OBSTETRICS

Perinatal mortality in second- vs firstborn twins: a matter of birth size or birth order?

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OBJECTIVE: Second-born twins on average weigh less than first-born twins and have been reported at an elevated risk of perinatal mortality. Whether the risk differences depend on their relative birth size is unknown. The present study aimed to evaluate the association of birth order with perinatal mortality by birth order—specific weight difference in twin pregnancies.

STUDY DESIGN: In a retrospective cohort study of 258,800 twin pregnancies without reported congenital anomalies using the US matched multiple birth data 1995-2000 (the available largest multiple birth dataset), conditional logistic regression was applied to estimate the odds ratio (OR) of perinatal death adjusted for fetus-specific characteristics (sex, presentation, and birthweight for gestational age).

RESULTS: Comparing second vs first twins, the risks of perinatal death were similar if they had similar birthweights (within 5%) and were increasingly higher if second twins weighed progressively less (adjusted ORs were 1.37, 1.90, and 3.94 if weighed 5.0-14.9%, 15.0-24.9%, and ≥25.0% less, respectively), and progressively lower if they weighed increasingly more (adjusted ORs were 0.67, 0.63, and 0.36 if weighed 5.0-14.9%, 15.0-24.9%, and ≥25.0% more, respectively) (all $P < .001$). The perinatal mortality rates were not significantly different in cesarean deliveries or preterm (<37 weeks) vaginal deliveries but were significantly higher in second twins in term vaginal deliveries (3.1 vs 1.8 per 1000; adjusted OR, 2.15; $P < .001$).

CONCLUSION: Perinatal mortality risk differences in second vs first twins depend on their relative birth size. Vaginal delivery at term is associated with a substantially greater risk of perinatal mortality in second twins.

Key words: birth order, birthweight difference, perinatal mortality, twins

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Twins account for an increasingly higher proportion of births over recent decades, rising from 18.9 per 1000 births in 1980 to 33.2 per 1000 births in 2009 in the United States,[1,2] a relative increase of 75%. Perinatal health care expenses cost about 5 times more for twins than for singletons.[3] Twins are at 2-4 times higher risk of perinatal mortality than singletons.[4]

Studies have reported an increased risk of perinatal death comparing second-born vs first-born twins.[5-9] It has been proposed (but not yet validated) that this may be mainly a problem of more stillbirths in the second twins,[5] or this may be restricted to term deliveries.[9] In the absence of congenital anomalies, birthweight and gestational age are well-known major determinants of perinatal mortality. As a twin pair is delivered to the same mother usually at the same gestational age, birthweight or fetal growth is likely a major contributor to perinatal mortality risk difference between second and first twins.

Previous studies have shown that second twins on average weigh less than first twins,[6] and birthweight discordant twin pairs have higher perinatal mortality rates than nondiscordant twin pairs[10,11] but have not considered birth order—specific weight difference (which one is heavier?) in comparing perinatal mortality risk differences between second and first twins. We hypothesize that the perinatal mortality risk difference in second-born vs first-born twins depends on their relative birth size. The primary objective of the present study was to evaluate the association of birth order with perinatal mortality by birth order—specific weight difference in twin pregnancies.

Materials and Methods

This was a retrospective cohort study of twin births, using the US National Center for Heath Statistics's (NCHS) 1995-2000 matched multiple birth data set (the largest available linked multiple birth dataset).[12] The NCHS-matched

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multiple birth data contain information on maternal and pregnancy characteristics and perinatal and infant mortality for all multiple births in years 1995-2000 in the Unites States. There were a total of 658,424 twin births.

Because the study aimed to evaluate the association of birth order with perinatal mortality, we excluded unmatched twins and births with unknown birth order (n = 77,685 births) (11.8%). Overall perinatal mortality rate was much higher for births with vs without missing data on birth order (116.3 vs 34.5 per 1000; $P < .001$).

Because the study's main aim was to determine the effect of birth order on perinatal mortality by birth order–specific weight difference, we further excluded: (1) twin pairs with any reported congenital anomalies in either twin (first or second); (2) twin pairs missing data on birthweight in either twin; (3) births recorded at extreme gestational ages (<23 weeks or >42 weeks) or extreme birthweights (<500 g or >6000 g) or implausible birthweight for gestational age[13]; and (4) twin sets not delivered at the same gestational week.

The final study cohort included 517,600 twin births in 258,800 twin pregnancies. Research ethics approval was waived by the Shanghai Xinhua hospital Research Ethics Board because the study was based on the anonymized matched multiple birth dataset downloadable from the NCHS web site.

The NCHS multiple birth dataset contained variables on fetal sex (boy/girl), presentation (breech/malpresentation, yes/no) (missing 1.0%), mode of delivery (cesarean/vaginal) (missing 0.7%), induction or stimulation of labor (missing 0.8%), prolonged (defined as >20 hours) or dysfunction labor (yes/no) (missing 1.0%), fetal distress (missing 6.8%), gestational age (weeks), and birthweight (grams). The NCHS birth database contained an indicator variable for breech/malpresentation (impossible to distinguish between breech and other malpresentations). If the answer was a no, we classified the fetus as normal vertex presentation.

The NCHS birth database contained indicator variables for primary cesarean section and repeat cesarean section. If the answer was a yes to either question, we classified the birth as cesarean delivery; if the answer was a no to both questions, we classified the birth as vaginal delivery. The NCHS birth database contained 21 items for reporting 20 specific and other congenital anomalies. These fields were used to capture and exclude twin pairs with any reported congenital anomaly in either twin (first or second born). Fetal distress in the NCHS data is a nondescriptive term equivalent to the most contemporary use of the term nonreassuring fetal status.

The primary outcome was perinatal death because it is a more robust indicator of mortality risk than stillbirth and neonatal death that are influenced by variations in personal judgments and registration practices (whether a dead newborn is registered as a stillbirth or neonatal death), especially for births at borderline of viability.[14] Secondary outcomes included the components of perinatal death-stillbirth (fetal deaths at a gestation of ≥20 weeks) and neonatal death (deaths during the first 4 weeks or 0-27 days of life after birth).

Cause-specific neonatal mortality were analyzed according to the classification scheme by International Collaborative Effort on Perinatal and Infant Mortality for asphyxia and injuries (may be related to delivery), immaturity-related conditions, infections, sudden infant death syndrome, and others.[15] Causes of death are missing for all stillbirth records in the NCHS birth data.

The primary exposure of interest was birth order. Because it is very unlikely that a second twin was delivered vaginally following delivery of a first twin by cesarean section in a twin set, the frequency of such implausible records was used as an indicator of data quality in birth order. There were 782 pairs of first twin cesarean–second twin vaginal (implausible) births, and 10,959 pairs of first twin vaginal–second twin cesarean (plausible) births, indicating a birth order recording error rate of about 6.7%. Birth order was reversed to normal for these 782 pairs of first twin cesarean–second twin vaginal births, giving a total of 11,741 twin pairs of first twin vaginal–second twin cesarean births. Because it is unlikely that second twin's cesarean delivery following first twin's vaginal delivery is a planned event, all such births were classified as vaginal births in intention-to-treat analyses. Cesarean section deliveries of 15,731 twin pairs in cases of induction or stimulation of labor and prolonged or dysfunctional labor (an indication of failed trial of labor/vaginal delivery) were also classified as vaginal births in intention-to-treat analyses.

Stratified analyses were conducted to assess perinatal mortality risk differences between second- and firstborn twins by birth order–specific weight difference: within 5% (similar), first twins heavier by 5.0-14.9%, 15.0-24.9%, and 25.0% or greater or second twins heavier by 5.0-14.9%, 15.0-24.9%, and ≥25.0% (7 strata). To compensate for the fact that boys on average weighed about 3.6% (84 g) more than girls based on exploratory data analysis in the study cohort, birthweight of girls in different-sex twin pairs was artificially inflated by 3.6% before calculating birthweight differences in different-sex twin pairs for the purpose of comparably grouping birthweight percentage differences for all twin pairs (same sex or different sex).

To gain insight on perinatal mortality risk changes in second vs first twins by gestational age, we evaluated the risk changes in clinically important gestational age categories: extremely preterm (23-27 weeks), very preterm (28-31 weeks), mild preterm (32-36 weeks), and term (≥37 weeks). The fetuses-at-risk approach was applied to estimate gestational age stratum-specific mortality rates to avoid a potential collider effect of stratification by gestational age at birth.[16] The fetuses-at-risk denominator is the number of all fetuses at risk of death (both born and yet unborn babies).

The unit of data analysis was the fetus. Conditional logistic regression (appropriate for paired data) was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of perinatal death, stillbirth, and neonatal death comparing second vs first twins. Adjusted ORs were controlled for important known fetus-specific risk factors: