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Authors
Zhang-Rutledge, Kathy
Jacobs, Marni
Patberg, Elizabeth
et al.

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Interval growth across gestation in pregnancies with fetal gastroschisis

Kathy ZHANG-RUTLEDGE, MD[1], **Marni JACOBS, PhD**[1], **Elizabeth PATBERG, MD**[2], **Nancy FIELD, MD**[3], **Kerry HOLLIMAN, MD**[4], **Katie M. STROBEL, MD**[5], **Aisling MURPHY, MD**[4], **Diana ROBLES, MD**[6], **Ms. Naseem RANGWALA, BA**[6], **Juan M. GONZALEZ, MD**[6], **Teresa N. SPARKS, MD, MAS**[6] **University of California Fetal-Maternal Consortium (UCfC)**

[1]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Diego

[2]Department of Obstetrics and Gynecology, University of California, Irvine

[3]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, Davis

[4]Department of Obstetrics and Gynecology, University of California, Los Angeles

[5]Department of Pediatrics, University of California, Los Angeles

[6]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco

Abstract

Background: Gastroschisis is frequently complicated by fetal growth restriction, preterm delivery, and prolonged neonatal hospitalization. Prenatal management and delivery decisions are

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Corresponding author: Kathy Zhang-Rutledge, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Diego, 9300 Campus Point Drive, MC 7433, La Jolla, California 92037, zhang.kat@gmail.com, Phone: 858-249-1207; Fax: 858-657-7212.

CRediT author statement
Kathy Zhang-Rutledge: Conceptualization, Investigation, Project administration, Resources, Visualization, Roles/Writing - original draft
Marni Jacobs: Formal analysis, Software, Visualization, Writing - review & editing
Elizabeth Patberg: Conceptualization, Investigation, Writing - review & editing
Nancy Field: Investigation
Kerry Holliman: Investigation, Writing - review & editing
Katie M. Strobel: Investigation, Writing - review & editing
Aisling Murphy: Methodology, Supervision
Diana Robles: Investigation, Roles/Writing - original draft
Naseem Rangwala: Investigation
Juan M. Gonzalez: Methodology, Supervision
Teresa N. Sparks: Conceptualization, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing - review & editing

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often based upon estimated fetal weight and interval growth, however appropriate interval growth from week to week across gestation for these fetuses is poorly understood.

Objectives: To determine the median increase in overall estimated fetal weight and individual biometric measurements across each week of gestation in pregnancies with fetal gastroschisis, and to assess if lower in utero fetal weight gain is predictive of postnatal growth or adverse neonatal outcomes.

Study Design: This was a retrospective cohort study of pregnancies with gastroschisis evaluated at five institutions of the University of California Fetal-Maternal Consortium (UCfC) from December 2014 to December 2019. Inclusion criteria were prenatally diagnosed gastroschisis with at least one ultrasound performed at a UCfC institution. Estimated fetal weight (EFW) and individual biometric measurements were recorded for each ultrasound performed at a UCfC institution from the time of gastroschisis diagnosis until delivery. Median EFW and biometric measurements were calculated for each gestational age in 1-week increments. Neonatal outcomes collected were birth weight, length of stay, complications of gastroschisis (bowel atresia, bowel stricture, ischemic bowel prior to closure, or severe pulmonary hypoplasia), and growth failure at discharge.

Results: We identified 95 pregnancies with fetal gastroschisis who, in aggregate, had 360 growth ultrasounds at a UCfC institution. The median interval growth was 130 grams per week. The median EFW and abdominal circumference in fetal gastroschisis cases approximated the 10^{th} percentile on the Hadlock growth curve across gestation. Moreover, the median biparietal diameter, head circumference, and femur length measurements remained below the 50^{th} percentile on the Hadlock growth curve across gestation. The median birth weight for neonates with less than median weekly prenatal weight gain was less than for those with greater than median weekly prenatal weight gain (2185 grams versus 2780 grams, $p < 0.01$). There were no differences in prenatal weight gain trajectory when comparing neonates who had or did not have bowel complications of gastroschisis.

Conclusions: In this multi-center cohort of pregnancies with fetal gastroschisis, the median interval growth was 130 grams per week, and overall, in utero growth closely followed the 10^{th} percentile on the Hadlock curve. Poor prenatal growth in cases of fetal gastroschisis correlates with lower neonatal weights but did not predict a more complicated course.

Condensation:

The interval growth in fetal gastroschisis is 130 grams per week, and poor prenatal growth does not predict complicated postnatal course.

Keywords

fetal anomaly; abdominal wall defect; fetal growth restriction; postnatal growth; nomograms; biometric parameters

Introduction

Gastroschisis is an abdominal wall defect that results in herniation of intra-abdominal contents. It affects approximately 5 in every 10,000 live births, and the incidence appears to be increasing across the United States.[1–4] Gastroschisis is frequently complicated by fetal growth restriction (FGR), preterm delivery, stillbirth, and prolonged neonatal intensive care unit (NICU) hospitalization.[5–10] Over 60% of neonates with gastroschisis have birth weights < 10th percentile for their gestational age.[11]

Given the elevated risk of FGR and stillbirth, pregnancies with fetal gastroschisis undergo serial growth ultrasounds and frequent antenatal surveillance. While the intention behind these interventions is to preempt an adverse outcome, these additional monitoring modalities can also increase the risk of obstetrical interventions and iatrogenic preterm birth. Earlier gestational age at birth for neonates with gastroschisis is the prenatal factor most associated with increased neonatal complications including death, re-operation, gastrostomy, and necrotizing enterocolitis.[12] Importantly, while it is known that fetuses with gastroschisis are at increased risk of FGR, interval growth from week to week across gestation for these fetuses is poorly understood. As important prenatal management and delivery decisions are based upon estimated fetal weight (EFW) and interval growth, defining expected interval growth across gestation in pregnancies with fetal gastroschisis is necessary to accurately identify those with poor fetal growth.

We aimed to determine the median increase in overall EFW and individual biometric measurements across each week of gestation in pregnancies with fetal gastroschisis, as well as to determine if in utero fetal weight gain was predictive of a more complicated postnatal course. We hypothesized that fetuses with gastroschisis would follow a slower growth curve, particularly in the third trimester, and that poor interval growth would be associated with greater risks of adverse neonatal outcomes.

Materials and Methods

This was a retrospective cohort study of pregnancies with fetal gastroschisis evaluated at one of the five institutions of the University of California Fetal-Maternal Consortium (UCfC) from December 2014 to December 2019. The UCfC is a multi-institutional collaboration of tertiary academic medical centers that includes UC Davis, UC Irvine, UC Los Angeles, UC San Diego, and UC San Francisco. This study was performed under the UCfC multi-institutional review board reliance registry (IRB #10–04093).

Inclusion criteria were prenatally diagnosed cases of gastroschisis that had at least one prenatal ultrasound performed at 24 weeks gestation or later at a UCfC institution and also delivered at a UCfC institution. Our primary aim was to determine the median increase in overall EFW and individual biometric measurements (biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL)) across each week of gestation in pregnancies with fetal gastroschisis. Our secondary aim was to determine if in utero weight gain was predictive of postnatal growth or adverse neonatal outcomes.

Physicians from each UCfC site collected maternal, pregnancy, and neonatal variables through chart review. Maternal and pregnancy data included age, parity, body mass index (BMI), ethnicity and race, alcohol usage, smoking history, illicit drug use, and prenatal or postnatal diagnostic genetic testing results if performed. Data collected for each prenatal ultrasound performed at a UCfC site were gestational age (GA), EFW in grams, EFW percentile by GA, individual biometric measurements in centimeters (cm) (BPD, HC, AC, FL), quantity of amniotic fluid, and umbilical artery (UA) Doppler measurements if performed. All UCfC institutions used the Hadlock equation to calculate EFW and percentiles, as this formula has been shown to correlate most closely with birth weight.[8,13,14] Inclusion of the AC in the calculation of EFW was left to the providers' discretion, although the vast majority of cases had AC incorporated. Median EFW, BPD, HC, AC, and FL were calculated for each GA in 1-week increments. Weekly gain for each of these metrics was then calculated for each case as the difference in grams or cm from one ultrasound to the next, divided by the number of weeks between measures. The median weekly gain for the cohort was then computed. For cases that had only one EFW calculated at a UCfC site, the biometry measurements were used to calculate median weekly EFW, BPD, HC, AC, and FL; however, these cases were not used to calculate weekly weight gain given the single measurement at one point in time. Fetal growth restriction (FGR) was defined as EFW $<10^{th}$ percentile for GA on the Hadlock growth curve. Oligohydramnios was defined as amniotic fluid index (AFI) < 5 cm or maximum vertical pocket (MVP) < 2 cm.

Neonatal outcomes collected were GA at delivery, birth weight, length of stay in the hospital, complications of gastroschisis (bowel atresia, bowel stricture, ischemic bowel prior to closure, or severe pulmonary hypoplasia), and neonatal growth parameters (weight in grams, length in cm, and head circumference in cm) with their respective z-scores at birth, 14 days, 30 days, and at discharge. We calculated z-scores using means and standard deviations from Fenton et al. for preterm infants (< 37 weeks GA) and from the World Health Organization for term infants.[15,16] Neonatal growth failure was defined as a z-score decrease in weight or length z-score of > 0.8 from birth.[17] In this study, we focused on weight growth failure.

Statistical analyses were performed using Microsoft Excel and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Mean values with standard deviation were reported for normally distributed continuous data, while median values with interquartile range (IQR) were reported for non-parametric continuous data and compared with the Wilcoxon-Mann-Whitney test. A p-value < 0.05 was considered statistically significant. We graphed the median EFW and biometric parameter measurements across gestation for fetuses with gastroschisis and compared against the trajectories of non-anomalous fetuses using Hadlock's growth curve.[13] We calculated the performance characteristics for the last prenatal growth ultrasound in predicting SGA by reporting the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Additionally, the discrepancy between the EFW and birth weight was calculated in neonates who had a growth ultrasound < 1 week before delivery. We graphed postnatal growth trajectories by subgroups of less than or greater than median prenatal weight gain. Generalized estimating equations with group by time interaction terms were used to estimate postnatal growth trajectories and account for repeat measures of the same patient, controlling for GA at birth. A group by time interaction term was included in the model to evaluate significant differences in growth trajectories, and non-linear trajectories were evaluated by including a quadratic time variable.

Results

We identified 95 pregnancies with fetal gastroschisis who, in aggregate, had 360 growth ultrasounds at a UCfC institution. Of these, 10 pregnancies had only one ultrasound at a UCfC institution and thus were not used to calculate interval growth. Overall, the women in our cohort were young, the majority were nulliparous, and Hispanic and White were the most common self-identified racial/ethnic groups (Table 1). Additionally, cases were relatively evenly distributed across the five UCfC institutions. There were no cases of fetal demise or stillbirth.

Fifty-nine pregnancies (62%) were dated by or confirmed by a first trimester ultrasound at ≤ 13 completed weeks gestation, 32 pregnancies (34%) were dated by or confirmed by an ultrasound at > 13 to ≤ 20 weeks gestation, and 3 pregnancies (3%) were dated by last menstrual period and consistent with > 20 weeks gestation ultrasounds. One pregnancy (1%) was dated by a third trimester ultrasound as the mother initiated prenatal care late in gestation. Six cases underwent prenatal diagnostic testing and 8 neonates had postnatal testing with karyotype and/or chromosomal microarray, and all had normal results.

Fifty-seven pregnancies (60%) were diagnosed with FGR during the pregnancy, with 40 of these pregnancies (70%) remaining growth restricted until delivery. Of the 74 pregnancies with any UA Doppler studies performed, nine (12%) had an elevated systolic / diastolic ratio > 95th percentile, but none developed absent or reverse end diastolic flow. No pregnancies developed oligohydramnios.

The median weekly increase in growth across gestation for EFW, BPD, HC, AC, and FL are summarized in Table 2. Median interval growth calculated from the 85 fetuses with more than one ultrasound was 130 grams per week (IQR 111–163). Greater weekly interval increase in EFW was observed in the third trimester: 182 grams per week (IQR 135–205) in the 3rd trimester compared to 79 grams per week (IQR 65–93) in the 2nd trimester. In only 7 ultrasounds for 2 fetuses, AC was not used in the calculation of EFW at the discretion of local providers. Excluding these 7 ultrasounds without AC in the interval median growth calculations did not alter our results. Similar trends were observed in the weekly interval increase for each biometric measurement, with greater interval increase observed during the third trimester (Table 2).

Table 3 shows the median EFW, BPD, HC, AC, and FL for each individual GA week from 24 to 38 weeks gestation. Based on the incremental weekly growth in each of these parameters, we created fetal growth charts for EFW, BPD, HC, AC, and FL in pregnancies with gastroschisis. Figure 1a graphs the median EFW for fetuses with gastroschisis by GA week relative to non-anomalous fetuses on the Hadlock growth curve.[13] Figures 1b–d show the median measurements for each biometric parameter also plotted against non-anomalous fetuses on the Hadlock growth curve.[13] The median EFW and AC measurements in fetal gastroschisis cases approximated the threshold for FGR across gestation. Moreover, the median BPD, HC, and FL measurements remained below the 50th percentile on the Hadlock growth curve across gestation. Fluctuations in these trends seen in later gestational ages reflect the small number of ongoing pregnancies at those points with ultrasounds performed.

The median GA at delivery was 37 weeks (IQR 35.5–37.7), and 49% of the 95 pregnancies in the cohort were delivered preterm. Twenty-five pregnancies (53%) of those that delivered preterm were due to spontaneous preterm labor or preterm premature rupture of membranes, while the remainder were delivered for medically indicated reasons. The median birth weight was 2526 grams (IQR 2173–2949) and median length of stay in the hospital for the neonate after birth was 29 days (IQR 22–52). Twenty-eight neonates (29%) were diagnosed with SGA. The performance measures of FGR diagnosed at the last prenatal growth ultrasound in predicting SGA are as follows: sensitivity 60%, specificity 66%, positive predictive value 43%, negative predictive value 80%, and accuracy 64%. Thirty-two prenatal growth ultrasounds were performed < 1 week prior to delivery, and 30 of these EFWs (94%) were within 20% of the actual birth weight. The corresponding estimated coefficient of reliability was 0.77.

Ninety-three neonates had postnatal growth data available. The 46 neonates with gastroschisis who had less than median weekly prenatal weight gain were significantly smaller at birth than the 47 neonates who had greater than median weekly prenatal weight gain: 2185 grams (IQR 2035–2510) versus 2780 grams (IQR 2512–3235), respectively ($p < 0.01$). Figure 2 plots these neonatal growth patterns, stratified by prenatal growth less than or greater than the median. No statistically significant difference was observed in the postnatal weight gain trajectory between the two groups ($p = 0.47$). The median neonatal length of stay did not differ significantly between neonates who had less than versus greater than median weekly prenatal weight gain (32 days versus 29 days, $p = 0.79$).

Finally, 12 out of 93 neonates (13%) were diagnosed with a complication of gastroschisis after birth. Comparing neonates with a complication of gastroschisis to those without, there were no significant differences in prenatal growth trajectories ($p = 0.11$) or birth weight (median birth weight 2665 grams for gastroschisis with complications versus 2511 grams for those without complications; $p = 0.96$). Fifty-four of 83 neonates (65%) with anthropometric data at the time of discharge were diagnosed with weight or length growth failure at discharge. Comparing neonates who had growth failure at discharge and those who had adequate growth at discharge, there were no significant differences in prenatal growth trajectories ($p = 0.22$).

Structured Discussion/ Comment

Principal Findings

In this multicenter cohort of pregnancies with fetal gastroschisis, 60% were diagnosed with FGR and the median interval growth was 130 grams per week, with greater growth observed in the third trimester. The overall in utero growth trajectory for EFW as well as AC closely followed the 10^{th} percentile on the Hadlock curve. This pattern suggests that “appropriate” growth in a fetus with gastroschisis approximates the growth trajectory of a non-anomalous fetus at the 10^{th} percentile when BPD, HC, AC, and FL are routinely utilized to calculate EFW. Additionally, neonates with gastroschisis who had less than median weekly prenatal weight gain had smaller birth weights than those with greater prenatal weight gain.

Prenatal Considerations

Previous studies have similarly reported a right-shift of the 50th percentile for EFW in fetuses with gastroschisis.[8,18,19] These studies, however, did not evaluate what constitutes adequate interval growth per week. Because AC measurements may be falsely low in cases of gastroschisis due to exteriorization of abdominal contents, and the overall EFW is based upon biometry measurements including AC, this may partially explain our findings as well as those in other studies.[8,18,19] Even so, EFW calculated < 1 week from delivery had relatively good correlation with actual birth weight and the accuracy of prenatal ultrasound in predicting SGA in our cohort was similar to results from another contemporary study.[20] Our findings provide useful data because interval growth can serve as an important tool in clinical management decisions.

Features intrinsic to the open abdominal wall defect may explain the prenatal growth patterns seen in fetuses with gastroschisis. Abnormal UA Doppler studies are rare in pregnancies with gastroschisis, which is confirmed in our study, and suggests that placental insufficiency does not drive the smaller growth pattern.[21,22] Fetuses with gastroschisis have been suggested to have significantly more digestive and inflammatory compounds, including protein, interleukins, ferritin, lipase, and amylase, in the amniotic fluid compared to non-anomalous fetuses.[23,24] After birth, cord serum total protein is significantly less in neonates with gastroschisis compared to normal neonates.[22]

Postnatal Considerations

Poor prenatal growth in cases of fetal gastroschisis correlates with lower neonatal weights, and while they did not appear to "catch up" with their peers who exhibited greater weekly weight gain prenatally, their growth trajectory did not deteriorate postnatally and did not predict length of stay in the NICU. Other studies have also found that prenatal growth in cases of fetal gastroschisis is predictive of neonatal weight but not of neonatal complications.[26,27] We also did not find a relationship between poor fetal weight gain and gastroschisis complications after birth. It is likely that postnatal growth failure and complications of gastroschisis are multifactorial events stemming from poor absorption, chronic inflammation, prematurity, and other factors.[28,29]

Research Implications

Future studies are needed to understand the prenatal risks associated with poor interval growth, specifically stillbirth, spontaneous preterm birth, and medically indicated preterm birth. Further, research investigating the degree of deficiency in proteins and other digestive compounds in fetuses with gastroschisis could elucidate potential contributing mechanisms for growth restriction. The resulting inflammation from spillage of digestive compounds into the amniotic cavity may also contribute to the common outcomes of spontaneous preterm labor and premature rupture of membranes that we observed in our cohort.

Strengths and Limitations

A major strength of our study is the diverse cohort of fetal gastroschisis cases across several large institutions in California, allowing for more generalizable results. Cases of fetal gastroschisis had multiple ultrasounds performed at the same tertiary institution, conferring a higher likelihood of reliable interval growth measurements across gestational weeks. Our data collection was thorough, and few cases in our cohort had missing data. Importantly, our study also contributes novel data regarding interval growth overall and for each biometric parameter during each week across gestation, and our study correlates prenatal growth patterns to postnataln outcomes. However, our study does have limitations. We noted variation across UCfC institutions in their ultrasound methodology and frequency for fetuses with gastroschisis. One site, for example, occasionally excluded AC for the calculation of EFW. There is potential for inter-observer variability in ascertainment of fetal biometric measurements, and there are limitations to prenatal ultrasound estimation of fetal weight.[30] While this is a relatively large cohort of cases of fetal gastroschisis, our numbers remain small given rarity of this disorder. Outcomes such as stillbirth were too rare to assess in our cohort, and it is possible that other comparisons did not reach statistical significance for this reason.

Conclusions

In summary, the growth of fetuses with gastroschisis approximates the 10th percentile on the Hadlock curve for non-anomalous fetuses, and the median weekly interval growth is 130 grams, with greater growth observed in the third trimester. The growth patterns in this cohort can be used in clinical practice to stratify pregnancies with gastroschisis that are potentially of greater concern. Future research will be important to elucidate the reasons for this smaller in utero growth potential, risks to the pregnancy in the setting of poor interval growth and implications for prenatal management, and relationships to longer-term adverse childhood outcomes.

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AJOG at a Glance:

A. Fetal gastroschisis is often complicated by fetal growth restriction, which complicates the decision for timing of delivery. In this study, we sought to define "appropriate" interval growth in fetal gastroschisis and assess the relationship of prenatal weight gain to postnatal growth and outcomes.

B. The median interval growth in fetal gastroschisis is 130 grams per week, and median estimated fetal weight (EFW) in gastroschisis closely resembles the 10^{th} percentile EFW in non-anomalies fetuses. We describe the median prenatal interval growth for individual biometric parameters. Poor prenatal growth in gastroschisis is associated with low birth weight but not adverse neonatal outcomes.

C. We define "appropriate" interval growth in fetal gastroschisis as 130 grams per week and show that prenatal growth does not predict adverse neonatal outcomes.

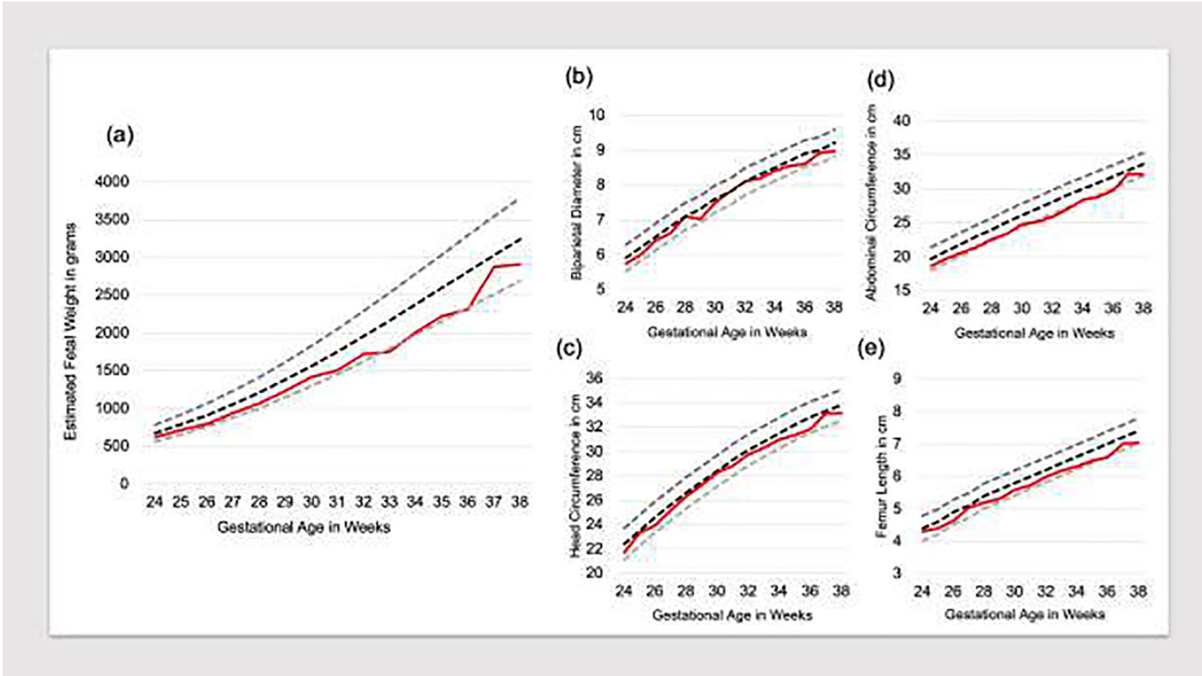

Figure 1.

Median estimated fetal weight (a), biparietal diameter (b), head circumference (c), abdominal circumference (d), and femur length (e) by completed gestational weeks and plotted on nomograms from non-anomalous fetuses. Red line represents fetuses with gastroschisis. Dashed black line represents 50th percentile. Upper and lower dashed grey lines represent 90th and 10th percentile, respectively.

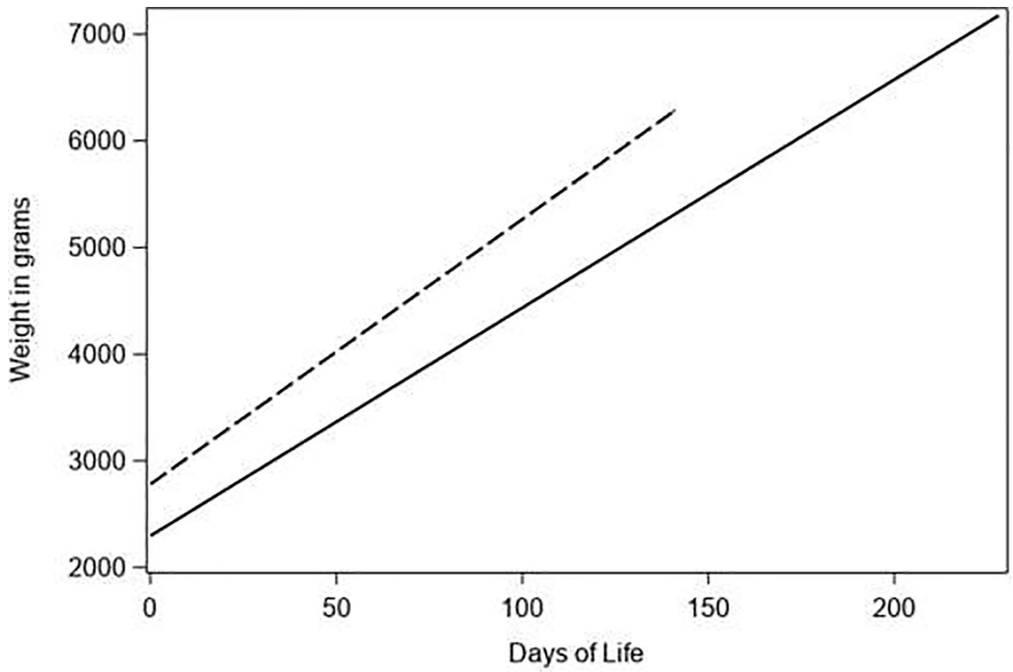

Figure 2.

Postnatal growth for neonates with gastroschisis. Solid line represents median weights for neonates with less than median weekly prenatal weight gain. Dashed line represents median weights for neonates with less than median weekly prenatal weight gain. The endpoints for median weights differ due to variation in discharge timepoint.

Table 1:

Maternal demographics for pregnancies with fetal gastroschisis.

Demographic	Value (N = 95)
Maternal age in years, mean (standard deviation)	23.6 (4.7)
Maternal BMI, mean (standard deviation)	27.5 (5.7)
Nulliparous, n (%)	61 (64%)
Ethnicity/Race, n (%)	
Asian/ Pacific Islander	3 (3%)
Black	1 (1%)
Other/mixed	2 (2%)
White	37 (39%)
Hispanic	52 (55%)
Social History, n (%)	
Any smoking	7 (7%)
Alcohol use in pregnancy	1 (1%)
Other drug use in pregnancy	12 (13%)
University of California Fetal-Maternal Consortium site, n (%)	
UC Davis	17 (18%)
UC Irvine	19 (20%)
UC Los Angeles	19 (20%)
UC San Diego	14 (15%)
UC San Francisco	26 (27%)

Table 2:

Median weekly increase in estimated fetal weight and biometric measurements (biparietal diameter, head circumference, abdominal circumference, and femur length) for pregnancies with gastroschisis.

	N[a]	Median	IQR
Estimated fetal weight			
Median weekly gain overall (g)	85	130	111–163
Median weekly gain in 2nd trimester (g)	42	79	65–93
Median weekly gain in 3rd trimester (g)	71	182	136–205
Biparietal Diameter			
Median weekly gain (cm)	85	0.25	0.23–0.28
Median weekly gain in 2nd trimester (cm)	42	0.29	0.24–0.32
Median weekly gain in 3rd trimester (cm)	71	0.22	0.17–0.27
Head Circumference			
Median weekly gain (cm)	85	0.90	0.77–0.99
Median weekly gain in 2nd trimester (cm)	42	1.06	0.99–1.18
Median weekly gain in 3rd trimester (cm)	71	0.69	0.58–0.82
Abdominal Circumference			
Median weekly gain (cm)	85	0.99	0.87–1.10
Median weekly gain in 2nd trimester (cm)	43	1.02	0.87–1.19
Median weekly gain in 3rd trimester (cm)	71	0.99	0.68–1.15
Femur Length			
Median weekly gain (cm)	85	0.21	0.19–0.24
Median weekly gain in 2nd trimester (cm)	42	0.25	0.22–0.27
Median weekly gain in 3rd trimester (cm)	71	0.20	0.16–0.24

cm, centimeter. g, grams. IQR, interquartile range.

[a]Number of fetuses included in the calculation of median weekly gain. Only 85 of the 95 fetuses that had more than one ultrasound reporting biometry were used in the calculations.

Table 3:

Median estimated fetal weight, biparietal diameter, head circumference, abdominal circumference, and femur length for each individual GA week in pregnancies with gastroschisis.

GA	Estimated Fetal Weight (g)		Biparietal Diameter (cm)		Head Circumference (cm)		Abdominal Circumference (cm)		Femur Length (cm)	
	N[a]	Median	N[a]	Median	N[a]	Median	N[a]	Median	N[a]	Median
24	12	615	12	5.7	12	21.7	12	18.6	12	4.3
25	19	714	19	6.0	19	23.3	19	19.7	19	4.4
26	13	791	12	6.4	12	23.9	13	20.6	12	4.6
27	17	938	17	6.6	17	25.2	17	21.4	17	5.0
28	23	1064	23	7.1	23	26.3	23	22.6	23	5.2
29	17	1233	17	7.0	17	27.2	17	23.4	17	5.3
30	22	1416	22	7.5	22	28.3	22	24.8	22	5.6
31	30	1502	28	7.8	29	28.8	30	25.1	29	5.7
32	27	1717	27	8.1	27	29.7	27	25.9	27	6.0
33	14	1753	14	8.2	13	30.3	14	27.0	14	6.2
34	32	2008	32	8.4	32	31.0	32	28.4	32	6.3
35	28	2223	28	8.5	28	31.3	28	28.8	27	6.5
36	19	2315	20	8.6	20	31.8	19	29.8	19	6.6
37	12	2873	12	8.9	12	33.1	12	32.2	12	7.0
38	2	2909	2	9.0	2	33.1	2	32.1	2	7.0

cm, centimeter. g, grams. GA, gestational age.

[a]Number of fetuses included in the calculation of median weekly gain. Only 85 of the 95 fetuses that had more than one ultrasound reporting biometry were used in the calculations.