OBSTETRICS

Metaanalysis of the prevalence of intrauterine fetal death in gastroschisis

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OBJECTIVE: The objective of this study was to review the medical literature that has reported the risk for intrauterine fetal death (IUFD) in pregnancies with gastroschisis.

STUDY DESIGN: We systematically searched the literature to identify all published studies of IUFD and gastroschisis through June 2011 that were archived in MEDLINE, PubMed, or referenced in published manuscripts. The MESH terms *gastroschisis* or *abdominal wall defect* were used.

RESULTS: Fifty-four articles were included in the metaanalysis. There were 3276 pregnancies in the study and a pooled prevalence of IUFD of 4.48 per 100. Those articles that included gestational age of IUFD had a pooled prevalence of IUFD of 1.28 per 100 births at ≥36 weeks' gestation. The prevalence did not appear to increase at >35 weeks' gestation.

CONCLUSION: The overall incidence of IUFD in gastroschisis is much lower than previously reported. The largest risk of IUFD occurs before routine and elective early delivery would be acceptable. Risk for IUFD should not be the primary indication for routine elective preterm delivery in pregnancies that are affected by gastroschisis.

Key words: abdominal wall defect, fetal death, gastroschisis, IUFD, stillbirth

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Gastroschisis is an abdominal wall defect of unclear cause and increasing incidence worldwide; current estimates are near 5 per 10,000 births.[1] There have been great improvements in survival in this patient population

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because >95% of infants survive from birth to initial hospital discharge.[2] However, there remain many questions about perinatal management and, in particular, about the optimal gestational age at delivery. Intrauterine fetal death (IUFD) is more common in pregnancies that are affected by congenital anomalies. Among all major congenital anomalies, 2% of pregnancies result in stillbirth,[3] which is much higher than the 0.6% baseline rate in the general population.[4,5] This higher risk of stillbirth results in a higher frequency and level of antenatal monitoring and, in some cases, elective delivery at <39 weeks' gestation.[6] Decisions regarding obstetric management must be based on accurate knowledge of the risk for fetal death.

The mean age of spontaneous labor in pregnancies that are affected by gastroschisis is between 36 and 37 weeks' gestation,[7] yet the average age of delivery is approximately 1 week earlier. This discrepancy leads to the conclusion that infants with gastroschisis deliver early either for fetal/maternal indications or electively.[8] Although some clinicians advocate for early delivery to improve postnatal clinical outcomes (such as earlier initiation of enteral feeds and shorter hospitalization time), the literature does not document a consistent benefit.[9-11] Therefore, the primary rationale for elective delivery before the onset of labor may be the prevention of IUFD.[12]

The reported incidence of IUFD in pregnancies that are affected by gastroschisis is as high as 12.5%.[13] Although the cause for the increased risk of IUFD is unknown, hypotheses include umbilical cord compression after acute intestinal dilation,[14] oligohydramnios,[15] cardiovascular compromise that is related to high protein loss through the defect and subsequent hypovolemia,[16] and cytokine-mediated inflammation.[17,18] Additionally, there is increased risk for volvulus and vascular compromise that could lead to fetal death.[19] Studies that have documented high rates of IUFD are limited by small numbers, and many were conducted at a time when prenatal diagnosis of gastroschisis was uncommon. These studies found that most IUFDs occurred late in the third trimester. Obstetricians developed the practice of early elective delivery based on these studies. Additional

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studies that have suggested lower rates of IUFD are also limited by sample sizes and evaluations of single institutions or populations. Our own experience suggests a much lower rate of IUFD than 10-12%. The limitations of individual studies compromise ascertainment of the true incidence of IUFDs with gastroschisis.

We present a metaanalysis to generate a more accurate representation of the prevalence of IUFD among infants with prenatal diagnosis of gastroschisis. We hypothesize that the prevalence of IUFD is less than previously reported and that the risk of IUFD does not vary with gestational age.

Materials and Methods

We conducted a metaanalysis of the published, English-language literature that is related to gastroschisis.

Literature search

A systematic search was done independently by 2 of the authors (A.S., K.S.) who reviewed the literature to identify all published studies through June 2011 that were archived in MEDLINE and PubMed or were referenced in published articles. The MESH terms *gastroschisis* or *abdominal wall defect* were used. Abstracts were reviewed initially and excluded based on predetermined criteria that included non-English language, nonhuman subjects, or no relation to gastroschisis. The remaining articles were selected for full text review, which led to further exclusion of articles that did not report the number of IUFDs, case reports, studies with small sample sizes ($n < 10$), and datasets that did not represent the total population (eg, case series of live births with gastroschisis or if the total number of pregnancies with gastroschisis was not disclosed). When there were multiple studies that used the same dataset, we included only 1 article and prioritized the article that reported the gestational age of IUFD. If both articles reported gestational age at IUFD, the article with the larger number of infants was included. The included articles were divided into those with a stated gestational age at IUFD and those without.

Data extraction

Data regarding all reported pregnancies, including termination of pregnancy, were extracted independently from all included studies by 2 authors (A.S., K.S.). Extracted data included gestational age at delivery, gestational age at IUFD, country of origin, year the study was published, presence of comorbidities in addition to gastroschisis, and obstetric delivery plan. *IUFD* was defined as an unplanned fetal death or stillbirth at any gestational age. The mean or median gestational age at delivery was extracted for each study. *Early delivery plan* was defined as systematic elective delivery at any predefined gestational age, compared with awaiting the onset of spontaneous labor or delivery because of maternal or fetal indications.

Quality assessment

A scoring system that was based on a previous metaanalysis was used to create a grading scale for the articles.[20] Studies were independently graded (A.S., K.S.) with the use of a standardized evaluation form that had been developed for the purpose of this metaanalysis. Each study was assigned a grade of 1-5 according to the quality of reporting of 5 factors. Variables were chosen to represent the factors that we believed to be essential for contributing valid data (population-based data, prospective data collection) or essential for understanding results (identified obstetric delivery plan, reported gestational age at birth, and reported gestational age at the time of IUFD). Differences between reviewers' grades were resolved by consensus among all 3 authors. The quality markers that were chosen for this study were identified before the start of data abstraction. The rate of IUFD was compared among studies on the basis of the assigned quality assessment scores.

Statistical analysis

The rate of IUFD was calculated for each study with the number of IUFDs reported in the numerator and the number of live births plus IUFDs in the denominator. Pregnancies that were terminated electively were not included in the numerator or denominator, because these pregnancies were considered not at risk for an IUFD. A random-effects model was used to aggregate individual effect sizes to create a pooled prevalence of IUFD. Random-effects models are based on the assumption that the studies that were selected for analysis are a sample of all potential studies by incorporating between-study variability in the overall pooled estimation.[21] Pooled prevalence estimates of IUFD with 95% confidence intervals were reported from these models with the use of the Der Simonian-Laird random-effects method.[22] All rates were calculated as deaths per 100 total births, with total births being the summation of live births and fetal deaths. Subgroup analyses were performed for the prevalence of IUFD with the following stratifications: gestational age, early delivery plan, study site (within US vs international), study grading, and years in which the study occurred.

Homogeneity across studies was tested with the I^2 index, which provides a measure (or percentage) of the variation in prevalence attributable to between-study heterogeneity.[23,24] An I^2 value of $>75\%$ is interpreted as high heterogeneity.[24] Post-hoc sensitivity analyses were conducted to investigate the potential sources of heterogeneity from specific studies that may have biased the analyses. Studies that potentially influenced heterogeneity were removed from analyses, and the results were compared with the original findings. A forest plot was created to illustrate the prevalence of each study, with 95% confidence intervals, that contributed to the analysis along with the pooled prevalence estimate. Finally, all studies that reported mean/median gestational ages of the live births of gastroschisis were divided into 3 time periods: before 1990, 1990-1999, and after 2000. The mean/median birth rates of gastroschisis were described for each time period to determine trends in timing of delivery.

Results

Study and patient characteristics

Our search produced 1123 results. Review of these abstracts resulted in 100