Balancing the risks of stillbirth and neonatal death in the early preterm small-for-gestational-age fetus

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OBJECTIVE: Timing of delivery for the early preterm small-for-gestational-age (SGA) fetus remains unknown. Our aim was to estimate the risk of stillbirth in the early preterm SGA fetus compared with the risk of neonatal death.

STUDY DESIGN: We performed a retrospective cohort study of singleton pregnancies that underwent second-trimester anatomy ultrasound (excluding fetal anomalies, aneuploidy, and pregnancies with incomplete neonatal follow-up data). *SGA* was defined as birthweight <10th percentile by the Alexander standard. Life-table analysis was used to calculate the cumulative risks of stillbirth per 10,000 ongoing SGA pregnancies and of neonatal death per 10,000 SGA live births for 2-week gestational age strata in the early preterm period (24-33 weeks 6 days of gestation). We further examined the composite risk of expectant management and then compared the risk of expectant management with the risk of immediate delivery.

RESULTS: Of 76,453 singleton pregnancies, 7036 SGA pregnancies that met inclusion criteria were ongoing at 24 weeks of gestation; there were 64 stillbirths, 226 live births, and 18 neonatal deaths from 24-33 weeks 6 days of gestation. As the risk of stillbirth increases with advancing gestational age, the risk of neonatal death falls, until the 32-33 weeks 6 days of gestation stratum. The relative risk of expectant management compared with immediate delivery remains <1 for each gestational age strata.

CONCLUSION: Our findings suggest that the balance between the competing risks of stillbirth and neonatal death for the early preterm SGA fetus occurs at 32-33 weeks 6 days of gestation. These data can be useful when delivery timing remains uncertain.

Key words: fetal growth restriction, preterm, SGA, stillbirth

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The small for gestational age (SGA) fetus carries an increased risk for stillbirth.[1] When SGA is diagnosed in the early preterm period, the clinician is faced with a difficult scenario. The decision to abandon expectant management and proceed to delivery to avoid stillbirth must be delicately balanced with the risks of prematurity and neonatal death.

The first randomized trial on delivery timing in the preterm fetus who is estimated to be growth restricted demonstrated that early delivery to avoid stillbirth was counterbalanced by neonatal death.[2] Further, long-term follow-up examination showed no difference in childhood neurologic outcomes, which suggests that progressive fetal exposure to hypoxemia and acidemia with expectant management may not be associated with irreversible neurologic impairment as previously thought.[3] Additionally, in a prospective study of fetuses who were estimated to be SGA with evidence of placental dysfunction, gestational age at delivery was demonstrated to be the dominant risk factor for neonatal outcomes relative to other risk factors for neonatal morbidity.[4] Although the complications of prematurity weigh heavily on the decision to deliver, it is only the surviving fetus who will go on to become a neonate and the surviving neonate who will go on to experience the sequelae of prematurity. Therefore, the first step in clarification of the optimal timing of delivery for the preterm SGA fetus to understand the competing risks of death, stillbirth, and neonatal death. The objective of our investigation was to estimate the risk of stillbirth compared with the risk of neonatal death in the early preterm SGA fetus.

Methods

We conducted a retrospective cohort study of singleton pregnancies presenting to Washington University School of Medicine perinatal ultrasound units for routine anatomic survey from 1990-2009. We used the perinatal database at Washington University. Our medical center is an academic tertiary care center that serves as a major regional and national referral center. Our perinatal database is

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a large, well-maintained system with dedicated research personnel for the collection of data and maintenance. Self-report questionnaires are used to collect maternal demographic information and medical and obstetric histories. The questionnaires are administered at the initial ultrasound visit. Follow-up information is obtained by trained research personnel from the medical record. In the event that the patient delivers outside of the medical system, follow-up information is obtained through telephone contact with the patient and/or referring physician. Further details of data collection and management have been published previously.[5]

Ultrasound scans were performed by certified sonographers dedicated to performing obstetric and gynecologic examinations. Final diagnosis was made by the attending maternal fetal medicine physician. The gestational age was assigned by ultrasound dates if >5 days from last menstrual period in the first trimester or >10 days from last menstrual period in the second trimester. SGA was assigned by birthweight using the population-based chart published by Alexander et al[6] and defined as birthweight <10th percentile for the gestational age at delivery. We excluded pregnancies that were complicated by prenatally diagnosed major fetal anomalies and aneuploidy and those that were without neonatal follow-up information or birthweight data (Figure 1).

Given that our aim was to compare the risks of stillbirth with neonatal death in the early preterm period, we examined the risks of stillbirth and neonatal death from 24-33 weeks 6 days of gestation utilizing the method of life-table analysis described by Smith.[7] First, we calculated the risk of stillbirth by week. Within our database, *stillbirth* is defined as intrauterine fetal death at ≥20 weeks of gestation but deliveries at <24 weeks of gestation or at ≥34 weeks of gestation were excluded from the analyses in accordance with the aim of this study. We calculated the conditional probability of stillbirth per 10,000 ongoing SGA pregnancies. To account for censoring, deliveries that may have occurred during the particular time period for which the probability was calculated, one-half of the deliveries during that time period were subtracted from the denominator. Therefore, the conditional probability (P) of stillbirth (SB) during time period n given ongoing SGA pregnancies at the beginning of that time period n is (OPn) and the number of births B: P(SB)n = SBn/(OPn-1/2Bn).

The clinical question of timing of delivery is not limited to the conditional probability of stillbirth because, if expectant management is chosen, then the fetus remains in utero during this time period and is exposed to the risks of stillbirth in the weeks preceding delivery. Therefore, the risk of stillbirth for the fetus at 28 weeks of gestation that is currently in utero at 26 weeks of gestation is the cumulative probability of stillbirth at 26, 27, and 28 weeks of gestation. The cumulative probabilities of stillbirth were calculated from the conditional probabilities as 1 − (probability of survival), where the probability of survival is 1 − (probability of death). Therefore, the cumulative probability (CP) of stillbirth (SB) during time n: CP(SB)n = 1 − [(1 − Cn_1)(1 − Cn_2)…..(Cn_x)].

To compare the risk of stillbirth with the risk of neonatal death over time, the risk of neonatal death was calculated per live births. *Neonatal death* was defined as death by 30 days of life. Neonatal deaths were relatively rare; therefore, gestational age strata were collapsed into 2-week intervals. The conditional probability (P) of neonatal death (D) during time period n with live births (L) was calculated as: P(D)n = Dn/Ln.

To compare the risk of neonatal death to the risk of stillbirth over time, we then collapsed stillbirths into 2-week strata and calculated the conditional and cumulative probabilities of stillbirth for each stratum. To explore a lower threshold of SGA, a secondary analysis was performed to evaluate the risks of neonatal death and stillbirth with SGA defined by birthweight <5th percentile.

Finally, because the cumulative probability is a retrospective calculation used to project risk into the future and the point in time when SGA was diagnosed is not known, we also took a prospective approach to the probability of death by estimating the relative risk of expectant management for 2 weeks compared with immediate delivery, as previously described by Rosenstein et al.[8] Using this approach, the composite risk of expectant management for a time period is the sum of the conditional probability of stillbirth during that time period and the probability of neonatal death in the following time period. This method assumes delivery in the subsequent interval of time.

Descriptive statistics were used to calculate maternal characteristics of SGA pregnancies that delivered from 24-33 weeks 6 days of gestation for stillbirths, neonatal deaths, and neonates who survived >30 days of life. The cumulative risk of stillbirth with 95% confidence interval (CI) and the risk of neonatal death with 95% CI were calculated for the 2-week gestational age strata as stated earlier, then risk ratios with 95% CI were determined. Given the 20-year study period, sensitivity analysis was performed to assess changes in clinical practice or technology over time. The risk of stillbirth among SGA pregnancies that delivered at >24 weeks of gestation was assessed and compared using χ^2 for 2 time periods that were determined by days from initiation of enrollment of 50% of the study cohort. Statistical analysis was calculated with STATA software (version 12; StataCorp, College Station, TX).

Results

Of 76,453 singleton pregnancies, there were 7036 ongoing SGA pregnancies at 24 weeks of gestation that met the inclusion criteria and 290 SGA births from 24-33 weeks 6 days of gestation. Figure 1 shows the details of the study population and breakdown of the outcomes of SGA births. Table 1 demonstrates relevant maternal demographic characteristics of the ongoing SGA pregnancies that delivered from 24-33 weeks 6 days gestation that resulted in stillbirth, neonatal death, or neonatal survival at >30 days of life.

The number of ongoing SGA pregnancies, stillbirths, live births, and neonatal deaths per week is given in Table 2 along with the conditional and cumulative probabilities of stillbirth per 10,000 ongoing SGA pregnancies. With increasing gestational age, the