this analysis. Moreover, any aging errors that may have occurred would be equally likely to have occurred among all pregnancies, and are not likely to be a source of bias in the present study.

The results presented here should not be expected to reflect fetal growth patterns among all samples of fetuses from pregnancies complicated by an episode of preterm labor. Indeed, even within the present population, while maternal height and neonatal weights of the study sample are in line with larger samples from this population (Erazo et al., 2005; González et al., 2004), it cannot be excluded that the present observations reflect sample-specific biological processes that are not identifiable from the data collected in this study. The present observations suggest that further investigation of phenotypic variability in growth patterns related to the timing of preterm labor is an important line of investigation. This

study was not designed to address this question. It is notable that about 24% of the women experiencing an episode of preterm labor were also found to have a medically-diagnosed condition known to affect fetal growth. While it is of interest to understand how these pathologies might be expressed in fetal growth, the sample size in the present data set limited further clarification of growth patterns associated with what are likely to be multiple etiologies underlying the preterm labor syndrome.

Advantages of the present study included the natural history, prospective design which allowed fetal growth patterns to be examined from a relatively robust sample size. Careful attention to clinical details permitted the identification of pregnancies complicated by preterm labor and clarified that few of the study women experienced intra-amniotic infection, reducing the likelihood that infection was causal in the reported patterns. These early life-history details are important for clarifying the context of the observed fetal growth trajectories. The possibility that some women may have experienced preterm labor symptoms, but chose not to present for medical care cannot be ruled out.

Short-comings of the present study included the irregularity of growth assessment timing, necessitating statistical approaches to describe trends in repeated measures and limiting the specificity with which growth rate changes can be confirmed. Likewise, as the mechanisms underlying fetal growth patterns are not confined to maternal signals, the lack of data on father's height was limiting. Father's height effects, such as those mediated through genetic factors on skeletal growth, including IGF-2 imprinting (Godfrey et al., 2005), may contribute both to growth rate and the duration of pregnancy (Lie et al., 2006). Likewise, any population-specific influences remain to be described (e.g., Bennett et al., 2008).

The lack of maternal energetic associations (maternal weight and BMI) on fetal growth among the PTL sample may reflect the realities of how the theoretical construct "maternal constraint" is operationalized (Dunger et al., 2006; Leon, 2008; Ounsted and Ounsted, 1986). Attention to markers of periconceptual nutrition and maternal energetic status during pregnancy would have been helpful in further understanding the results observed in the present study.

Considerations for further research.—The present observations raise questions regarding the sensitivity and specificity of abdominal dimensions, or the composite variable, estimated fetal weight, as indicators of fetal well-being. If, as the growth patterns imply, the fetuses in the present sample were responding to a stressful prenatal environment with abdominal circumference perturbations, single biometric assessments may not be indicative of the fetus under prenatal stress. The dynamic nature of fetal growth across gestation revealed in the present study presents the challenge of translating basic research findings to clinically useful indicators.

Expanding the birth outcome horizon.—The present study observations contribute to an expanding perspective on variability in fetal growth patterns and gestational duration. The clinical narratives of pregnancy history represent trajectories of variable risk, with details that are often missing from both larger epidemiological studies and smaller growth-oriented research. Further collaborations between clinically detailed pregnancy studies and

auxological investigation are likely to provide important insights into the variability of human fetal growth phenotypes. As has become increasingly clear, the mechanisms that underlie these patterns may further elucidate lifespan health.

The present study is important for the identification of perturbations in abdominal circumference trajectories associated with allometric and proportionality differences across gestation. As no abdominal circumference measurements were available at birth among this sample, the data remain suggestive of an important pathway that may underlie the energetic stories behind size at birth and subsequent health risks. The observations of escalating rates of fatty liver among children (Roberts, 2005) suggest this is an important collateral avenue of investigation, as a background to the augmenting metabolic syndrome findings among ever younger ages (Mimoun et al., 2008).

The mechanisms underlying the unique growth patterns described here are unknown. Expanding competences in the identification of biomarkers hold promise of increasing knowledge of the relationships between fetal growth biology and reproductive experience (Romero et al., 2006). Increasing appreciation of the phenotypic variability in fetal growth is likely to be a central advance.

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Figure 1. Estimated fetal weight growth of the sample.

Estimated fetal weight growth compared between fetuses delivered from pregnancies complicated by an episode of preterm labor (PTL, solid lines) and those delivered from uncomplicated pregnancies (dashed lines). Results from multilevel regression implementation of *mkspline, marginal* with nodes at 22 and 28 weeks (STATA 10, Stata Corp., 2007). The results are presented here in two segments for visual clarity, for mid-trimester to the end of the second trimester (upper panel) and the growth pattern from 30 weeks (lower panel). See Table 4 for inferential statistics evaluating the uncomplicated versus PTL differences in the curves. [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]

Figure 2.

By 22 weeks, the fetuses who would experience an episode of preterm labor (solid lines) were larger than their peers from uncomplicated pregnancies (dotted lines), following increased growth trajectories at late mid-trimester for biparietal diameter (BP), femur diaphyseal length (FDL) and abdominal circumference (AC). Sex-adjusted z-scores are in the vertical axis and gestational age in weeks are in the horizontal axis. [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]

Figure 3.

From 22 to 28 weeks, abdominal circumference (AC) faltered among the fetuses from pregnancies complicated by an episode of preterm labor (solid lines), while femur (FDL) and biparietal diameter (BP) continued to grow. Growth among fetuses from uncomplicated pregnancies is illustrated by the dashed lines. Sex-adjusted z-scores are in the vertical axis and gestational age in weeks is in the horizontal axis. [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]

Figure 4.

From 28 to 34 gestational weeks, abdominal circumference growth (AC) increased significantly more among the fetuses from pregnancies complicated by preterm labor (solid lines) in comparison to those from uncomplicated pregnancies (dashed lines). Sex-adjusted z-scores are in the vertical axis and gestational age in weeks is in the horizontal axis. [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]

Figure 5. Growth rates of biparietal diameter (BPD), head circumference (HC) and femur diaphyseal length (FDL) regressed on abdominal circumference growth rate.

Abdominal circumference growth rate positively predicted limb and head growth rates for all fetuses prior to 28 gestational weeks. Among the uncompromised pregnancies (Unc), head dimensions were preferred, with head circumference, biparietal diameter, and femur diaphyseal length receiving positive effects from the midtrimester (< 22 weeks) to mid-gestation (>22 to < 28 weeks). A similar pattern was found among fetuses from pregnancies compromised by an episode of preterm labor (PTL) at the midtrimester, albeit with greater effects on biparietal diameter and femur length ($p=0.07$, $p=0.03$, respectively). Preferential growth of biparietal diameter and femur length were found across mid-gestation ($p<0.05$); multilevel regression with interaction term for group and abdominal circumference growth rate, *xtreg, re*, STATA 10, StataCorp, 2007.)

Figure 6. Head and limb dimensions regressed on abdominal circumference: within- and between-group relationships compared (data from Table 5 with dimensions paired by group). The size of head and limb dimensions are compared between groups in the top panel, controlling for abdominal circumference. Relatively larger sizes were found among the fetuses from pregnancies complicated by an episode of preterm labor (PTL) compared to their peers across mid-gestation (22–28 weeks), and relatively smaller sizes were the case subsequently (28–34 weeks). The bottom panel compares the within-group allometry of head and limb dimensions relative to abdominal circumferences. Among the fetuses who would experience an episode of preterm labor, head and limb dimensions were relatively larger than abdominal circumference across gestation, with a preference for biparietal diameter. Among the fetuses from uncomplicated pregnancies, a modest lag in effects on the femur at mid-gestation was followed by a consistent relationship among all dimensions.

Figure 7. Fetal morphology.

Fetuses exposed to preterm labor (PTL) had significantly larger biparietal diameters and longer femurs relative to their abdominal circumference until 28 weeks compared to their peers from uncomplicated pregnancies. The y-axis represents the differences in regression coefficients for abdominal circumference size noted in Table 5 (PTL minus uncomplicated groups). Compared to their peers from uncompromised pregnancies, each z-score of abdominal circumference predicted significantly larger z-scores for femur and biparietal dimensions among the fetuses who would experience an episode of preterm labor (PTL) prior to 28 weeks, and significantly smaller z-scores subsequently.

TABLE 1.

Maternal characteristics

	Uncomplicated	PTL	<i>p</i> -value
Maternal height (m)	1.56 ¹ (1.52–1.6) 3692	1.56 (1.53–1.6) 174	1.00
Maternal weight (kg)	59 (52–66) 3582	57.5 (50–64) 172	0.46
²Maternal BMI (kg/m²)	23.9 (21.8–26.7) 3574	23.3 (21.1–26.3) 178	0.14
Age (yrs)	25 (21–30) 3628	23.5 (21–26) 170	0.41
Primiparity	35%	38%	0.59
Smoke³	11.1%	9.7%	0.55
Alcohol³	3.7%	2.8%	0.55
Cesarean delivery	17.9%	18.8%	0.77

¹Data are median (interquartile range) and sample size for continuous variables.

²Diagnosed medical complications were entered as a covariate among the PTL group.

³Dichotomous variables: presence/absence of self-reported smoking and alcohol consumption.

TABLE 2.

Fetal characteristics

	Uncomplicated	PTL	<i>p</i> -value
Gestational age at birth (weeks)	¹ 39.7 (38.9–40.4) (3706)	³⁹ (38.2–39.9) ² (176)	0.01
Birth weight (grams)	3420 (3150–3710)	3310 (3090 – 3570)	
³ Birth weight percentile	47 (23–71)	42.5 (28.5–66)	0.10
Males	53 * (29–76)	47 (31–71)	0.32
Females	41 (20–66)	41 (21–61)	1.00
Sex (males)	52.0 %	52.2 %	0.96
Gestational age at PTL (weeks)		32.4 (29.1–34.6)	
Time from PTL to birth (weeks)		6.5 (4.5–10.1)	

¹Data are median (interquartile range) and sample size for continuous variables.

²Fetuses exposed to gestational diabetes excluded.

³Gestational age and sex-corrected percentile by reference to the population (González et al., 2004).

* Within group sex differences ($p < 0.001$ for uncomplicated pregnancies, $p=0.35$ for PTL).

TABLE 3.

Maternal effects on birth weight percentiles

¹ BW %	Uncomplicated β	<i>p-value</i>	² PTL β	<i>p-value</i>	R ²
³ Maternal Height	0.14	<0.001	0.01	0.59 *	0.02
³ Maternal Weight	0.25	<0.001	-0.04	0.01 *	0.06
³ Maternal BMI	0.20	<0.001	-0.04	0.02 *	0.04
Primiparity	-0.16	<0.001	0.01	0.49 *	0.025
Smoking	-0.03	0.06	0.02	0.37 *	0.0002
Age	0.12	<0.001	-0.10	0.10 *	0.01

¹ Gestational age and sex-corrected percentile by reference to the population (González et al., 2004).

² Regression with maternal medical complication as a covariate for BMI.

³ Maternal z-score values were the predictors.

* *p*-value for the interaction term (group and effect).

BW, birthweight; BMI, body mass index.

TABLE 4.

Fetal size, growth rate and change in growth rates at 22, 28 and 34 weeks

Size				Growth rate				Growth rate change
Age ^I	z-score	z	p	Age ^I	slope	z	p	p
Estimated Fetal Weight								
22 ²	-0.42			22 ²	0.22			
PTL	-0.33	2.61	0.01		0.22	1.56	0.11	0.12
28	0.43			22-28 ²	0.15			
PTL	0.45	0.54	0.59		0.13	-2.01	0.045	0.046
34	1.15			28-34 ²	0.12			
PTL	1.18	2.01	0.045		0.13	1.56	0.12	0.06
>34				34 ²	0.05			
PTL					0.04	-0.21	0.82	0.41
Abdominal Circumference								
22	-0.47			22	0.20			0.00
PTL	-0.39	2.41	0.02		0.20	0.98	0.32	0.32
28	0.36			22-28	0.14			0.00
PTL	0.35	-0.15	0.88		0.13	-2.25	0.025	0.05
34	1.23			28-34	0.14			0.67
PTL	1.26	1.62	0.10		0.16	2.11	0.035	0.02
>34				>34	0.07			0.00
PTL					0.07	0.18	0.86	0.33
Head Circumference								
22	-0.53			22	0.19			
PTL	-0.45	2.59	0.01		0.19	1.01	0.31	0.31
28	0.41			22-28	0.17			
PTL*	0.46	1.18	0.24		0.16	-0.23	0.81	0.57
34	1.19			28-34	0.12			
PTL	1.19	0.43	0.67		0.12	-0.21	0.82	0.98
>34 ²				>34	0.05	3.83	0.00	
PTL					0.04	-0.61	0.54	0.70
Biparietal Diameter								
22	-0.53			22	0.18			
PTL	-0.45	2.65	0.01		0.19	2.25	0.025	0.025
28	0.42			22-28	0.16			
PTL	0.46	1.28	0.20		0.15	-1.42	0.16	0.06
34	1.21			28-34	0.13			
PTL	1.24	1.19	0.23		0.14	0.97	0.34	0.21

Size				Growth rate			Growth rate change	
Age ¹	z-score	z	p	Age ¹	slope	z	p	p
>34 ²				>34	0.05			
<i>PTL</i>					<i>0.05</i>	<i>-0.57</i>	<i>0.57</i>	<i>0.40</i>
Femur Diaphyseal Length								
22	-0.52			22	0.19			0.00
<i>PTL</i>	<i>-0.43</i>	<i>2.36</i>	0.02		<i>0.19</i>	<i>0.76</i>	<i>0.45</i>	<i>0.45</i>
28	0.37			22–28	0.16			0.00
<i>PTL</i>	<i>0.44</i>	<i>1.89</i>	<i>0.06</i>		<i>0.15</i>	<i>-0.38</i>	<i>0.71</i>	<i>0.57</i>
34	1.19			28–34	0.13			0.00
<i>PTL</i>	<i>1.23</i>	<i>1.49</i>	<i>0.14</i>		<i>0.14</i>	<i>0.37</i>	<i>0.72</i>	<i>0.70</i>
>34 ²				>34	0.08			
<i>PTL</i>					<i>0.08</i>	<i>-0.35</i>	<i>0.73</i>	<i>0.63</i>

¹ Gestational age in weeks for size and growth rate

² Uncomplicated pregnancy sample contrasted with pregnancies complicated by an episode of preterm labor, shown in italics (*PTL*).

Results of size comparisons assessed as the y-intercept values at 22, 28 and 34 weeks from the piecewise regression investigating growth rates and growth rate changes between groups. The inflection points represent slopes compared between ages 16 and 22 weeks, >22 and 28 weeks, and >28 to 34 weeks. The analysis represents the results from a multilevel model with individuals nested in groups. The approach permitted both slopes and intercepts to vary, to account for individual and group differences in growth rates (*xtmixed, mle*, STATA 10, Stata Corp. 2007). Significant effects in bold.

TABLE 5.

Regression coefficients for head and limb dimensions regressed on abdominal circumference

Uncomplicated Preterm Labor					
	Coefficient	Coefficient	<i>z</i>	<i>p</i> -value	* <i>R</i> ²
Femur diaphyseal length					
22					0.98, 0.91, 0.92
<i>I</i> _{Size}	−2.01	−1.95	1.11	0.27	
² _{AC}	0.62	0.67	1.36	0.17	
22–28					0.82, 0.43, 0.45
<i>I</i> _{Size}	−0.01	0.03	2.71	0.01	
² _{AC}	0.63	0.82	2.89	0.004	
28–34					0.73, 0.28, 0.35
Size	0.53	0.42	−2.27	0.02	
AC	0.45	0.54	2.10	0.04	
Head circumference					
22					0.95, 0.97, 0.96
<i>I</i> _{Size}	−1.66	−1.60	1.58	0.12	
² _{AC}	0.70	0.75	1.79	0.07	
22–28					0.55, 0.44, 0.45
Size	0.02	0.06	2.39	0.02	
AC	0.72	0.79	1.10	0.27	
28–34					0.73, 0.28, 0.34
Size	0.52	0.46	−1.38	0.24	
AC	0.46	0.52	1.20	0.23	
Biparietal diameter					
22					0.98, 0.95, 0.96
<i>I</i> _{Size}	−1.66	−1.58	2.14	0.03	
² _{AC}	0.68	0.74	2.34	0.02	
22–28					0.86, 0.44, 0.47
Size	−0.01	0.05	3.29	0.001	
AC	0.72	0.89	2.38	0.02	
28–34					0.74, 0.25, 0.32
<i>I</i> _{Size}	0.52	0.40	−2.14	0.03	
AC	0.46	0.58	2.18	0.03	

*I*_{Size} controlling for abdominal circumference.² Interaction between group and abdominal circumference.**R*² within group, between groups and overall (*xtreg*, *re*). All variables were *z*-score values.

Maternal height (MH), maternal weight (MW), and maternal body mass index (BMI) effects on fetal abdominal circumference (AC), head circumference (HC), biparietal diameter (BP), femur diaphyseal length (FDL) compared for fetuses from uncomplicated pregnancies (Unc) and those complicated by an episode of preterm labor (PTL). All variables are z-scores. Significant effects are in bold.

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