Original Research

Factors Associated With Gastroschisis Outcomes

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OBJECTIVE: To identify perinatal variables associated with adverse outcomes in neonates prenatally diagnosed with gastroschisis.

METHODS: A retrospective review was conducted of all inborn pregnancies complicated by gastroschisis within the five institutions of the University of California Fetal Consortium from 2007 to 2012. The primary outcome was a composite adverse neonatal outcome comprising death, reoperation, gastrostomy, and necrotizing enterocolitis. Variables collected included antenatal ultrasound findings, maternal smoking or drug use, gestational age at delivery, preterm labor, elective delivery, mode of delivery, and birth weight. Univariate and multivariate analysis was used to assess factors associated with adverse outcomes. We also evaluated the association of preterm delivery with neonatal outcomes such as total parenteral nutrition cholestasis and length of stay.

RESULTS: There were 191 neonates born with gastroschisis in University of California Fetal Consortium institutions at a mean gestational age of 36 3/7±1.8 weeks. Within the cohort, 27 (14%) had one or more major adverse outcomes, including three deaths (1.6%). Early gestational age at delivery was the only variable identified as a significant predictor of adverse outcomes on both univariate and multivariate analysis (odds ratio 1.4, 95% confidence interval 1.1–1.8 for each earlier week of gestation). Total parenteral nutrition cholestasis was significantly more common in neonates delivered at less than 37 weeks of gestation (38/115 [33%] compared with 11/76 [15%]; $P<.001$).

CONCLUSION: In this contemporary cohort, earlier gestational age at delivery is associated with adverse neonatal outcomes in neonates with gastroschisis. Other variables, such as antenatal ultrasound findings and mode of delivery, did not predict adverse neonatal outcomes.

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Gastroschisis is an abdominal wall abnormality that results in herniation of bowel and other abdominal contents. In the United States, the rate of gastroschisis has increased from 2.32 per 10,000 live births in 1995 to 4.42 per 10,000 live births in 2005.[1] Risk factors for gastroschisis include tobacco and illicit drug use, low socioeconomic status, low body mass index, and young maternal age.[1–3]

Although the overall neonatal mortality rate for gastroschisis remains low at 5–10%, pregnancies with gastroschisis have a relatively high incidence of fetal growth restriction, preterm delivery, and neonatal

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complications such as bowel atresia, perforation, stricture, ischemia, and necrotizing enterocolitis.[4,5]

Numerous studies have examined prognostic factors for outcomes of gastroschisis.[6–9] It has been hypothesized that prolonged exposure to amniotic fluid may lead to inflammatory changes and damage to the exteriorized bowel.[10,11] Researchers have assessed ultrasound findings, including size of the abdominal wall defect, bowel wall dilation, and bowel wall thickness.[6–9,12,13] Although some studies have demonstrated that these findings are predictive of adverse outcomes, others report insufficient evidence to support use in clinical management.[8,9,14–16] It is also theorized that elective preterm delivery may improve outcomes by preventing ongoing bowel injury.[17–19] However, this theory remains unproven and there is no consensus regarding perinatal management of gastroschisis.[20]

Identifying prenatal predictors and optimizing perinatal management could minimize adverse outcomes among neonates with gastroschisis. The aim of this study is to identify perinatal variables associated with adverse outcomes in neonates prenatally diagnosed with gastroschisis.

MATERIALS AND METHODS

A retrospective review was conducted on all inborn pregnancies complicated by gastroschisis within the five institutions of the University of California Fetal Consortium from 2007 to 2012. The University of California Fetal Consortium is a multiinstitutional collaboration of the University of California medical centers and includes University of California Davis, University of California Irvine, University of California Los Angeles, University of California San Diego, and University of California San Francisco. All institutions participating in the University of California Fetal Consortium are tertiary academic medical centers with a full complement of perinatal, neonatal, and surgical services.

Cases of gastroschisis were initially identified by International Classification of Diseases, 9th Revision codes. Maternal and neonatal variables were abstracted through an individual chart review at each institution. All patients included in the analysis received prenatal and postnatal care within the same institution. Neonates who were transferred into a University of California Fetal Consortium institution after delivery for postnatal care were excluded. A multiinstitutional review board reliance registry approved the study (Institutional Review Board No. 10-04093). The primary outcome was a composite adverse neonatal outcome comprising neonatal death, bowel complications (intestinal atresia, stricture, or ischemia) requiring reoperation, gastrostomy, and necrotizing enterocolitis.

Demographic information was collected including maternal age, parity, zip code of residence, smoking, and drug use. Other perinatal variables collected were gestational age at delivery, preterm labor, mode of delivery, and whether delivery was electively scheduled. Findings from the last ultrasound scan before delivery were reviewed, because they were most likely to correlate with neonatal status. The perinatal ultrasonographic variables assessed were presence of fetal bowel dilation (subjectively assessed by a physician and ultrasonographer), intrauterine growth restriction (estimated fetal weight less than the 10th percentile), and oligohydramnios (amniotic fluid index less than 5 cm). Because gastroschisis is not usually associated with chromosomal abnormalities, genetic testing was not performed routinely in our cohort.

Adverse neonatal outcomes were collected including neonatal death, bowel complications (intestinal atresia, stricture, or ischemia) requiring reoperation, gastrostomy, and necrotizing enterocolitis. Other newborn characteristics including birth weight, small for gestational age (SGA; birth weight less than the 10th percentile for gestational age), Apgar score less than 5 at 5 minutes, presence of meconium at delivery, method of gastroschisis defect closure, neonatal length of stay, ventilator days, days to initiation of feeds and full feeds, total parenteral nutrition (TPN) cholestasis, presence of other neonatal anomalies, and readmission within 1 month were also collected.

Perinatal and neonatal variables were analyzed to determine whether they were associated with adverse outcomes in neonates with gastroschisis. Because there is debate regarding the need to deliver neonates with gastroschisis preterm, we examined differences in neonatal outcomes based on timing of delivery (preterm less than 37 weeks of gestation or term 37 weeks of gestation or greater). Univariate analysis was performed using Fisher's exact test for assessing the relationship between categorical variables and Wilcoxon rank-sum test for comparing continuous variables between groups. Those predictors with P values $<.20$ on univariate analysis were included in the multivariate model. In cases in which predictors were clearly associated, we selected only the variable that had the lowest P value on univariate analysis. Potential predictor variables included in the models were gestational age, maternal smoking, maternal drug use, elective delivery, Apgar score less than 5 at 5 minutes, and institutional site. Forward stepwise regression was then used to identify the most significant variables. To assess the robustness of our stepwise selected model, a mixed effects logistic regression model was constructed using institutional site as a random effect.

$P<.05$ was considered statistically significant. Statistical analyses were performed using SAS 9.3.

RESULTS

There were 191 neonates born with gastroschisis at the five University of California Fetal Consortium institutions from 2007 to 2012. Among the cohort, 87% lived in urban areas and 13% in rural areas. Of those who lived in urban areas, 64% were from areas with greater than 99% urban dwellers, whereas 33% were from mixed urban and rural communities.

Table 1 shows maternal and neonatal demographics of the cohort. The mean gestational age of delivery was 36 3/7±1.8 weeks. The mean maternal age was 22±4.4 years, and the majority of women (66%) were nulliparous. In the cohort, 15% smoked tobacco and 6% reported use of illicit drugs during pregnancy. Based on the last ultrasound scan before delivery, 25% had intrauterine growth restriction (IUGR), 7% had oligohydramnios, and 45% had bowel dilation. Of all the deliveries, 75 (39%) were scheduled electively. The cesarean delivery rate was 34%, of which 19 (29%) were elective cesarean deliveries.

The mean birth weight for all neonates was 2,469±500 g; 42 (22%) were SGA. Meconium was present in 56% of deliveries, and 4% had Apgar scores less than 5 at 5 minutes. Primary closure was performed in 42% of patients. The median (interquartile range) length of neonatal intensive care unit stay was 31 days (range 24–45 days), ventilator days was 5 days (range 3–9 days), days to initiation of feeds was 15 days (range 11–21 days), and days to full feeds was 24 days (range 21–36 days). Thirteen neonates (7%) had other anomalies, including cardiac (dextrocardia, pulmonary valve stenosis, atrial septal defect), neurologic (optic nerve hypoplasia, cerebral dysgenesis, absent cavum septum pellucidum, tethered spinal cord), renal (multicystic kidney, vesicoureteral reflux, hydronephrosis), severe combined immunodeficiency, arthrogryposis, and amniotic band syndrome with club feet.

Of the 191 neonates in the cohort, 27 (14%; 95% confidence interval [CI] 7.9–17.3%) had one or more major adverse outcomes (Table 2). Three neonates (1.6%; 95% CI 0%–3.3%) died after delivery with time to death ranging from 2 to 9 days. Two of the neonatal deaths had entire liver evisceration associated with gastroschisis and pulmonary hypoplasia. The third death was the result of an in utero volvulus and resultant short gut syndrome. There were no stillbirths.

Reoperation was required in 26 neonates for intestinal atresia or stricture (10%) and bowel ischemia (1%). Thirteen neonates (7%) required a gastrostomy tube for oral aversion or prolonged gastrointestinal dysmotility. All neonates with gastrostomy were discharged home with tubes in place. Two neonates (1%) had necrotizing enterocolitis complicating their hospitalization. Six neontates (3%) were discharged home on TPN.

On univariate analysis, gestational age at delivery, spontaneous preterm labor, and birth weight were significantly different between neonates without and with adverse outcomes (Table 3). We also identified differences in adverse outcomes between University of California Fetal Consortium institutional sites ($P<.002$) which was likely attributable to one outlier institution with a 45% adverse outcome rate. When excluding the one outlier institution, adverse outcomes were not different between institutions (adverse outcomes rate of 7–14%, $P=.62$).

On multivariate analysis, each earlier week of gestation (odds ratio [OR] 1.4, 95% CI 1.1–1.8), maternal smoking (OR 4.3, 95% CI 1.1–10.5), and institutional site ($P<.001$) were identified as significant predictors of adverse neonatal outcomes. When site

Table 1. Maternal and Neonatal Demographics (N=191)

Variable	Value
Maternal age (y)	22.2±4.4
Nulliparous	126 (66)
Smoking	29 (15)
Drug use	12 (6)
Gestational age at delivery (wk)	36 3/7±1.8
Birth weight (g)	2,469±500
Delivery at less than 37 wk of gestation	115 (60)
Cesarean delivery	65 (34)
Preterm labor	54 (28)
Other fetal anomalies* (n=190)	13 (7)
Male sex	107 (56)

Data are mean±standard deviation or n (%).
* Data are missing.

Table 2. Adverse Neonatal Outcomes

Outcome	Adverse Outcome (%)
Neonates with adverse outcome	27 (14)
Specific adverse outcomes*	
Intestinal atresia or stricture	19 (10)
Insertion of gastrostomy tube	13 (7)
Intestinal ischemia before closure	2 (1)
Necrotizing enterocolitis	2 (1)
Death	3 (1.6)

Data are incidents and % of total study population (N=191).
* Some neonates had more than one adverse outcome.

Table 3. Univariate Analysis of Perinatal and Neonatal Predictors of Composite Adverse Outcomes

Variable	Total (n=191)	No Adverse Outcome (n=164)	Adverse Outcome* (n=27)	P†
Perinatal predictors				
Gestational age (wk)	36 3/7±1.8	36.5±1.7	35.4±2.1	.004
Maternal smoking	29 (15)	22 (13)	7 (26)	.14
Maternal drug use	12 (6)	8 (5)	4 (15)	.07
IUGR (less than 10th percentile)‡ (n=186)	46 (25)	39 (24)	7 (27)	.81
Oligohydramnios (amniotic fluid index less than 5 cm)‡ (n=190)	13 (7)	10 (6)	3 (11)	.40
Bowel dilation‡ (n=190)	86 (45)	71 (44)	15 (56)	.30
Cesarean delivery	65 (34)	54 (33)	11 (41)	.51
Elective delivery	75 (39)	68 (41)	7 (26)	.14
Spontaneous preterm labor	54 (28)	40 (24)	14 (52)	.01
Neonatal predictors				
Delivery at less than 37 wk of gestation	115 (60)	94 (57)	21 (78)	.06
Meconium	106 (56)	92 (56)	14 (52)	.68
5-min Apgar score less than 5‡ (n=188)	7 (4)	4 (2)	3 (11)	.06
Birth weight (g)	2,469±500	2,498±478	2,294±593	.04
Small for gestational age	42 (22)	36 (22)	6 (22)	1.00
Other anomalies	13 (7)	11 (7)	2 (7)	.69
Primary closure‡ (n=190)	79 (42)	69 (42)	10 (38)	.83

IUGR, intrauterine growth restriction.
Data are mean±standard deviation or n (%) unless otherwise specified.
* Adverse outcomes includes death, bowel complications (intestinal atresia, stricture, or ischemia) requiring reoperation, gastrostomy, and necrotizing enterocolitis.
† Comparison between no adverse outcome group and adverse outcome group by Fisher's exact test or Wilcoxon rank-sum test.
‡ Data are missing.

was treated as a random effect to control for site-to-site variation, neonatal outcomes worsened with each earlier week of gestation (OR 1.4, 95% CI 1.1–2.0), and maternal smoking was associated with adverse neonatal outcomes (OR 3.4, 95% CI 1.1–10.5).

The other variables of maternal drug use and mode of delivery did not differ between groups. Antenatal ultrasound findings of IUGR, oligohydramnios, and bowel dilation were also not predictive of adverse neonatal outcomes (Table 3). The presence of meconium, SGA, 5-minute Apgar score, and other fetal anomalies were similar between those without and with adverse outcomes (Table 3).

In our cohort, 75 (39%) deliveries were elective. Those electively delivered had a later gestational age at delivery compared with those not electively delivered (37 0/7±1.4 weeks of gestation compared with 36 0/7±1.9 weeks of gestation, $P<.001$). Neonates electively delivered had higher birth weights (2,600±472 g compared with 2,384±500 g, $P<.01$) and lower rates of preterm delivery (40% compared with 73%, $P<.001$). However, there was no difference in SGA (21% compared with 22%, $P=1.0$) and adverse outcomes (9% compared with 17%, $P=.14$) between the two groups.

As would be expected, those with adverse outcomes had longer neonatal intensive care unit lengths of stay (93 [range 68–128] days compared with 28.5 [range 24–39] days, $P<.001$), more ventilator days (10 [range 5–16] days compared with 5 [range 3–9] days, $P<.003$), and longer time to initiation of feeds (27 [range 25–71] days compared with 14 [range 11–19] days, $P<.001$). There was no association of adverse outcomes with silo placement (58% of neonates without adverse outcomes had silo placement compared with 63% of those with adverse outcomes, $P=.83$).

As seen in other studies, our cohort had a high rate of preterm birth with 115 (60%) neonates delivered before 37 weeks of gestation. Table 4 shows

Table 4. Indications for Preterm Delivery (n=115)

Indication	n (%)
Spontaneous preterm labor	54 (47)
Nonreassuring fetal heart tracing	19 (17)
Intrauterine growth restriction	10 (9)
Oligohydramnios	6 (5)
Compromised bowel*	13 (11)
Other	4 (3)
Unknown	9 (8)

* Compromised bowel is defined as ultrasonographic findings concerning for dilated bowel, bowel infarct, bowel perforation, or herniation of other abdominal viscera.

the indications for preterm delivery. There were fewer adverse outcomes in neonates delivered at 37 weeks of gestation or greater, although this difference was not statistically significant (six [8%] adverse outcomes with delivery at 37 weeks of gestation or greater compared with 21 [18%] adverse outcomes with delivery at less than 37 weeks of gestation, $P=.06$). A majority of adverse outcomes (46%) occurred in neonates delivered less than 35 weeks of gestation compared with neonates delivered 35 weeks of gestation or greater (9%, $P<.001$). Total parenteral nutrition cholestasis was higher in those who delivered before 37 weeks of gestation (33% with delivery before 37 weeks of gestation compared with 15% with delivery after 37 weeks of gestation, $P<.001$). The overall rate of TPN cholestasis within the cohort was 26%. Ventilator days, days to initiation of feeds, and full feeds was not different in those who delivered before compared with after 37 weeks of gestation (Table 5).

DISCUSSION

Much investigation on gastroschisis has focused on identifying reliable prenatal predictors to minimize risk of fetal demise and neonatal complications.[6–9,12–16,21] In our cohort, prenatal predictors such as IUGR, oligohydramnios, and bowel dilation on ultrasonography were not found to be predictive of adverse neonatal outcomes. Neonatal variables such as the presence of meconium, SGA, 5-minute Apgar score, and other fetal anomalies were also not predictive of adverse outcomes.

Neonates in our cohort experienced bowel complications similar to those reported in other studies. Intestinal problems such as bowel atresia, stricture, or ischemia have been reported to occur in neonates with gastroschisis at rates as high as 25%.[22] Our adverse outcome rate of 14% comprised neonatal death, bowel complications (intestinal atresia, stricture, or ischemia) requiring reoperation, gastrostomy, and necrotizing enterocolitis. All the neonates with adverse outcomes had significantly longer lengths of stay, ventilator days, and time to initiation of feeds. Despite a typical complication frequency, our mortality rate of 1.6% was significantly lower than reported previously.[1,4,23] This may reflect advances in medical care. Two of the fetal deaths had liver evisceration, which is consistent with other studies that have demonstrated higher rates of mortality with liver herniation.[24]

Gestational age and maternal smoking were found to be predictors of adverse neonatal outcomes. However, 28% of preterm neonates were delivered after spontaneous preterm labor. The underlying etiology for spontaneous preterm labor is typically unknown and may account in part for the worse outcomes observed in lower gestational age neonates. Biologic plausibility for an association between smoking and gastroschisis includes carbon monoxide exposure, vascular injury, and inflammatory changes.[25,26]

Much debate exists regarding appropriate timing and mode of delivery for the neonate with gastroschisis. Proponents of early delivery believe prolonged intraamniotic bowel exposure increases the risk of complications, and they recommend elective preterm delivery.[17–19] Baud et al[27] found induction at 37 weeks of gestation was associated with lower rate of sepsis, bowel damage, and neonatal death compared with pregnancies managed expectantly beyond 37 weeks of gestation. In contrast, a randomized controlled trial of 42 pregnancies with gastroschisis demonstrated no difference in outcomes between elective delivery at 36 weeks of gestation compared with awaiting spontaneous labor.[28] Our data found that neonates born preterm have a higher rate of TPN cholestasis, and those born before 35 weeks of gestation are at most risk for adverse outcomes.

The primary strength of our study is that it is a large multiinstitutional cohort of perinatal predictors

Table 5. Neonatal Outcomes Based on Gestational Age at Delivery

Outcome	Total (n=191)	Delivery at Less Than 37 Wk (n=115)	Delivery at 37 Wk or Greater (n=76)	P*
Adverse outcome	27 (14%)	21 (18%)	6 (8%)	.06
Length of stay (d)	31 (24–45)	32.5 (23–47)	29 (24–44)	.73
Ventilator days	5 (3–9)	5.5 (3–9)	5 (3–10)	.89
Days to initiation of feeds	15 (11–21)	15 (11–75)	14 (11–19)	.25
Days to full feeds	24 (21–36)	25 (19–37)	23.5 (21–75)	.84
TPN cholestasis	49 (26%)	38 (33%)	11 (15%)	<.001

TPN, total parenteral nutrition.
Data are n (%) or median (interquartile range) unless otherwise specified.
* Comparison between no adverse outcome group and adverse outcome group by Fisher's exact test or Wilcoxon rank-sum test.

and neonatal outcomes of gastroschisis. This study includes a large catchment area in California with patients from urban and rural areas. Data were examined within the last 7 years, providing a contemporary examination of various management strategies for gastroschisis and reflecting current advances in perinatal and neonatal technology and care.

Our study is limited in that it is based on a retrospective chart review. There was variation in availability of data, prenatal ultrasonographic surveillance, and obstetric management at each University of California Fetal Consortium institution. Although our initial analysis suggested site was predictive of adverse outcomes, we found that a single outlier site was responsible for these differences. When this site was excluded, site was not predictive of adverse outcomes. Site-specific practices are likely captured with other covariates including mode of delivery, gestational age at delivery, and method of closure. Finally, although the study size was relatively large, it may be insufficiently powered to assess all predictors.

As the prevalence of gastroschisis continues to increase both globally and domestically, clinicians and families should be aware of potential neonatal complications. During prenatal counseling, families should be aware that neonates with gastroschisis are at risk for serious complications, including intestinal atresia, stricture, ischemia, necrotizing enterocolitis, feeding intolerance requiring gastrostomy, and prolonged hospital stays. The overall mortality rate for gastroschisis is low, unless liver herniation is present.

In conclusion, our data suggest ultrasound findings of bowel dilation, IUGR, and oligohydramnios do not warrant early delivery because they do not appear to be associated with adverse outcomes. We found no differences in outcomes with vaginal or cesarean delivery suggesting gastroschisis should not be an indication for elective cesarean deliveries. Finally, this study demonstrates an association between earlier gestational age and adverse neonatal outcomes, and it found no evidence to support routine induction of delivery.

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