Animal studies indicate that either the fetus or the intrauterine environment, both of which set the pattern for fetal growth, may affect the timing of parturition. The authors examined the association between fetal growth and timing of spontaneous onset of labor in humans among low-risk white US women with singleton pregnancies (1987–1991). They restricted the data to pregnancies which had a reliable date of the last menstrual period, normal fetal growth in the first half of pregnancy, and no history of or current pregnancy complications that might have impaired fetal growth (n = 3,360). Subjects received ultrasound examinations at 15–22 and 31–35 weeks' gestation. Fetal growth was adjusted for parity, fetal sex, and maternal prepregnancy weight and height. Results showed that slower or faster fetal growth in the second half of pregnancy resulted in substantially lower or higher birth weight, respectively. However, fetal growth in the second half of pregnancy, even at extremes (2 standard deviations below or above the mean), did not have a meaningful impact on the timing of parturition; neither did fetal growth acceleration or deceleration in late pregnancy. Thus, in low-risk pregnancies where fetal growth is normal in early gestation, fetal growth in the second half of pregnancy does not affect the timing of normal parturition.

Animal studies indicate that either the fetus or the intrauterine environment may affect the timing of parturition (1). For example, studies carried out in sheep and cows have demonstrated that activation of the fetal hypothalamic-pituitary-adrenal axis plays an essential role in the initiation of labor (2). Timing of birth in mice is closely linked to maturation of the fetal lungs (2). Furthermore, in primates, an adverse intrauterine environment may activate the fetal hypothalamic-pituitary-adrenal axis and result in impaired fetal growth and premature (but not necessarily preterm) onset of parturition (3). These findings have led to speculation that an unfavorable intrauterine environment might trigger earlier parturition in humans.

However, the mechanisms of normal parturition differ substantially between humans and animals (4, 5), and most in vivo experiments conducted in primates cannot ethically be replicated in humans. Therefore, the role the fetus and intrauterine environments may play in the timing of human parturition is much less clear.

Another long-standing statistical challenge in studying the timing of human parturition is medical intervention, that is, induction of labor or elective cesarean delivery. Spontaneous physiologic processes are not observed in these women. These interventions occur more frequently in complicated pregnancies with fetal growth restriction. Furthermore, the more severe the fetal growth restriction is, the more likely the baby is to be delivered through medical intervention. This selective (informative) censoring can substantially distort findings regarding the relation between fetal growth (a proxy for intrauterine environment and fetal maturity) and timing of normal parturition if a correct statistical method is not used to minimize its impact.

In the current analysis, we used data from a large, prospective cohort study carried out in a low-risk population of...
pregnant women. We restricted the data to pregnancies which had a reliable date of the last menstrual period (LMP) and normal fetal growth in the first half of pregnancy. We used a competing-risks model to examine whether fetal growth in the second half of pregnancy was associated with the timing of spontaneous onset of labor.

MATERIALS AND METHODS

Study population

The Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS) Trial was a multicenter US study of pregnant women at low risk for adverse outcomes. The trial was designed to test the hypothesis that routine screening with standardized ultrasonography on 2 occasions would reduce perinatal morbidity and mortality. The institutional review boards at all study sites approved the protocol.

A detailed description of the trial is provided elsewhere (6). Briefly, from November 1987 to May 1991, pregnant women who were 18 years of age or older, who spoke English, whose LMP was known within 1 week, and whose gestational age was less than 18 weeks at recruitment were designated as potentially eligible for the study. Excluded were women with a previous stillbirth, a prior small-for-gestational-age infant, irregular menstrual cycles, a discrepancy between uterine size and dates of more than 3 weeks, diabetes, chronic hypertension, or chronic renal disease. Eligible women were randomly assigned to either the ultrasound-screening group or the control group. Women in the ultrasound-screening group underwent sonographic examinations at 15–22 and 31–35 weeks' gestation.

Women were interviewed at recruitment. Information on demographic characteristics and reproductive history was recorded. Antepartum, intrapartum, and neonatal information was abstracted from the antenatal medical records and from inpatient hospital records. All ultrasound examinations were performed in one of the 28 ultrasound laboratories participating in the RADIUS Trial. Sonographic biometry of the fetus included biparietal diameter, head circumference, abdominal circumference, and femur length. Quality control procedures for ultrasonography and data abstraction were implemented (details given previously (6)).

A total of 15,151 women were recruited for the RADIUS Trial. By means of a computer-generated scheme, 7,617 subjects were individually randomized to the screening group and 7,534 subjects were randomized to the control group. We used data from women who were randomized to the ultrasound-screening group (n = 7,617). Multifetal pregnancies were excluded (n = 68). Because over 90% of the subjects in the RADIUS Trial were white and the ultrasound standards for dating and for fetal weight estimation were derived from white populations (7, 8), we limited our study to white women (n = 7,026). We further excluded stillbirths and babies with any congenital anomalies based on neonatal diagnosis (n = 238), women who had previously had a low-birth-weight baby (n = 53), and women with any of the following complications in the current pregnancy: antepartum vaginal bleeding, placenta previa, placental abrup-

tion, or pregnancy-related hypertensive disorders (n = 361). This left 6,374 subjects for analysis.

First day of the LMP

Women reported their first day of the LMP at enrollment. We used ultrasound measurements of their first fetal biometry to validate gestational age using Hadlock's formula (7) and calculated an ultrasound-based LMP. We restricted our study population to women whose self-reported LMP was within 3 days of the ultrasound-based LMP (n = 3,360). This restriction essentially screens out pregnancies with fetal growth restriction or overgrowth in the first half of pregnancy, because ultrasound dating uses fetal size to estimate duration of gestation. A large fetus is assigned to a longer gestation, while a small fetus is assigned to a shorter gestation, irrespective of whether fetal growth is normal. When the self-reported LMP and the ultrasound dating match, the fetus is most likely to have had normal growth. Since most of our subjects underwent the first ultrasound examination at 18–20 weeks, it is reasonable to assume that fetal growth had been normal in the first half of these pregnancies. Self-reported LMP was used as the starting point for calculation of gestational age.

Estimated fetal weight and adjusted fetal growth

Estimated fetal weight was calculated on the basis of head and abdominal circumferences and femur length (8). Ultrasound measurements taken between 17 and 21 weeks and between 31 and 34 weeks were used to calculate the estimated fetal weight for early and late pregnancy. Only trial-assigned ultrasound measurements were used. Birth weight was used as fetal weight at delivery; that is, each fetus had 3 data points.

For each fetus, the difference in estimated fetal weights between two time points was first calculated, which represents fetal growth. The distribution of estimated fetal weight differences was normal. We then used multiple linear regression to adjust for several other variables. For example, to assess fetal growth between the first (e.g., at 18 weeks) and second (e.g., at 32 weeks) ultrasound examinations, we used the following model: difference in estimated fetal weight (between 18 and 32 weeks) = day of first examination (day 126) + estimated fetal weight at 126th day + days between the 2 examinations + sex of the fetus (male vs. female) + parity (0 vs. ≥1) + maternal prepregnancy weight + maternal height. Based on the above model, a z score was calculated as (observed difference in estimated fetal weight – expected difference in estimated fetal weight)/standard deviation (SD) for each fetus. This z score represents fetal growth between 18 and 32 weeks, adjusted for sex, parity, and maternal prepregnancy body mass. If a fetus has a z score of −2, its growth is 2 SD below what it should be during that period given the fetus’s sex, parity, and the mother’s prepregnancy weight and height and in relation to all other subjects in the cohort. We then examined the relation between adjusted fetal growth and duration of gestation.
Fetal growth acceleration or deceleration

We compared growth during 2 periods: from 17–21 weeks to 31–34 weeks (V1) and from 31–34 weeks to delivery (V2). V1 and V2 were expressed as z scores (described above). If V2 − V1 was positive, indicating that fetal growth was faster in the second period than in the first period, the fetus was considered to have undergone growth acceleration or catch-up growth in the second period. If V2 − V1 was negative, the fetus was considered to have undergone growth deceleration or a slowdown in growth. We then examined the relation between growth acceleration and deceleration and duration of gestation.

Other variables

Onset of labor was categorized as spontaneous, premature rupture of the fetal membranes, or prelabor induction or cesarean delivery (called elective delivery hereafter). Other maternal and fetal characteristics used in our analysis included maternal age, education, smoking at enrollment, history of macrosomia birth, and blood pressure at enrollment.

Statistical analysis

We used chi-squared tests and analysis of variance for categorical and continuous variables, respectively. Because onset of labor had 3 mutually exclusive causes—spontaneous, premature rupture of the fetal membranes, or elective—and the presence of one cause precluded any possibility of the others, we used a competing-risks model. The only assumption that the model makes about time to onset of labor due to different causes is that a woman cannot encounter distinct types of labor onset at the same instant.

In constructing the competing-risks model, we first used a Cox proportional hazards model to estimate the cause-specific hazard ratio for each of the 3 causes separately. Duration of gestation from LMP to delivery was used as the time to event. Common risk factors that may affect onset of labor (listed above) were included in the model. To assess the probability of spontaneous onset of labor by a certain time in the presence of competing causes, we calculated the predicted cumulative incidence of spontaneous onset of labor by gestational age (in days). We computed an array of cumulative incidence functions based on specific (fixed) maternal characteristics but various fetal growth velocities. The predicted cumulative incidence function of spontaneous onset of labor takes into account other competing causes of labor onset. The differences in the predicted cumulative incidence at a given gestational age reflect the effects of fetal growth on spontaneous onset of labor. A detailed description of the competing-risks model is provided elsewhere (9).

RESULTS

In this low-risk white population, the mean maternal age was 28 years (SD, 4); 46% of the women were nulliparous; and 72% had some college education or were college graduates. The mode of labor/delivery was spontaneous onset for 69%, premature rupture of the fetal membranes for 8%, and elective delivery for 23%.

Table 1 presents data on birth weight, mode of labor/delivery, and duration of gestation according to adjusted fetal growth. From early in the second trimester to delivery, infants who grew very slowly (2 SDs below the mean or ≤−2 SDs) had much lower birth weights (mean birth weight = 2,685 g) than infants with normal growth (mean birth weight = 3,515 g; P < 0.001). Growing too slowly or too quickly was more likely to result in elective delivery (P < 0.01). Fetal growth at the extremes (≤−2 SDs or ≥2 SDs) was associated with a gestation period that was longer by 2–3 days than that of normal fetal growth (analysis of variance: P < 0.01). However, there was no uniform direction or clear dose-response pattern.

We then divided the whole duration into 2 periods (Table 2). From early in the second trimester to the middle of the third trimester (period 1), duration of gestation appeared to be slightly shorter in pregnancies with either fetal growth restriction (≤−2 SDs) or overgrowth (≥+2 SDs) by 2–3 days,
on average, than in pregnancies with normal fetal growth (analysis of variance: $P = 0.19$). However, from the middle of the third trimester to delivery (period 2), both slower growth ($\leq -2$ SDs) and faster growth ($\geq +2$ SDs) seemed to be associated with a longer duration of gestation ($P < 0.01$), which is the opposite of the finding in period 1. Again, there was no uniform direction or clear dose-response pattern.

Table 3 shows how fetal growth acceleration or deceleration between periods 1 and 2 may affect duration of gestation. Although growth deceleration or acceleration resulted in lower or higher mean birth weight, respectively ($P < 0.01$), it did not have substantive effects on duration of gestation ($P > 0.05$).

Finally, we used a competing-risks model to examine whether fetal growth was associated with spontaneous onset of labor, taking the risks of premature rupture of the fetal membranes and elective delivery into account. Figure 1 shows the predicted cumulative incidence of spontaneous

Table 2. Fetal Growth During 2 Periods of Pregnancy, Mode of Labor/Delivery, and Duration of Gestation in Low-Risk White US Women, 1987–1991

<table>
<thead>
<tr>
<th>Fetal Growtha</th>
<th>No. of Subjects</th>
<th>Mean Birth Weight, g</th>
<th>Mode of Labor/Delivery, %</th>
<th>Mean Duration of Gestation, days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spontaneous Onset of Labor</td>
<td>Premature Rupture of Fetal Membranes</td>
</tr>
<tr>
<td>Adjusted fetal growth during the period from 17–21 weeks to 31–34 weeks (period 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$-2$ SDs or below</td>
<td>63</td>
<td>3,064</td>
<td>76</td>
<td>13</td>
</tr>
<tr>
<td>Between $-1$ and $-2$ SDs</td>
<td>386</td>
<td>3,275</td>
<td>74</td>
<td>7</td>
</tr>
<tr>
<td>Within $\pm 1$ SD</td>
<td>2,222</td>
<td>3,539</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>Between $+1$ and $+2$ SDs</td>
<td>352</td>
<td>3,799</td>
<td>69</td>
<td>8</td>
</tr>
<tr>
<td>$+2$ SDs or above</td>
<td>78</td>
<td>4,013</td>
<td>61</td>
<td>17</td>
</tr>
<tr>
<td>Adjusted fetal growth during the period from 31–34 weeks to delivery (period 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$-2$ SDs or below</td>
<td>69</td>
<td>2,842</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>Between $-1$ and $-2$ SDs</td>
<td>397</td>
<td>3,109</td>
<td>75</td>
<td>9</td>
</tr>
<tr>
<td>Within $\pm 1$ SD</td>
<td>2,312</td>
<td>3,523</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>Between $+1$ and $+2$ SDs</td>
<td>372</td>
<td>4,013</td>
<td>67</td>
<td>8</td>
</tr>
<tr>
<td>$+2$ SDs or above</td>
<td>88</td>
<td>4,395</td>
<td>65</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

a Fetal growth was adjusted for sex of the fetus, parity, and maternal prepregnancy weight and height.

b Numbers in parentheses, SD.

Table 3. Fetal Growth Acceleration and Deceleration in Late Pregnancy, Mode of Labor/Delivery, and Duration of Gestation in Low-Risk White US Women, 1987–1991

<table>
<thead>
<tr>
<th>Fetal Growtha</th>
<th>No. of Subjects</th>
<th>Mean Birth Weight, g</th>
<th>Mode of Labor/Delivery, %</th>
<th>Mean Duration of Gestation, days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spontaneous Onset of Labor</td>
<td>Premature Rupture of Fetal Membranes</td>
</tr>
<tr>
<td>Deceleration by 2 SDs or more</td>
<td>222</td>
<td>3,393</td>
<td>75</td>
<td>9</td>
</tr>
<tr>
<td>Deceleration by 1–2 SDs</td>
<td>478</td>
<td>3,465</td>
<td>70</td>
<td>8</td>
</tr>
<tr>
<td>Within 1 SD</td>
<td>1,698</td>
<td>3,520</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>Acceleration by 1–2 SDs</td>
<td>466</td>
<td>3,629</td>
<td>71</td>
<td>7</td>
</tr>
<tr>
<td>Acceleration by 2 SDs or more</td>
<td>237</td>
<td>3,768</td>
<td>70</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation.

a Fetal growth was adjusted for sex of the fetus, parity, and maternal prepregnancy weight and height.

b Numbers in parentheses, SD.
onset of labor by day of gestation in the presence of competing risks. Pregnancies with slow fetal growth (at −2 SDs) tended to have a slightly later parturition than pregnancies with normal (at 0 SDs) or fast (at +2 SDs) growth. For example, by 280 days, 56% of women with normal fetal growth had delivered. The corresponding percentages were 55% and 51% for women with fast and slow fetal growth, respectively. The 95% confidence intervals for all 3 curves overlapped substantially (not shown), indicating that the differences were not statistically significant.

**DISCUSSION**

Our prospective study showed that in low-risk pregnancies, when fetal growth is normal in early gestation, fetal growth in the second half of pregnancy, even at extremes (2 SDs above or below the mean), is not associated with the timing of spontaneous onset of labor; neither is growth acceleration or deceleration in late pregnancy.

Our findings seem to contradict another line of epidemiologic evidence. Studies with mixed high- and low-risk populations have shown that women with spontaneous preterm labor tend to have a significantly higher proportion of babies that are small for gestational age at birth (10–14). Does this suggest that the fetus may have initiated premature parturition due to a poor intrauterine environment as demonstrated in animal models (3)? Not necessarily. Preterm labor often involves pathways that are very different from those of normal parturition at term (e.g., intrauterine infection) (5). Confounding may also play a role in this association. For instance, poor placental implantation and development could cause both fetal growth restriction and early parturition (15). Low socioeconomic status may affect fetal growth, risk of intrauterine infection, and preterm labor (16). In both cases, the association between fetal growth and timing of parturition is not causal but a correlation. To avoid such potential confounding, we selected low-risk pregnancies that had normal fetal growth in the first half of gestation.

The mechanism initiating human parturition remains elusive. In recent years, a “placental clock” theory appears to have gained attention. Smith et al. (2, 17) have proposed that the timing of parturition is associated with gene expression and exponential production of corticotropin-releasing hormone by the placenta. Placental corticotropin-releasing hormone enters both maternal and fetal circulation and, in turn, stimulates the maternal and fetal pituitary glands to produce adrenocorticotropin hormone, which causes the maternal and fetal adrenal cortex to release cortisol. Cortisol further stimulates placental production of corticotropin-releasing hormone in a positive feedback mechanism (18). A cascade of biochemical reactions ensues, including production of prostaglandins and oxytocin, and labor starts. (A detailed description of endocrine pathways is provided elsewhere (5).) This theory suggests that the placenta rather than the fetus may be the initiator in normal human parturition.

Several limitations of our study should be noted. First of all, our ultimate goal was to test whether the fetus and the intrauterine environment play a role in the timing of normal human parturition. However, our study lacked objective and accurate measures of fetal and maternal endocrine pathways and “intrauterine environment.” Fetal growth is implied as a surrogate measure in the current investigation. Because fetal growth is a crude proxy for intrauterine environment, we can only report the association between fetal growth and the timing of parturition; we can make no further inferences.

Second, ultrasound estimation of fetal weight using the Hadlock formula (8) has an average error of 8%–10% when compared with actual birth weight (19). The error comes from both measurement error and inaccurate estimation by the formula. This misclassification is likely to be nondifferential. Thus, our results may have been drawn towards the null to an unknown degree. However, all sonographers in this trial were trained, and the measurements were taken in a standardized fashion with well-implemented quality control procedures. Furthermore, given the fact that even at fetal growth extremes the duration of gestation did not vary substantially, nor did the association have a consistent pattern, we do not believe that our main findings (in Table 1) can be totally explained by ultrasound errors. Nonetheless, the latter may to some degree explain the seemingly contradictory patterns in Table 2.

Our study had several distinct strengths. It was a large, prospective study. All women must have had regular menstrual cycles, firm LMP dates, and low-risk pregnancies. Ultrasound examinations were conducted in a systematic and controlled manner. Use of the competing-risks model further minimized the impact of elective delivery (i.e., informative censoring) on the timing of spontaneous onset of labor.

In summary, our study shows that in low-risk pregnancies, when fetal growth is normal in early gestation, fetal growth during the second half of gestation has little impact on the timing of spontaneous onset of labor.
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The opinions and assertions contained herein are those of the authors and do not necessarily reflect the views of the above investigators.

Conflict of interest: none declared.

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