OBSTETRICS

# Gastroschisis: mortality risks with each additional week of expectant management

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**BACKGROUND:** Prior studies have evaluated the overall risk of stillbirth in pregnancies with fetal gastroschisis. However, the gestational age at which mortality is minimized, balancing the risk of stillbirth against neonatal mortality, remains unclear.

**OBJECTIVE:** We sought to evaluate the gestational age at which prenatal and postnatal mortality risk is minimized for fetuses with gastroschisis.

**STUDY DESIGN:** This was a retrospective cohort study of singleton pregnancies delivered between 24 0/7 and 39 6/7 weeks, using 2005 through 2006 US national linked birth and death certificate data. Among pregnancies with fetal gastroschisis, prospective risk of stillbirth and risk of infant death were determined for each gestational age week. Risk of infant death with delivery was further compared to composite fetal/infant mortality risk with expectant management for 1 additional week.

**RESULTS:** Among 2,119,049 pregnancies, 860 cases (0.04%) of gastroschisis were identified. The overall stillbirth rate among gastroschisis cases was 4.8%, and infant death occurred in 8.3%. Prospective risk of stillbirth became more consistently elevated beginning at 35 weeks, rising to 13.9 per 1000 pregnancies (95% confidence interval, 10.8–17.1) at 39 weeks. Risk of infant death concurrently nadired in the third trimester, ranging between 62.4-66.8 per 1000 live births between 32-39 weeks. Comparing mortality with expectant management vs delivery, relative risk was significantly greater with expectant management between 37-39 weeks, reaching 1.90 (95% confidence interval, 1.73–2.08) at 39 weeks with a number needed to deliver of 17.49 (95% confidence interval, 15.34–20.32) to avoid 1 excess death.

**CONCLUSION:** Risk of prenatal and postnatal mortality for fetuses with gastroschisis may be minimized with delivery as early as 37 weeks.

**Key words:** gastroschisis, intrauterine fetal demise, neonatal death, stillbirth

## Introduction

Gastroschisis occurs in approximately 3-5 of every 10,000 live births, with an estimated 90-97% of cases identified prenatally.[1,2] Most cases are thought to occur either sporadically or in a multifactorial nature, and risk factors include young maternal age, non-Hispanic white maternal race/ethnicity, tobacco use, and several environmental factors and medications.[1-4] The majority of gastroschisis cases occur as isolated defects, although 6-15% are associated with additional anomalies.[5-9] Important perinatal risks associated with gastroschisis include a 28% to >50% chance of early delivery, numerous concomitant morbidities, and mortality in up to 10% of infants.[1,3,8-10]

Several studies have evaluated stillbirth among cases of fetal gastroschisis, with overall rates reported from 0-14%.[1,6,7,9-12] Stillbirth risk may further increase in cases with concomitant oligohydramnios or when additional anomalies are present.[1,5] Many of the existing studies are based on small cohorts, though, and there has been limited investigation of stillbirth risk by gestational age (GA). A recent meta-analysis[12] found that stillbirth risk with fetal gastroschisis was greatest <36 weeks of gestation, and other literature has supported higher stillbirth rates throughout the third trimester in general.[1,13] Some studies have advocated for delivery ≤37 weeks of gestation because of increased stillbirth risk over time, potentially from increasing bowel inflammation and other factors.[14,15] Others have supported delivery at later term GAs due to improved neonatal outcomes and lower medical costs.[16,17] The GA at which mortality is minimized for fetuses with gastroschisis, balancing the risk of stillbirth against neonatal mortality, thus remains unclear.

We designed a large retrospective cohort study to investigate the prospective risk of stillbirth for each GA week among pregnancies with fetal gastroschisis, as well as the risk of neonatal death. Our objective was to determine the GA at which risk of mortality with expectant management begins to outweigh that with delivery of fetuses with gastroschisis, to improve our understanding of the GA at which mortality is minimized with delivery.

## Materials and Methods

This was a retrospective cohort study of pregnancies in the United States during the years 2005 through 2006, using linked live birth certificate and infant death data from the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC).[18] Institutional review board approval and informed consent were not required for this study because of the publicly available and de-identified nature of the NCHS linked file.[19]

The NCHS established a national linked file using unique linkage numbers to match data from individual states. This file includes birth information for infants born in 2005 through 2006, as well as information about death if this occurred within the first 12 months of life (whether the death occurred in 2005, 2006, or 2007). A revised US Standard Certificate of Live Birth was implemented beginning in 2003, and was

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phased in over time. Using this revised version, gastroschisis became coded as an independent outcome. By 2005, 12 states (Florida, Idaho, Kansas, Kentucky, Nebraska, New Hampshire, New York excluding New York City, Pennsylvania, South Carolina, Tennessee, Texas, and Washington) and Puerto Rico had implemented the revised birth certificate, representing 31% of all births for 2005. By 2006, 19 states (California for selected items, Delaware, Florida, Idaho, Kansas, Kentucky, Nebraska, New Hampshire, New York excluding New York City, North Dakota, Ohio, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont, Washington, and Wyoming) and Puerto Rico had implemented the revised version, representing 49% of all births. Birth certificate information was linked successfully to nearly 99% of corresponding infant death records.

The primary outcomes of interest for this study were rates of stillbirth, infant death, and composite fetal/infant mortality by GA week. Rates of stillbirth and infant death among pregnancies with fetal gastroschisis were compared to the reference population. The reference population was defined as singletons delivered between 24 0/7 and 39 6/7 weeks of gestation without gastroschisis or other anomalies. Inclusion criteria for the gastroschisis subgroup were singletons with gastroschisis delivered between 24 0/7 and 39 6/7 weeks of gestation, with other fetal anomalies excluded. Pregnancies continuing >40 weeks of gestation were excluded given the infrequency with which delivery of fetuses with gastroschisis occurs after this GA. Gastroschisis was defined by the CDC as an abnormality of the anterior abdominal wall lateral to the umbilicus, resulting in herniation of the abdominal contents directly into the amniotic cavity without a protective membrane.[20] A unique coded variable for gastroschisis allowed us to identify and analyze cases meeting our study criteria.

NCHS guidelines allow for GA correction if the estimated due date by last menstrual period estimate is significantly different from that based on ultrasound; thus, pregnancy dating was based on the best obstetric estimate.[20] The guidelines also recommend early ultrasound for the purpose of re-dating, and GA correction following birth is not permitted. Records that were missing GA information were not included in our analyses. All states reported information about the best obstetric estimate over years 2005 through 2006 except for California, although our cohort was limited to those states using the revised 2003 birth certificate as described previously.

Stillbirth was defined as fetal demise occurring between 20 0/7 weeks of gestation and birth. We used the pregnancies at-risk life table method described by Smith[21] to calculate the risk of stillbirth for each GA week. This method incorporates a prospective estimation of stillbirth risk and a half-week correction to account for the assumption of evenly distributed stillbirths during each GA week. As such, it includes the number of stillbirths during a given GA week in the numerator, and divides by the total number of ongoing pregnancies minus half the number of deliveries during that same GA week. It is assumed that stillbirth did not occur prior to the GA week in question, meaning that risk of stillbirth is conditional rather than cumulative. The prospective risk of stillbirth for each GA week was reported per 1000 ongoing pregnancies. The risk of infant death was calculated as the number of live infants born during each GA week who died within the first year of life, divided by the total number of live births at that GA. Infant death risk was reported per 1000 live births. To even short-term fluctuations in the data and demonstrate overall trends, we applied a moving average algorithm using simple 3-point smoothing,[22] with each GA week given equal weight.

In addition to risks of stillbirth and infant death, the composite risk of fetal/infant mortality with 1 additional week of expectant management was estimated for each GA.[23] Composite risk was calculated as the sum of the stillbirth risk during each GA week plus the risk of infant death with delivery during the following GA week. Calculation of composite risk enabled us to evaluate the clinical decision point of mortality risk with delivery at a given GA (infant death) vs expectant management for 1 additional week (composite risk, which incorporates the risk of stillbirth during the additional week plus risk of infant death with delivery 1 week later).[23,24] The composite risk of expectant management compared to risk of infant death with delivery was also graphed from 32-39 completed weeks of gestation, to identify the point at which mortality risk with expectant management began to exceed that with delivery.

Additional calculations included the risk difference between expectant management and delivery (mortality risk with expectant management minus that with delivery). Negative values for risk difference indicated a higher mortality risk with delivery, while positive values indicated higher risk with expectant management for 1 additional week. Number needed to treat (NNT) was calculated, representing the number needed to either manage expectantly for 1 additional week (in the setting of a negative value for risk difference) or deliver (in the setting of a positive value for risk difference) to prevent 1 excess death. NNT was calculated as the reciprocal of the absolute risk difference. We further calculated the relative risk (RR) of expectant management vs delivery for each GA week.

Statistical analyses were performed using Excel (Microsoft Corp, Redmond, WA) and Stata (Version 11.0; StataCorp, College Station, TX) software. The $\chi^2$ test compared proportions, Wilcoxon rank sum examined nonparametric continuous variables, and logistic regression generated adjusted odds ratios (AOR). For the multivariable model calculating odds of stillbirth, we adjusted for GA at birth, parity, maternal ethnicity, extremes of maternal age (<20 and >35 years), maternal education level, tobacco use, chronic hypertension, and number of prenatal visits. We chose to include each of these factors because clinically, they may be related to both gastroschisis and the outcome of stillbirth, and the large size of our data set allowed for adjustment of numerous