Interval growth across gestation in pregnancies with fetal gastroschisis

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BACKGROUND: Gastroschisis is often complicated by fetal growth restriction, preterm delivery, and prolonged neonatal hospitalization. Prenatal management and delivery decisions are often based on estimated fetal weight and interval growth; however, appropriate interval growth from week to week across gestation for these fetuses is poorly understood.

OBJECTIVE: This study aimed 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 whether 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 5 institutions of the University of California Fetal-Maternal Consortium from December 2014 to December 2019. The inclusion criteria were prenatally diagnosed gastroschisis with at least 1 ultrasound performed at a University of California Fetal-Maternal Consortium institution. Estimated fetal weight and individual biometric measurements were recorded for each ultrasound performed at a University of California Fetal-Maternal Consortium institution from the time of gastroschisis diagnosis to delivery. Median estimated fetal weight and biometric measurements were calculated for each gestational age in 1-week increments. Neonatal outcomes collected were birthweight, length of stay, complications of gastroschisis (bowel atresia, bowel stricture, ischemic bowel before 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 University of California Fetal-Maternal Consortium institution. The median interval growth was 130 g/wk. The median estimated fetal weight and abdominal circumference in fetal gastroschisis cases were approximately the tenth percentile on the Hadlock growth curve across gestation. Moreover, the median biparietal diameter, head circumference, and femur length measurements remained below the 50th percentile on the Hadlock growth curve across gestation. The median birthweight for neonates with less than the median weekly prenatal weight gain was less than for those with greater than the median weekly prenatal weight gain (2185 g vs 2780 g; $P<.01$). There was no difference in prenatal weight gain trajectory when comparing neonates who had or did not have bowel complications of gastroschisis.

CONCLUSION: In this multicenter cohort of pregnancies with fetal gastroschisis, the median interval growth was 130 g/wk, and overall, in utero growth closely followed the tenth 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.

Key words: abdominal wall defect, biometric parameters, fetal anomaly, fetal growth restriction, nomograms, postnatal growth

Introduction

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

Given the elevated risk of FGR and stillbirth, pregnancies with fetal gastroschisis undergo serial growth ultrasounds and frequent antenatal surveillance. Although 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 GA at birth for neonates with gastroschisis is the prenatal factor most associated with increased neonatal complications, including death, reoperation, gastrostomy, and necrotizing enterocolitis.[12] Importantly, although 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 on 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 and to determine whether 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 of pregnancy, and that poor interval growth would be

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AJOG MFM at a Glance

Why was this study conducted?

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

Key findings

The median interval growth in fetal gastroschisis was 130 g/wk, and the median estimated fetal weight (EFW) in gastroschisis closely resembled the tenth percentile EFW in fetuses with no anomaly. We described the median prenatal interval growth for individual biometric parameters. Poor prenatal growth in gastroschisis was associated with low birthweight but not adverse neonatal outcomes.

What does this add to what is known?

We have defined "appropriate" interval growth in fetal gastroschisis as 130 g/wk and have shown that prenatal growth does not predict adverse neonatal outcomes.

associated with greater risks of adverse neonatal outcomes.

Materials and Methods

This was a retrospective cohort study of pregnancies with fetal gastroschisis evaluated at 1 of 5 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 (institutional review board number 10-04093).

The inclusion criteria were prenatally diagnosed cases of gastroschisis that had at least 1 prenatal ultrasound performed at 24 weeks of gestation or later at a UCfC institution and women who 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 medical record reviews. Maternal and pregnancy data included age, parity, body mass index, 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 GA, EFW in grams, EFW percentile by GA, individual biometric measurements in centimeters (BPD, HC, AC, and FL), quantity of amniotic fluid, and umbilical artery (UA) Doppler measurements if performed. All UCfC institutions used the Hadlock equation to calculate the EFWs and percentiles, as this formula has been shown to correlate most closely with birthweight.[8,13,14] Inclusion of the AC in the calculation of EFW was left to the providers' discretion, although most 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 calculated for each case as the difference in grams or centimeters from 1 ultrasound to the next, divided by the number of weeks between measures. Moreover, the median weekly gain for the cohort was computed. For cases that had only 1 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 1 point in time. FGR was defined as an EFW of <tenth percentile for GA on the Hadlock growth curve. Oligohydramnios was defined as an amniotic fluid index of <5 cm or a maximum vertical pocket of <2 cm.

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

Statistical analyses were performed using Microsoft Excel and the Statistical Analysis System (version 9.4; SAS Institute Inc, Cary, NC). Mean values with SD were reported for normally distributed continuous data, whereas median values with interquartile range (IQR) were reported for nonparametric continuous data and compared with the Wilcoxon-Mann-Whitney test. A P value of <.05 was considered statistically significant. We graphed the median EFW and biometric parameter measurements across gestation for fetuses with gastroschisis and compared it with the trajectories of nonanomalous fetuses using the Hadlock growth curve.[13] We calculated the performance characteristics for the last prenatal growth ultrasound in predicting small for gestational age (SGA) by reporting the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. In addition, the discrepancy between the EFW and birthweight

TABLE 1
Maternal demographics for pregnancies with fetal gastroschisis

Demographic	Value (N=95)
Maternal age (y)	23.6±4.7
Maternal BMI (kg/m^2)	27.5±5.7
Nulliparous	61 (64)
Ethnicity and race	
Asian or Pacific Islander	3 (3)
Black	1 (1)
Other or mixed	2 (2)
White	37 (39)
Hispanic	52 (55)
Social history	
Any smoking	7 (7)
Alcohol use in pregnancy	1 (1)
Other drug use in pregnancy	12 (13)
University of California Fetal-Maternal Consortium site	
UC Davis	17 (18)
UC Irvine	19 (20)
UC Los Angeles	19 (20)
UC San Diego	14 (15)
UC San Francisco	26 (27)

Data are presented as mean±standard deviation or number (percentage).

BMI, body mass index; *UC*, University of California.

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was calculated in neonates who had a growth ultrasound of <1 week before delivery. We graphed the postnatal growth trajectories by subgroups of less than or greater than the 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 differences in growth trajectories, and nonlinear 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 1 ultrasound at a UCfC institution and thus were not used to calculate interval growth. Overall, the women in our cohort were young, most women were nulliparous, and Hispanic and White were the most common self-identified racial and ethnic groups (Table 1). In addition, cases were relatively evenly distributed across the 5 UCfC institutions. There was no case of fetal demise or stillbirth.

Here, 59 pregnancies (62%) were dated by or confirmed by a first-trimester ultrasound at ≤13 completed weeks of gestation, 32 pregnancies (34%) were dated by or confirmed by ultrasound at >13 to ≤20 weeks of gestation, and 3 pregnancies (3%) were dated by last menstrual period and consistent with >20 weeks of gestation ultrasounds. Notably, 1 pregnancy (1%) was dated by a third-trimester ultrasound as the mother initiated prenatal care late in gestation. Furthermore, 6 cases underwent prenatal diagnostic testing, and 8 neonates had postnatal testing with karyotype and/or chromosomal microarray. Nonetheless, all cases had normal results.

In addition, 57 pregnancies (60%) were diagnosed with FGR during the pregnancy, with 40 of these pregnancies (70%) continuing to have FGR until delivery. Of the 74 pregnancies with any UA Doppler studies performed, 9 (12%) had an elevated systolic or diastolic ratio of >95th percentile, but none developed absent or reverse end-diastolic flow. No pregnancy developed oligohydramnios.

The median weekly increases in growth across gestation for EFW, BPD, HC, AC, and FL are summarized in Table 2. The median interval growth calculated from the 85 fetuses with more than 1 ultrasound was 130 g/wk (IQR, 111−163). Greater weekly interval increase in EFW was observed in the third trimester of pregnancy: 182 g/wk (IQR, 135−205) in the third trimester of pregnancy compared with 79 g/wk (IQR, 65−93) in the second trimester of pregnancy. 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 of pregnancy (Table 2).

Table 3 shows the median EFW, BPD, HC, AC, and FL for each individual GA in weeks from 24 to 38 weeks of gestation. Based on the incremental weekly growth in each of these parameters, we created fetal growth graphs for EFW, BPD, HC, AC, and FL in pregnancies with gastroschisis. Figure 1, A illustrates the median EFW for fetuses with gastroschisis by GA in weeks relative to nonanomalous fetuses on the Hadlock growth curve.[13] In addition, Figure 1, B−D illustrates the median measurements for each biometric parameter plotted against

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

Variable	n[a]	Median	Interquartile range
EFW			
Median weekly gain overall (g)	85	130	111−163
Median weekly gain in the second trimester of pregnancy (g)	42	79	65−93
Median weekly gain in the third trimester of pregnancy (g)	71	182	136−205
BPD			
Median weekly gain (cm)	85	0.25	0.23−0.28
Median weekly gain in the second trimester of pregnancy (cm)	42	0.29	0.24−0.32
Median weekly gain in the third trimester of pregnancy (cm)	71	0.22	0.17−0.27
HC			
Median weekly gain (cm)	85	0.90	0.77−0.99
Median weekly gain in the second trimester of pregnancy (cm)	42	1.06	0.99−1.18
Median weekly gain in the third trimester of pregnancy (cm)	71	0.69	0.58−0.82
AC			
Median weekly gain (cm)	85	0.99	0.87−1.10
Median weekly gain in the second trimester of pregnancy (cm)	43	1.02	0.87−1.19
Median weekly gain in the third trimester of pregnancy (cm)	71	0.99	0.68−1.15
FL			
Median weekly gain (cm)	85	0.21	0.19−0.24
Median weekly gain in the second trimester of pregnancy (cm)	42	0.25	0.22−0.27
Median weekly gain in the third trimester of pregnancy (cm)	71	0.20	0.16−0.24

AC, abdominal circumference, *BPD*, biparietal diameter; *EFW*, estimated fetal weight; *FL*, femur length; *HC*, head circumference.

[a] The number of fetuses included in the calculation of median weekly gain. Only 85 of 95 fetuses that had >1 ultrasound reporting biometry were used in the calculations.

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nonanomalous 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 GAs 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 47 of 95 pregnancies (49%) in the cohort were delivered before term. Moreover, 25 pregnancies (53%) of those that delivered before term were due to spontaneous preterm labor or preterm premature rupture of membranes, whereas the remainder were delivered for medically indicated reasons. The median birthweight was 2526 g (IQR, 2173−2949), and the median length of stay in the hospital for the neonate after birth was 29 days (IQR, 22−52). Notably, 28 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 of 60%, specificity of 66%, positive predictive value of 43%, negative predictive value of 80%, and accuracy of 64%. Furthermore, 32 prenatal growth ultrasounds were performed <1 week before delivery, and 30 of the EFWs (94%) were within 20% of the actual birthweight. The corresponding estimated coefficient of reliability was 0.77.

A total of 93 neonates had postnatal growth data available. The 46 neonates with gastroschisis who had less than the median weekly prenatal weight gain were significantly smaller at birth than the 47 neonates who had greater than the median weekly prenatal weight gain: 2185 g (IQR, 2035−2510) vs 2780 g (IQR, 2512−3235), respectively (P<.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 2 groups (P=.47). The median neonatal length of stay did not differ significantly between neonates who had less than vs greater than the median weekly prenatal weight gain (32 vs 29 days; P=.79).

TABLE 3

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

GA	EFW (g)		BPD (cm)		HC (cm)		AC (cm)		FL (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

AC, abdominal circumference, *BPD*, biparietal diameter; *EFW*, estimated fetal weight; *FL*, femur length; *GA*, gestational age; *HC*, head circumference.

[a] The number of fetuses included in the calculation of median weekly gain. Only 85 of 95 fetuses that had >1 ultrasound reporting biometry were used in the calculations.

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Finally, 12 of 93 neonates (13%) were diagnosed with a complication of gastroschisis after birth. Comparing neonates with a complication of gastroschisis with those without, there was no significant difference in prenatal growth trajectories (P=.11) or birthweight (median birthweight, 2665 g for gastroschisis with complications vs 2511 g for those without complications; P=.96). Notably, 54 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 was no significant difference in prenatal growth trajectories (P=.22).

Comment

Principal findings

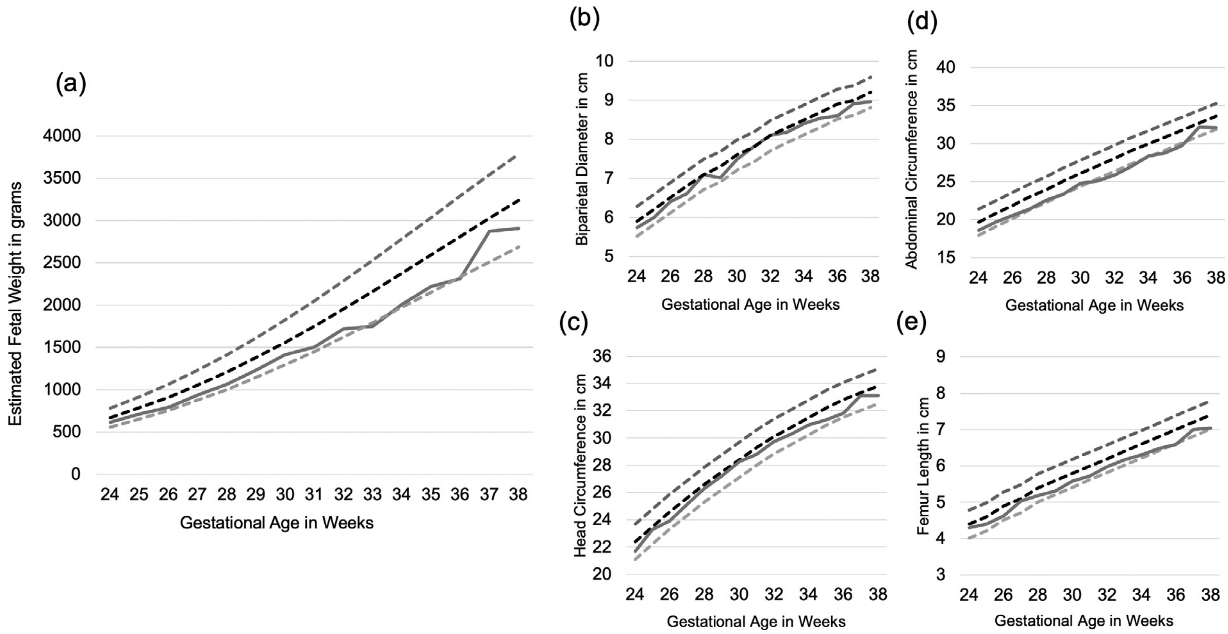
In this multicenter cohort of pregnancies with fetal gastroschisis, 60% of pregnancies were diagnosed with FGR, and the median interval growth was 130 g/wk, with greater growth observed in the third trimester of pregnancy. The overall in utero growth trajectory for EFW and AC closely followed the tenth percentile on the Hadlock curve. This pattern suggests that "appropriate" growth in a fetus with gastroschisis is approximately the growth trajectory of a nonanomalous fetus at the tenth percentile when BPD, HC, AC, and FL are routinely used to calculate EFW. In addition, neonates with gastroschisis who had less than the median weekly prenatal weight gain had smaller birthweights 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.[8–10] However, these studies did not evaluate what constitutes adequate interval growth per week. Because AC measurements may be falsely low in cases of gastroschisis because of exteriorization of abdominal contents, and the overall EFW is based on biometry measurements, including AC; this may partially explain our findings and those in other studies.[8–10] Nonetheless, EFW calculated <1 week from delivery had a relatively good correlation with actual birthweight, and the accuracy of prenatal ultrasound in predicting SGA in our cohort was similar to results from another contemporary study.[18] Our findings provided 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.[19,20] Fetuses with gastroschisis have been suggested to have significantly more digestive and

FIGURE 1
Median biometric measurement in fetal gastroschisis



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 nonanomalous fetuses. The red line represents the fetuses with gastroschisis. The dashed black line represents the 50th percentile. The upper and lower dashed gray lines represent the 90th and 10th percentiles, respectively.

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inflammatory compounds, including protein, interleukins, ferritin, lipase, and amylase, in the amniotic fluid compared with nonanomalous fetuses.[21–23] After birth, cord serum total protein is significantly less in neonates with gastroschisis compared with normal neonates.[20]

Postnatal considerations

Poor prenatal growth in cases of fetal gastroschisis correlates with lower neonatal weights, and although they did not seem to “catch up” with their peers who exhibited greater weekly weight gain prenatally, their growth trajectory did not deteriorate postnatally and did not predict the length of stay in the NICU. Importantly, other studies have found that prenatal growth in cases of fetal gastroschisis is predictive of neonatal weight but not of neonatal complications.[24,25] However, we 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.[26,27]

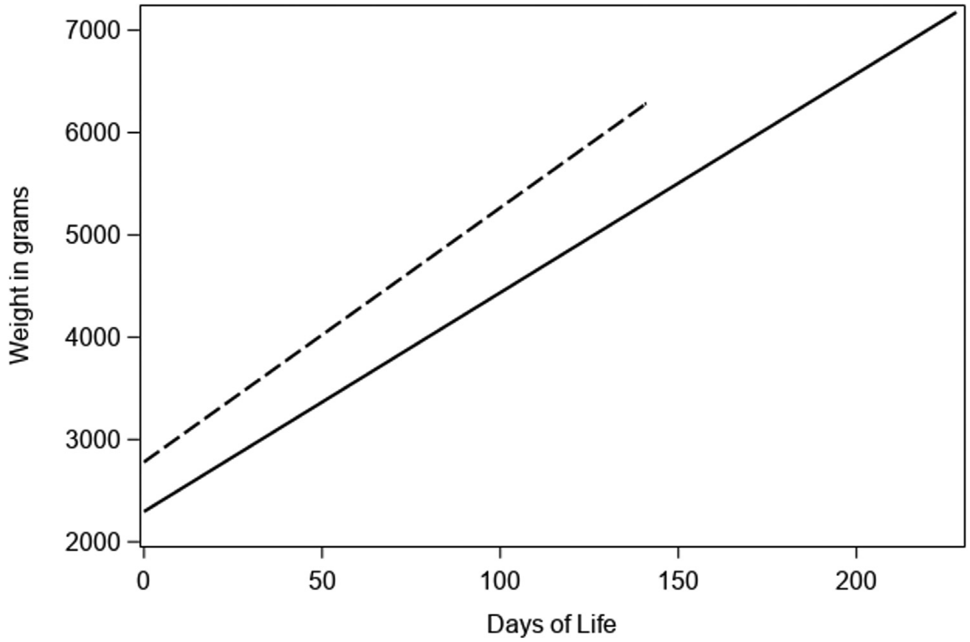
Research implications

Future studies are needed to understand the prenatal risks associated with poor interval growth, specifically stillbirth, spontaneous preterm birth, and medically indicated preterm birth. Furthermore, 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 was 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 contributed novel data regarding interval growth overall and for each biometric parameter during each week across gestation and correlated prenatal growth patterns to postnatal outcomes. However, our study had limitations. We noted a variation in ultrasound methodology and frequency for fetuses with gastroschisis across UCfC institutions. For example, 1 site occasionally excluded AC for the calculation of EFW. There was potential for interobserver variability in the ascertainment

FIGURE 2
Postnatal growth for neonates with gastroschisis



The solid line represents the median weights for neonates with less than the median weekly prenatal weight gain. The dashed line represents the median weights for neonates with less than the median weekly prenatal weight gain. The endpoints for median weights differ because of a variation in discharge time point.

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of fetal biometric measurements, and there were limitations to prenatal ultrasound estimation of fetal weight.[28,29] Although this was a relatively large cohort of cases of fetal gastroschisis, our numbers remained small given the 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

The growth of fetuses with gastroschisis was approximately the tenth percentile on the Hadlock curve for nonanomalous fetuses, and the median weekly interval growth was 130 grams, with greater growth observed in the third trimester of pregnancy. 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 long-term adverse childhood outcomes. ■

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajogmf.2021.100415.

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