

Stillbirth Risk Among Fetuses With Ultrasound-Detected Isolated Congenital Anomalies

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OBJECTIVE: To estimate the risk of stillbirth among pregnancies complicated by a major isolated congenital anomaly detected by antenatal ultrasonography and the influence of incidental growth restriction.

METHODS: A retrospective cohort study of all consecutive singleton pregnancies undergoing routine anatomic survey between 1990 and 2009 was performed. Stillbirth rates among fetuses with an ultrasound-detected isolated major congenital anomaly were compared with fetuses without major anomalies. Stillbirth rates were calculated per 1,000 ongoing pregnancies. Exclusion criteria included delivery before 24 weeks of gestation, multiple fetal anomalies, minor anomalies, and chromosomal abnormalities. Analyses were stratified by gestational age at delivery (before 32 weeks compared with 32 weeks of gestation or after) and birth weight less than the 10th percentile. We adjusted for confounders using logistic regression.

RESULTS: Among 65,308 singleton pregnancies delivered at 24 weeks of gestation or after, 873 pregnancies with an isolated major congenital anomaly (1.3%) were identified. The overall stillbirth rate among fetuses with a major anomaly was 55 per 1,000 compared with 4 per

1,000 in nonanomalous fetuses (adjusted odds ratio [OR] 15.17, 95% confidence interval [CI] 11.03–20.86). Stillbirth risk in anomalous fetuses was similar before 32 weeks of gestation (26/1,000) and 32 weeks of gestation or after (31/1,000). Among growth-restricted fetuses, the stillbirth rate increased among anomalous (127/1,000) and nonanomalous fetuses (18/1,000), and congenital anomalies remained associated with higher rates of stillbirth (adjusted OR 8.20, 95% CI 5.27–12.74).

CONCLUSION: The stillbirth rate is increased in anomalous fetuses regardless of incidental growth restriction. These risks can assist practitioners in designing care plans for anomalous fetuses who have elevated and competing risks of stillbirth and neonatal death.

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In the evaluation that ensues after a stillbirth, congenital anomalies are one of the most commonly identifiable causes.¹ However, with the routine use of ultrasound scanning, the diagnosis of a major anomaly often precedes the loss.^{2,3} There are minimal data with which to counsel patients regarding the ongoing rate of stillbirth among anomalous fetuses after ultrasound diagnosis, especially if the anomaly is isolated and not associated with a genetic syndrome.

Unlike other risk factors for stillbirth,^{4–6} guidelines for the antenatal management of pregnancies complicated by isolated fetal anomalies are limited. In addition to the risk of stillbirth, fetuses with congenital anomalies are at risk for growth restriction,^{7–9} and frequently pregnancy management is based on this subsequent diagnosis rather than the anomaly itself. Although fetal growth restriction is a known independent risk factor for stillbirth,^{10,11} the interaction between growth restriction and fetal anomalies and its effect on stillbirth is largely undefined.

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In this study, we sought to estimate the risk of stillbirth in fetuses with isolated congenital anomalies diagnosed during routine prenatal ultrasound evaluation and examine the influence of the incidental finding of growth restriction on the stillbirth risk using a large ultrasound database at a single institution.

MATERIALS AND METHODS

We performed a retrospective cohort study of all consecutive singleton pregnancies presenting for routine anatomic ultrasound examination at Washington University between 1990 and 2009. The study was conducted using an institutional perinatal database that includes ultrasonographic findings as well as demographic information, maternal medical history, pregnancy, and neonatal outcomes.¹² Approval for the study was granted by the Washington University School of Medicine human studies review board.

Pregnancies complicated by an isolated major fetal anomaly diagnosed prenatally were compared with pregnancies in which a major fetal anomaly was absent. Major congenital anomalies were defined as structural abnormalities likely to result in significant functional impairment or need for medical or surgical intervention. Decisions regarding which anomalies were considered “major” were guided by criteria used in the European Surveillance of Congenital Anomalies (EUROCAT) network.¹³ Anomalies included in the study were classified by the organ system affected and are listed in Box 1. Pregnancies were excluded if the fetus had more than one major anomaly or a chromosomal abnormality. Absence of other structural abnormalities was based on prenatal ultrasound findings only, whereas chromosomal abnormalities may have been diagnosed by either prenatal or postnatal genetic testing. Additionally, pregnancies complicated by minor anomalies, which included any structural abnormality not listed in Box 1, were excluded. Examples of minor anomalies that were excluded include minor markers for aneuploidy, polydactyly, and mild pyelectasis. Pregnancies resulting in delivery before 24 weeks of gestation were also not included in this analysis, because documentation regarding elective termination of pregnancy was not well captured within the database and local regulations do not permit elective termination after this gestational age.

Characteristics of pregnancies complicated by a major congenital anomaly and nonanomalous pregnancies were compared. Data including maternal medical and obstetric history, age, parity, race, and body mass index (calculated as weight (kg)/[height (m)]²) were recorded at the time of routine anatomic

Box 1. Major Structural Anomalies Included in the Study, by Organ System

- Cardiac (n=119)
 - Coarctation of the aorta
 - Tetralogy of Fallot
 - Transposition of the great vessels
 - Truncus arteriosus
 - Double-outlet or double-inlet ventricle
 - Hypoplastic left or right heart
 - Tricuspid atresia
 - Pulmonary atresia
 - Aortic stenosis
 - Ebstein anomaly
- Thoracic or respiratory (n=63)
 - Congenital pulmonary adenomatoid malformation
 - Pulmonary sequestration
- Neurologic (n=153)
 - Caudal regression
 - Dandy-Walker malformation
 - Encephalocele
 - Holoprosencephaly
 - Hydranencephaly
 - Hydrocephalus
 - Iniencephaly
 - Meningocele
 - Ventriculomegaly
- Gastrointestinal (n=140)
 - Anorectal atresia or imperforate anus
 - Duodenal atresia
 - Esophageal atresia
 - Gastroschisis
 - Omphalocele
 - Large bowel obstruction
 - Small bowel obstruction
 - Congenital diaphragmatic hernia
- Genitourinary (n=301)
 - Absent bladder
 - Bladder outlet obstruction or urethral atresia or stenosis
 - Cloacal persistence or cloacal or bladder extrophy
 - Hydroureter
 - Hydronephrosis
 - Renal dysplasia
 - Renal hypoplasia
 - Posterior urethral valves
 - Renal duplication
- Musculoskeletal (n=97)
 - Clubfoot
 - Limb reduction
 - Sirenomelia

ultrasound scan and stored in the perinatal database. Pregnancy outcome data included in the database such as gestational age at delivery, neonate birth weight, and diagnosis of complications such as gestational diabetes or preeclampsia were collected by a dedicated pregnancy outcome coordinator in an ongoing manner after delivery from the medical record for women delivering within our hospital



system or with use of a questionnaire administered to women who delivered elsewhere. If the questionnaire was not returned, the patient or referring health care provider was contacted by telephone. Pregnancies were considered complicated by growth restriction if the birth weight was less than the 10th percentile using the Alexander chart.¹⁴ Statistical comparisons were performed using the χ^2 test for categorical variables. The Mann–Whitney *U* test was used to compare gestational age at delivery and birth weight because these continuous variables were not normally distributed.

The stillbirth rate per 1,000 ongoing pregnancies beyond 23 6/7 weeks of gestation was calculated for pregnancies complicated by isolated major congenital anomaly and those pregnancies without major anomalies. To compare the stillbirth rates in anomalous and nonanomalous pregnancies, we calculated the relative risk of stillbirth with the 95% confidence interval. To determine whether stillbirths occurred early or late in gestation, we performed a stratified analysis based on gestational age at delivery before 32 weeks and 32 weeks or after. Stillbirth rates were calculated per ongoing pregnancies; thus, the denominator in the before 32 weeks of gestation stillbirth analysis included all women in the study, whereas the denominator in the 32 weeks of gestation or after strata only included women who were still pregnant at 32 0/7 weeks of gestation. The effect of incidental growth restriction was also investigated using stratified analysis. Multivariable logistic regression was used to adjust for relevant confounders. All characteristics associated with isolated major congenital anomaly in univariable analysis were included in the initial model. A backward, stepwise approach using the likelihood ratio test to assess the effect of the removal of covariates was used to create the final model, which included black race, maternal obesity (body mass index greater than 30), and pregestational diabetes. Additionally, we performed a sensitivity analysis excluding universally lethal anomalies including anencephaly or acrania and bilateral renal agenesis. We then calculated the rate of stillbirth per 1,000 ongoing pregnancies in each of the six organ system categories and compared these rates with the stillbirth rate in the nonanomalous control group by calculating relative risks and 95% confidence intervals (CIs). All statistical analyses were performed using STATA 10.0 special edition.

RESULTS

Within the perinatal ultrasound database, 76,453 singleton pregnancies were identified. After excluding pregnancies complicated by chromosomal abnormal-

ities, minor anomalies, or multiple major anomalies in the same fetus, 74,424 pregnancies remained. Delivery before 24 weeks of gestation occurred in 1,429 pregnancies (1.9%), of which 333 were among pregnancies complicated by an isolated major congenital anomaly and 1,096 were in nonanomalous pregnancies. In addition, 7,957 pregnancies were lost to follow-up (10.7%); 33 pregnancies were in the anomalous group and 7,924 in the nonanomalous group. The final cohort included 65,308 pregnancies, which was comprised of 873 pregnancies with an isolated major congenital anomaly (1.3%) and 64,165 nonanomalous pregnancies (Fig. 1).

Pregnancies complicated by an isolated major congenital anomaly were more likely to occur in women who were white, nulliparous, and of advanced maternal age. Maternal obesity, gestational diabetes, and chronic hypertension were more common in nonanomalous pregnancies. Median gestational age at delivery was earlier in pregnancies with an isolated anomaly. Overall median birth weight was lower in pregnancies with an isolated congenital anomaly; additionally, 24.4% of anomalous fetuses were also growth-restricted at birth, whereas only 11.5% of nonanomalous pregnancies were complicated by growth restriction (Table 1). The proportion of isolated congenital anomalies detected by ultrasonography was similar from 1990–1999 and 2000–2009 (1.29% compared with 1.39%, $P=.27$).

Fetuses with an isolated congenital anomaly had a 15-fold increased risk of stillbirth after adjusting for maternal obesity, pregestational diabetes, and black race. The stillbirth rate was highest (127/1,000 pregnancies) among pregnancies complicated by both

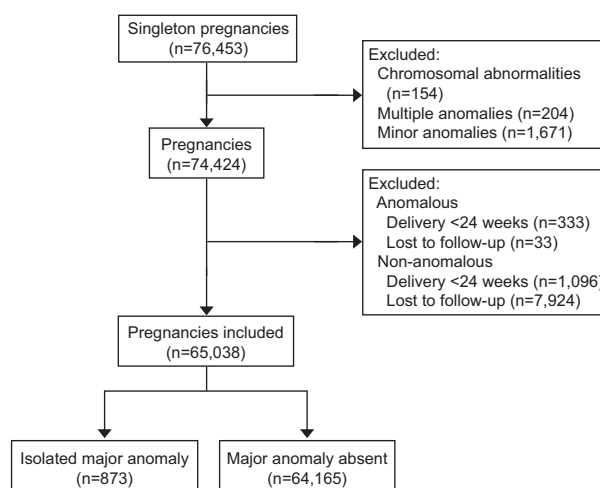


Fig. 1. Study flow diagram.

Frey. Stillbirth in Isolated Anomalies. *Obstet Gynecol* 2014.



Table 1. Baseline Characteristics of Pregnancies Complicated by a Fetus With an Isolated Major Structural Anomaly Compared With Pregnancies Without Major Fetal Anomalies

Characteristic	Isolated Major Anomaly Present (n=873)	Major Anomaly Absent (n=64,165)	P
Maternal age (y)			
Advanced maternal age (older than 34 y)	177 (20.3)	18,516 (28.9)	<.01
Race			
Black	176 (20.2)	14,732 (22.9)	<.01
White	598 (68.5)	39,305 (61.3)	
Other	99 (11.3)	10,128 (15.8)	
Nulliparous	369 (42.3)	24,742 (38.6)	.03
BMI (kg/m ²)			
30 or greater	142 (16.3)	12,695 (19.8)	.01
Diabetes			
Pre-GDM	24 (2.7)	1,189 (1.9)	.05
GDM*	25 (2.9)	3,250 (5.2)	<.01
Hypertension			
Chronic hypertension	12 (1.4)	1,558 (2.4)	.04
Preeclampsia or gestational† hypertension	67 (7.9)	5,085 (8.1)	.77
Amniocentesis performed during the pregnancy	192 (22.0)	7,311 (11.4)	<.01
Gestational age at delivery (wk)	38.1 (36.1–39.3)	39.1 (38.1–40.0)	<.01
Birth weight (g)	2,931 (2,260–3,433)	3,348 (2,951–3,689)	<.01
Birth weight less than 10% ile	213 (24.4)	7,376 (11.5)	<.01
History of prior stillbirth	14 (1.6)	1,454 (2.3)	.19

BMI, body mass index; GDM, gestational diabetes mellitus.

Data are n (%) or median (interquartile range) unless otherwise specified.

* Denominators for anomalies group (n=852) and nonanomalous group (n=62,449) as a result of missing data.

† Denominators for anomalies group (n=852) and nonanomalous group (n=62,446) as a result of missing data.

a congenital anomaly and growth restriction. However, because of the relatively high rate of stillbirth in nonanomalous growth-restricted pregnancies (18/1,000 pregnancies), the risk of stillbirth associated with

a major congenital anomaly in growth-restricted pregnancies (adjusted odds ratio [OR] 8.20, 95% CI 5.27–12.74) is lower than risk associated with a major congenital anomaly in nongrowth-restricted pregnancies

Table 2. Stillbirth Rate Among Fetuses With Isolated Major Structural Anomalies Compared With Fetuses Without Major Structural Anomalies

	Isolated Major Anomaly Present (n=873)	
	No. of Stillbirths/No. of Pregnancies	Stillbirth Rate/1,000 Ongoing Pregnancies (95% CI)
All*	48/873	55 (41–72)
Stillbirth rate at less than 32 wk of gestation*	23/873	26 (17–39)
Stillbirth rate at 32 wk of gestation or greater*	25/795	31 (20–46)
Birth weight less than 10% ile†	27/213	127 (85–179)
Stillbirth rate at less than 32 wk of gestation†	9/213	41 (20–79)
Stillbirth rate at 32 wk of gestation or greater†	18/191	94 (57–145)
Birth weight greater than 10% ile‡	21/660	32 (20–48)
Stillbirth rate at less than 32 wk of gestation§	14/660	21 (12–35)
Stillbirth rate at 32 wk or greater§	7/604	12 (5–24)

CI, confidence interval; RR, relative risk aOR, adjusted odds ratio.

* Adjusted for black race, obesity, and preeclampsia and gestational diabetes.

† Adjusted for obesity.

‡ Adjusted for black race and preeclampsia and gestational diabetes.

§ Adjusted for black race.



(adjusted OR 15.01, 95% CI 9.34–24.12). Among pregnancies complicated by an isolated anomaly, growth restriction was associated with a greater risk of stillbirth (adjusted OR 4.88, 95% CI 2.65–8.98). In pregnancies complicated by an isolated major congenital anomaly as well as incidental growth restriction, the stillbirth rate was higher at 32 weeks of gestation or greater than before 32 weeks of gestation. Conversely, a higher rate of stillbirth was found before 32 weeks of gestation rather than 32 weeks of gestation or greater in anomalous pregnancies that were not growth-restricted (Table 2).

Twenty-eight pregnancies were complicated by an anomaly considered always lethal, including anencephaly, acrania, and bilateral renal agenesis. A sensitivity analysis excluding these anomalies from the isolated major congenital anomaly group did not significantly affect the results of the primary analysis. Isolated major anomaly remained significantly associated with an increased risk of stillbirth compared with nonanomalous pregnancies (47/1,000 pregnancies [n=40] compared with 4/1,000 pregnancies [n=254]; adjusted OR 12.95, 95% CI 9.18–18.23). The stillbirth rate was also higher in pregnancies complicated an isolated congenital anomaly compared with nonanomalous pregnancies whether the pregnancy was also complicated by growth restriction (111/1,000 [n=21] compared with 18/1,000 [n=133] pregnancies; adjusted OR 7.17, 95% CI 4.40–11.70) or not (29/1,000 [n=19] compared with 2/1,000 [n=121] pregnancies; adjusted OR 14.49, 95% CI 8.87–23.70). Furthermore, in anomalous pregnancies, growth restriction was associated with an increased

risk of stillbirth (111/1,000 [n=21] compared with 29/1,000 [n=19] pregnancies; adjusted OR 4.42, 95% CI 2.29–8.52).

Pregnancies complicated by isolated major congenital anomalies in each of the organ system categories considered were at an increased risk of stillbirth relative to nonanomalous pregnancies. The highest stillbirth rate was found among fetuses with congenital heart disease (143/1,000 pregnancies) (Table 3).

DISCUSSION

We found that pregnancies complicated by isolated major congenital anomalies are associated with a 15-fold increased risk of stillbirth. Overall, one in every 18 pregnancies complicated by an isolated major anomaly will result in fetal death. Incidental growth restriction was associated with an even higher rate of stillbirth, occurring in approximately one in every eight pregnancies complicated by growth restriction and isolated congenital anomaly.

The results of this study can be used to counsel patients regarding the increased risk of stillbirth associated with isolated major congenital anomalies and develop antepartum management plans. Although growth restriction is a known risk factor for stillbirth,^{10,11} our data confirm that stillbirth rates are highest in fetuses that are both anomalous and growth-restricted. Furthermore, rates of stillbirth in nongrowth-restricted anomalous fetuses were higher than the stillbirth rate among nonanomalous, growth-restricted pregnancies. Increased fetal surveillance is often instituted for pregnancies complicated by a wide variety of conditions that

Major Anomaly Absent (n=64,165)				
No. of Stillbirths/No. of Pregnancies	Stillbirth Rate/1,000 Ongoing Pregnancies (95% CI)	RR (95% CI)	aOR (95% CI)	
254/64,165	4 (3–4)	13.89 (10.28–18.77)	15.17 (11.03–20.86)	
116/64,165	2 (1–2)	14.57 (9.36–22.68)	15.78 (10.01–24.89)	
138/63,054	2 (1–2)	14.37 (9.44–21.87)	15.06 (9.76–23.25)	
133/7,376	18 (15–21)	7.03 (4.76–10.39)	8.20 (5.27–12.74)	
70/7,376	9 (7–12)	4.45 (2.25–8.79)	4.79 (2.35–9.75)	
63/7,150	9 (7–11)	10.70 (6.46–17.70)	12.01 (6.96–20.76)	
121/56,789	2 (2–3)	14.93 (9.46–23.58)	15.01 (9.34–24.12)	
46/56,789	1 (0.6–1)	26.19 (14.47–47.40)	27.70 (15.12–50.72)	
75/55,904	1 (1–2)	8.64 (4.00–18.67)	8.92 (4.09–19.44)	



Table 3. Stillbirth Rate Among Fetuses With Isolated Major Structural Anomalies Compared With Fetuses Without Major Structural Anomalies by Organ System

	Major Anomaly Absent (n=64,165)	Major Anomaly Present	
		Cardiac (n=119)	Thoracic (n=63)
Stillbirth rate* (95% CI)	4 (3–4)	143 (85–219)	32 (4–110)
RR (95% CI)	Reference	36.09 (22.85–56.99)	8.02 (2.04–31.54)

CI, confidence interval; RR, relative risk.

* Stillbirth rate per 1,000 ongoing pregnancies.

are associated with increased stillbirth risk.⁴ However, fetal anomaly, with perhaps the exception of gastroschisis,¹⁵ is not considered an indication for testing unless the fetus is also growth-restricted. This management strategy may be misguided given the high risk of stillbirth in anomalous fetuses independent of growth restriction. Nevertheless, initiating antenatal surveillance in pregnancies complicated by an isolated fetal anomaly is a complex decision because the competing risk of neonatal demise increases with decreasing gestational age, particularly in anomalous fetuses.^{16–19} For specific anomalies, there may be a gestational age at which the risk of stillbirth exceeds the postnatal mortality risk and thus the initiation of antenatal surveillance with its incumbent false-positive rate²⁰ warrants consideration. Unfortunately, we did not collect specific data about fetal surveillance in this study; thus, further research is needed to better define the time point in gestation when the stillbirth rate approximates the neonatal death rate for individual anomalies.

Our finding that there is an association between fetal abnormality and stillbirth is consistent with prior studies.^{1,13,21,22} However, our study design allowed us to explore the relationship from a different perspective, with the goal of obtaining information with which to counsel women and families who have received the diagnosis of an isolated major fetal anomaly at the time of routine anatomic ultrasound scan and who elect to continue the pregnancy and reach a gestational age at which most nonanomalous fetuses are considered viable. Most other studies that have examined the association between stillbirth and fetal anomalies have done so from the perspective of evaluating causes of stillbirth,^{1,21,22} which does not provide data regarding the ongoing risk of stillbirth in an anomalous fetus. The EUROCAT study, a large international registry in Europe that has been in existence for more than 30 years, has provided much of the available information regarding risks associated with fetal anomalies.²³ However, multiple data sources are used for case ascertainment, which includes registries of infants who are diagnosed

postnatally up to age 1 year. The stillbirth risk calculated using data that include postnatal diagnosis would be expected to be lower than the stillbirth risk associated with fetal anomalies that are detected by ultrasound examination prenatally. Although ultrasound examination detects between 40 and 64% of fetal structural abnormalities,^{2,3,24} those that are detected on ultrasonography are more likely to be severe³ and thus may be associated with a higher risk of intrauterine death.

Most other studies evaluating the association between stillbirth and anomalies have included fetuses with multiple anomalies.¹³ It is difficult to attribute the risk of stillbirth associated with a single structural abnormality if fetuses with multiple anomalies are included. Additionally, it is more likely that a fetus with multiple anomalies has a genetic syndrome, which itself might be associated with increased mortality.^{25,26} Our use of only prenatal ultrasound findings to define the absence of other structural malformations but both prenatal and postnatal genetic testing to exclude pregnancies complicated by chromosomal abnormalities may seem incongruent. However, this reflects the stillbirth risk using prenatally available information. Although ultrasonography may not detect all structural abnormalities, prenatal genetic testing is available and offered to all women. Ultimately, data from our study could be used to counsel women about risk of stillbirth if the fetus does not have a chromosomal abnormality and has only a single anomaly detected on ultrasound scan, although there may be additional abnormalities not detectable prenatally.

The American College of Obstetricians and Gynecologists defines stillbirth as fetal death at 20 weeks of gestation or greater or a fetal weight 350 g or greater if the gestational age is unknown.⁴ We chose to exclude women who delivered before 24 weeks of gestation based on local regulations regarding termination of pregnancy. We acknowledge that there is a selection bias introduced by this approach because we surmise that pregnancies that are terminated are more likely to



Major Anomaly Present

Neurologic (n=153)	Gastrointestinal (n=140)	Urinary (n=301)	Musculoskeletal (n=97)
92 (51–149) 23.12 (13.82–38.65)	36 (12–81) 9.02 (3.78–21.52)	20 (7–43) 5.04 (2.26–11.22)	41 (11–102) 10.42 (3.96–27.41)

have had a more severe congenital anomaly. Our approach, however, would likely bias the results toward the null because the more severe congenital anomalies may be associated with higher stillbirth risk.

Overall, both isolated congenital anomaly and stillbirth are rare events. The large size of our single-center ultrasound database gave us the ability to perform this analysis. However, there was less precision of the risk estimates in some of the subgroup analyses as a result of the small numbers. The ultrasound and patient follow-up information in the database is more detailed than is typically recorded in larger national and international registries.²⁷ A limitation of this is that data collected at a single referral center could decrease the generalizability of our findings. Although there was follow-up available on 89.6% of women who underwent ultrasound evaluation at our center, some pregnancies were excluded because of incomplete data. Further investigation found that these women were more likely to be younger, black race, obese, and multiparous compared with women included in the study. It is unclear how the exclusion of these pregnancies would have affected our results. Additionally, chromosomal analysis was only performed in 73.9% of cases of isolated anomalies; thus, some cases of genetically abnormal fetuses could have been misclassified.

The study was conducted over an almost 20-year time period. Changes in ultrasound detection rates over this time period were likely minimal because a similar proportion of all pregnancies was found to be complicated by an isolated congenital anomaly. However, the availability and efficacy of postnatal care of fetuses with congenital anomalies over this time period may have affected our results. Some may argue that defining growth restriction using birth weight is another limitation because obstetric management is based on prenatal diagnosis of growth restriction. However, ultrasound assessment of fetal weight is largely inaccurate²⁸; thus, the use of birth weight provides a more direct approach to examining the true relationship between growth restriction and stillbirth. Furthermore, our finding that the stillbirth risk is high in pregnancies complicated by an isolated congenital anomaly regardless of incidental

growth restriction in anomalous fetuses means that reliance on prenatal assessment of fetal growth to guide management is unnecessary.

In summary, we found that pregnancies complicated by an isolated congenital fetal anomaly are at high risk of stillbirth regardless of the incidental diagnosis of growth restriction. Our data could be used to help obstetric care providers counsel patients receiving an antenatal diagnosis of an isolated anomaly. Although antenatal surveillance is frequently initiated in pregnancies at high risk for stillbirth, health care practitioners caring for these patients should weigh the competing risks of postnatal mortality with antenatal death. Critical evaluation of these competing risks, specific to individual anomalies, should be the focus of future studies.

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