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Risk of Stillbirth for Fetuses With Specific Birth Defects

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Abstract

OBJECTIVE: To estimate the risk of stillbirth (fetal death at 20 weeks of gestation or more) associated with specific birth defects.

METHODS: We identified a population-based retrospective cohort of neonates and fetuses with selected major birth defects and without known or strongly suspected chromosomal or single-gene disorders from active birth defects surveillance programs in nine states. Abstracted medical records were reviewed by clinical geneticists to confirm and classify all birth defects and birth defect patterns. We estimated risks of stillbirth specific to birth defects among pregnancies overall and among those with isolated birth defects; potential bias owing to elective termination was quantified.

RESULTS: Of 19,170 eligible neonates and fetuses with birth defects, 17,224 were liveborn, 852 stillborn, and 672 electively terminated. Overall, stillbirth risks ranged from 11 per 1,000 fetuses with bladder exstrophy (95% CI 0–57) to 490 per 1,000 fetuses with limb-body-wall complex (95% CI 368–623). Among those with isolated birth defects not affecting major vital organs, elevated risks (per 1,000 fetuses) were observed for cleft lip with cleft palate (10; 95% CI 7–15), transverse limb deficiencies (26; 95% CI 16–39), longitudinal limb deficiencies (11; 95% CI 3–28), and limb defects due to amniotic bands (110; 95% CI 68–171). Quantified bias analysis suggests that failure to account for terminations may lead to up to fourfold underestimation of the observed risks of stillbirth for sacral agenesis (13/1,000; 95% CI 2–47), isolated spina bifida (24/1,000; 95% CI 17–34), and holoprosencephaly (30/1,000; 95% CI 10–68).

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CONCLUSION: Birth defect-specific stillbirth risk was high compared with the U.S. stillbirth risk (6/1,000 fetuses), even for isolated cases of oral clefts and limb defects; elective termination may appreciably bias some estimates. These data can inform clinical care and counseling after prenatal diagnosis.

Major birth defects are common, occurring in one in every 33 pregnancies in the United States.[1] Birth defects are a known risk factor for stillbirth, are identified in one in every five stillborn fetuses, and are thus a major contributor to the stillbirth rate in the United States (6/1,000 fetuses in the general U.S. population; approximately 4,600 annual stillbirths with major birth defects).[2–4] Yet, little information is available on risk of stillbirth associated with most specific birth defects.[5–7]

Estimates of stillbirth risk are needed to inform clinical care and parent counseling after prenatal diagnosis of birth defects.[8,9] Prior research has suggested that enhanced prenatal monitoring of fetuses with gastroschisis may reduce stillbirth risk.[10–14] Robust estimates for a wide range of defects could identify other birth defects for which enhanced monitoring might be indicated.

The generation of accurate stillbirth risk estimates is complicated by the difficulty in identifying a sufficient number of well-characterized birth defect cases in both live birth and stillbirths, as well as in pregnancies ending in terminations. Compared with those with more moderate prenatally diagnosed birth defects, in the United States the odds of elective termination are 126 times higher for fetuses with severe non-neurologic birth defects and more than 300 times higher for fetuses with serious neurologic malformations.[15] Therefore, conventional estimates that do not account for elective termination owing to prenatal diagnosis of birth defects may underestimate stillbirth risks; this potential bias has not been quantified.[16–19]

We estimated birth defect-specific risk of stillbirth among fetuses with selected birth defects and quantified the potential bias owing to elective termination of pregnancy using data on more than 19,000 birth defect cases identified by the National Birth Defects Prevention Study.

METHODS

We used data from the retrospective cohort of birth defect cases that underlies the National Birth Defects Prevention Study, a large, population-based collaborative, multistate, case–control study of selected major birth defects (Appendices 1 and 2, available online at http://links.lww.com/AOG/B669) in the United States from 1997 to 2011.[20] Briefly, birth defect cases were identified using active case-finding methods by population-based surveillance systems in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah).[21] Within their respective catchment areas, each site abstracted and reviewed medical records for all potentially eligible surveillance-identified birth defect cases; records of all identified stillborn fetuses were reviewed for birth defects. Abstracted medical records for all identified birth defect cases were reviewed by clinical geneticists at each site to confirm each reported birth defect diagnosis. Institutional

Review Board approval was obtained by all study sites; individual consent was not required for the collection or analysis of data under these approvals.

Birth defect cases with a known or strongly suspected single gene or chromosomal disorder were ineligible for the National Birth Defects Prevention Study; genetic studies were not required. We excluded cases without confirmatory testing if review by board-certified geneticists identified features (eg, a pattern of major or minor anomalies, family history of disorder with known genetic basis) strongly suggested that the presence of a chromosomal or genetic disorder. Cases with the following pregnancy outcomes were eligible for inclusion in the study: live birth (any gestational age), pregnancy termination (any gestational age), or stillbirth (defined as a spontaneous fetal death at 20 weeks of gestation or more or a birth weight of 500 g or more). Spontaneous losses at less than 20 weeks of gestation were ineligible.

Cases were further reviewed by study clinical geneticists to confirm that each National Birth Defects Prevention Study–eligible birth defect case met standard criteria and to classify the birth defect pattern according to a standard algorithm.[22] Cases classified as “isolated” may have a single major birth defect, a primary birth defect with other resulting defects (eg, a fetus with hydrocephalus and clubbed feet due to spina bifida and no other defects), or a series of birth defects caused by a common disruption of development (eg, limb-body-wall complex). Fetuses with a defect classification other than “isolated” were categorized as having multiple birth defects.

We excluded cases with an unknown pregnancy outcome, a gestational age not reliably determined to be greater than or less than 20 weeks, live births or terminations at less than 20 weeks of gestation, and cases from study sites that enrolled only live births (New York before 2000, New Jersey); cases from study sites not enrolling terminations were included (Georgia before 1999, Massachusetts all years) resulting in analyses among nine states[20] (Fig. 1). Gestational age was obtained from medical or vital records or maternal report (for interviewed cases) and reviewed for consistency with birth weight and pregnancy outcome (details are described in Appendix 3, available online at http://links.lww.com/AOG/B669).

We excluded from our analyses those National Birth Defects Prevention Study–eligible birth defects which are most often diagnosed based on postnatal signs or symptoms (ie, biliary, small intestinal, colonic, or anorectal atresia and craniosynostosis), poorly identified prenatally and require autopsy or postnatal studies to confirm (ie, cerebellar hypoplasia), difficult to observe on physical exam in small or macerated fetuses (ie, hypospadias, glaucoma, cataracts, anophthalmia or microphthalmia, anotia or microtia, and choanal atresia), or poorly defined (ie, limb deficiency, not otherwise stated).[23–25] We further excluded isolated heart defects based on the low sensitivity of prenatal diagnosis during the study period and incomplete cardiology review for a subset of heart defect cases with high detection (eg, hypoplastic left heart syndrome).[23,26–29]

We considered the birth defect case population to be a cohort of fetuses with birth defects at risk of stillbirth (gestational age at delivery 20 weeks or more or birth weight 500 g or more). We calculated absolute birth defect-specific risk as the number of stillbirths divided

by the total number of live births and stillbirths with that defect. We then calculated estimates after restricting first to cases without a lethal birth defect (ie, limb-body-wall complex, anencephaly, agyria, hydranencephaly, vein of Galen malformation, tracheal atresia, bilateral renal agenesis), and second to isolated cases. For multiple major birth defects cases, the number of stillbirths, live births, and termination for specific birth defects are reported in Appendix 4, available online at http://links.lww.com/AOG/B669. Cases were included in analyses for each primary birth defect meeting study inclusion criteria. For example, a fetus categorized as "isolated spina bifida" who also had hydrocephalus due to the spina bifida would be included only in the spina bifida analysis in the "overall," "nonfatal" and "isolated" analyses. A fetus with cleft palate and a heart defect would be included in the "overall" and "nonfatal" cleft palate analyses but excluded from the "isolated" analysis.

Risks were calculated when there were at least 10 fetuses with a specific birth defect in the category of interest. We calculated two-tailed 95% CIs using the Poisson distribution when there were fewer than 20 stillbirths and using the exact binomial method otherwise.

We quantified the possible effect of termination of birth defect cases by estimating the lower and upper bounds of the possible birth defect-specific risk given our observed data without additional assumptions.[30] To do so, we calculated the risk of stillbirth after setting the outcome of terminated cases at their most extreme values: the lower bound was estimated with all elective terminations included in the denominator (calculated as the number of stillbirths divided by the total number with all outcomes [liveborn, stillborn, terminated]); the upper bound was estimated with all terminations included in the numerator and denominator (the number of stillborn cases plus all cases ending in termination, divided by the total number of outcomes). Note that both extremes are unrealistic and just meant to provide bounds of the stillbirth risk in the absence of any terminations: ie, the first (lower limit) had none of the terminations been stillbirths and the second (upper limit) had all been stillborn.

Terminations before 20 weeks of gestation may also remove high-risk fetuses from the population at risk of stillbirth; however, had the pregnancy continued, some would have been miscarried before 20 weeks of gestation. As a sensitivity analysis, we estimated risk bounds including all terminations for the overall analysis, regardless of gestational age, and calculated the absolute and change in the upper and lower risk bounds.

Risk estimates, bounds, and 95% CIs are reported as stillbirths per 1,000 birth defect cases. All analyses were conducted by the first author using SAS 9.4.

RESULTS

Of the 19,170 cases included in our analytic cohort (Fig. 1), 89.8% were liveborn (17,224), 4.4% were stillborn (n5852), and 3.5% (n5672) underwent termination for birth defects after 20 weeks of gestation. Most fetuses and neonates (79%, n515,198) had an isolated birth defect.

We report overall stillbirth risk estimates, bounds, and 95% CIs by specific birth defect in Figure 2. Stillbirth risk exceeded 40% for limb-body-wall complex (490/1,000 fetuses; [30/61 cases, risk bound: 320–670; 95% CI 368–623]) and anencephaly (420/1,000; [261/625 cases, risk bound: 300–590; 95% CI 379–457]) and was 230 per 1,000 for bilateral renal agenesis (64/276 cases; risk bound: 190–360; 95% CI 184–286), all of which are fatal by the end of the neonatal period ("perinatal lethal" defects). Additionally, risk estimates exceeded 10% for omphalocele (110/1,000 [68/589 cases; risk bound: 110–160; 95% CI 91–144]) and amniotic band syndrome including craniofacial anomalies (130/1,000 [9/72 cases; risk bound: 110–250; 95% CI 60–224]) or with limb anomalies only (140/1,000 [47/344 cases; risk bound: 140–140; 95% CI 102–178]). The birth defect with the lowest risk estimate was bladder exstrophy (11/1,000 [1/95 cases; risk bound: 11–11; 95% CI 0–57). Seven defects had a stillbirth risk and upper risk bound less than 20 per 1,000 affected fetuses. Although sacral agenesis had a stillbirth risk of 13 per 1,000 (2/152 cases; 95% CI 2–47), the upper risk bound was four times higher (57/1,000) than the observed risk after accounting for the potential effect of terminations.

After restricting to cases with nonfatal defects most stillbirth risk estimates and risk bounds did not change from those among all cases (Appendix 5, available online at http://links.lww.com/AOG/B669). However, the following stillbirth risk estimates (per 1,000) were reduced: omphalocele (from 115 to 105), sacral agenesis (13–7), and transverse and longitudinal limb deficiencies (41–36 and 25–21, respectively). Additionally, the risk bounds narrowed for these defects and others.

We present stillbirth risk estimates, bounds, and 95% CIs among fetuses with isolated birth defects by specific birth defect in Figure 3. Either no stillbirths or only one stillbirth occurred among the isolated cases of three defects: sacral agenesis (n=17), intercalary limb deficiency (n=61), and bladder exstrophy (n=70). Compared with the overall analysis, risk estimates were decreased after restricting to isolated defects, with the exception of the perinatal lethal birth defects. Among those with isolated birth defects not affecting major vital organs, risks of 10 per 1,000 or greater were found for cleft lip with cleft palate (10/1,000 [25/2,384 cases; risk bound: 10–10; 95% CI 7–15]), transverse limb deficiencies (26/1,000 [22/845 cases; risk bound: 11–24; 95% CI 16–39]), longitudinal limb deficiencies (11/1,000 [4/368 cases; risk bound: 11–24; 95% CI 3–28]), and limb defects due to amniotic bands (110/1,000 [18/161 cases; risk bound: 111–117; 95% CI 68–171]). Quantified bias estimates suggest that risk of stillbirth for isolated spina bifida (24/1,000 [33/1,347 cases; risk bound: 22–108; 95% CI 17–34]) and holoprosencephaly (30/1,000 [5/167 cases; risk bound: 27–120; 95% CI 10–68]) may be up to four times higher than observed risks after accounting for the potential effect of terminations.

Fewer than half (39%) of all elective terminations occurred before 20 weeks of gestation (n=422/1,094 total), but the proportion varied by specific defect (Appendix 6, available online at http://links.lww.com/AOG/B669). After inclusion of all elective terminations, lower bound estimates did not change for 15 estimates and changed by fewer than 5 cases per 1,000 for all defects except anencephaly, encephalocele, limb-body-wall complex, and amniotic band syndrome with craniofacial deformities (Appendix 7, available online at http://links.lww.com/AOG/B669). Upper bound estimates, did not change for three defects,

changed by 1–10 cases per 1,000 for 11 defects, by 11–50 cases for seven defects, and by more than 50 for anencephaly, encephalocele, and amniotic band syndrome with craniofacial deformities. The greatest changes in lower and upper bounds were for anencephaly (absolute change in lower and upper bounds: 268 and 940/1,000, respectively).

DISCUSSION

In this study we estimated the risks of stillbirth for specific birth defects and phenotypes, including many for which there are limited published data.[6,14,17,31] These estimates may be of immediate value for informing referral to specialist care, including centers with expertise in prenatally diagnosed birth defects, informing prenatal monitoring, and counseling parents.

In our study, the overall birth defect-specific stillbirth risk ranged from 11 per 1,000 to 490 per 1,000 affected fetuses; for comparison, these risks are 2–82 times higher than the overall stillbirth risk in the general population of pregnancies in the United States (6/1,000 fetuses).[3] Compared with the well-established 10 per 1,000 fetuses stillbirth risk associated with advanced maternal age (35 years or older), only fetuses with isolated cleft lip or palate had a lower risk of stillbirth.[3] Among those with survivable isolated birth defects, we found that defects affecting the abdominal wall (omphalocele, gastroschisis, and cloacal exstrophy) generally had higher risks of stillbirth than defects affecting the central nervous system (holoprosencephaly, spina bifida, encephalocele, and Dandy-Walker malformation). However, consideration of potential bias due to termination suggested that risks for most defects in these two groups are likely similar.

We found elevated risks among fetuses with an expected low risk of stillbirth: those with isolated birth defects with greater than 98% neonatal survival—in particular cleft lip with cleft palate and limb defects (1.6–11 times higher than U.S. general population).[19] Although the mechanisms driving these increased risks are unclear, our findings suggest that other factors alone or in combination with the birth defect may increase the risk of stillbirth. One possibility is that the cause of the birth defects may independently increase the risk of stillbirth; for example amniotic bands can entrap the umbilical cord, cutting off blood flow to the fetus.[32–34] This may partially explain why some of the highest stillbirth risks identified in this study were among amniotic band-associated birth defects. An additional examples are maternal prepregnancy diabetes and undiagnosed genetic or chromosomal disorders which are strongly associated with both birth defects and stillbirth.[35,36] Another possibility is that fetuses with any form of structural defect, relative to those who are normally formed, may be more vulnerable to additional stressors, such as maternal illness or obstetric complications.[37]

Nonetheless, our results provide some reassurance for parents and providers, because most fetuses with the examined birth defects survive to live birth and our results provide import information on the likelihood of survival to live birth for counseling parents of fetuses with a perinatal lethal defect. Additionally, knowledge of stillbirth risk for a fetus with a prenatally-diagnosed birth defect may be useful in implementing enhanced prenatal monitoring, expedited delivery and other preventive measures in high-risk pregnancies.[11,12,38] Although there is little research on prevention of stillbirth for most birth defects, multiple studies have

found enhanced monitoring and expedited delivery to be associated with lower risks of stillbirth among fetuses with gastroschisis.[10–14] However, as with monitoring in pregnancies without a fetal malformation, rigorous research is needed to develop effective strategies.[38]

Our study has several limitations. Although the overall sample size is large, data were limited for specific birth defects and subtypes. Data were captured over a 14-year period; thus, our estimates represent an average risk over this time. The exclusion of cases with chromosomal and single gene disorders meant that we were unable to generate estimates for fetuses with these conditions. However, most birth defect cases are not known to be associated with chromosomal and single gene disorders.[39] We did not require confirmed chromosomal testing as the poor success of available methods (ie, karyotype) among stillbirths would disproportionately exclude these cases, leading to an underestimate of stillbirth risk. Because genetic testing was not universal and testing methods during this time period were limited, some included cases may have unidentified genetic or chromosomal conditions. This limitation may particularly affect estimates for omphalocele as this defect is associated with various chromosomal disorders.[40] However, strongly-suspected genetic or chromosomal cases were excluded after geneticist review and eligibility criteria changed throughout the course of the study as new associations with single gene disorders were discovered which should limit the potential influence of these disorders.[20]

We were unable to examine the severity of individual birth defects; thus, our estimates represent an average risk across the full severity range of examined birth defects. Elective terminations for birth defects are incompletely captured by birth defect surveillance and were not enrolled by one study site for one year and another site for all years.[20] Therefore, the true risk bounds may be larger than our estimates. However, results of our sensitivity analysis suggest that at least a doubling of elective terminations would be needed to result in clinically meaningful changes in risk bounds.

Identification of birth defects among stillborn and terminated fetuses may be incomplete, particularly in the absence of autopsy. Consequently, if co-occurring birth defects remained undiagnosed, our results may underestimate risks for birth defects with decreased prenatal identification in addition to overestimating risks for isolated cases. However, most major birth defects among stillbirths are also identified by means other than autopsy.[23] In contrast to prior studies, we did not calculate estimates for defects with poor sensitivity of prenatal diagnosis, thus avoiding the misleading suggestion of low stillbirth risks (eg, 0% for congenital cataract and choanal atresia).[17]

Our study builds on prior research by using a very large population-based cohort which includes detailed clinical geneticist review of all cases.[5–7] Additionally, we present estimates of stillbirth risks for some very rare birth defects (ie, cloacal and bladder exstrophy, sacral agenesis, Dandy-Walker malformation) and phenotype-specific stillbirth risks within birth defect categories (eg, transverse limb deficiency).[16,17] Use of a population-based cohort avoids bias due to referral patterns that may affect single center or hospital network-based studies.[5,41] Importantly, quantification of potential bias due to elective termination allowed us to identify birth-defect specific risk estimates which may be biased to a clinically relevant degree and bounds improve comparability across areas with differing rates of termination for

birth defects. Furthermore, providing the maximum possible risk within the observed data may allow clinicians to account for the range of plausible estimates when determining appropriate clinical care. Although we are unable to provide direct estimates for fetuses with multiple birth defects, the risk of stillbirth for these fetuses will likely be similar to that of the highest risk defect present.

Although there are few studies with which to compare our results, our findings are broadly consistent with previous reports.[6,16,17] Therefore, results of our study–and in particular the risk bounds–are expected to generalize to other high-income countries; risks may be further elevated in middle- and low-income countries, depending on local context (eg, access to medical care).

In conclusion, we found that the stillbirth risk for the birth defects examined was increased. Our estimates may inform counseling, referral to specialists, and clinical care after prenatal diagnosis. Further evidence on birth defect-specific associated conditions and causes of stillbirth, risk by gestational age, modifiable risk factors, and clinical care measures is needed to advance stillbirth prevention for fetuses with major birth defects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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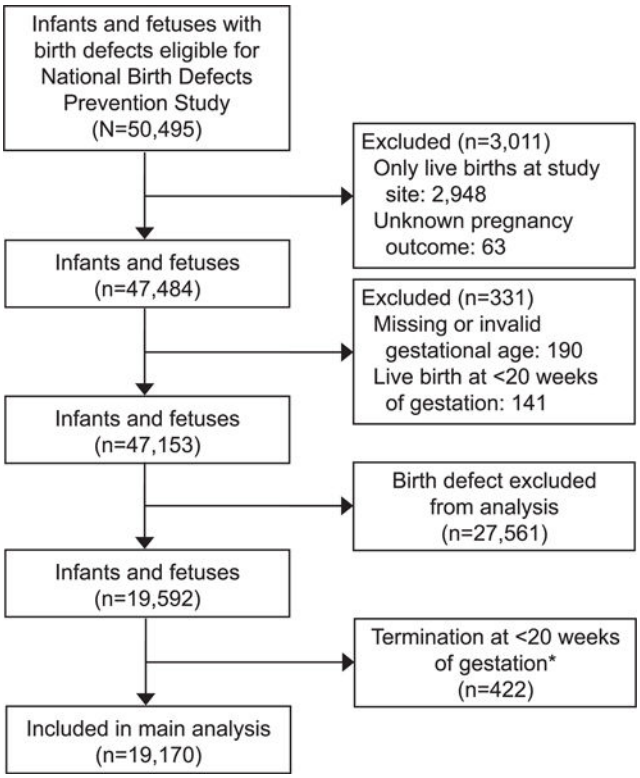
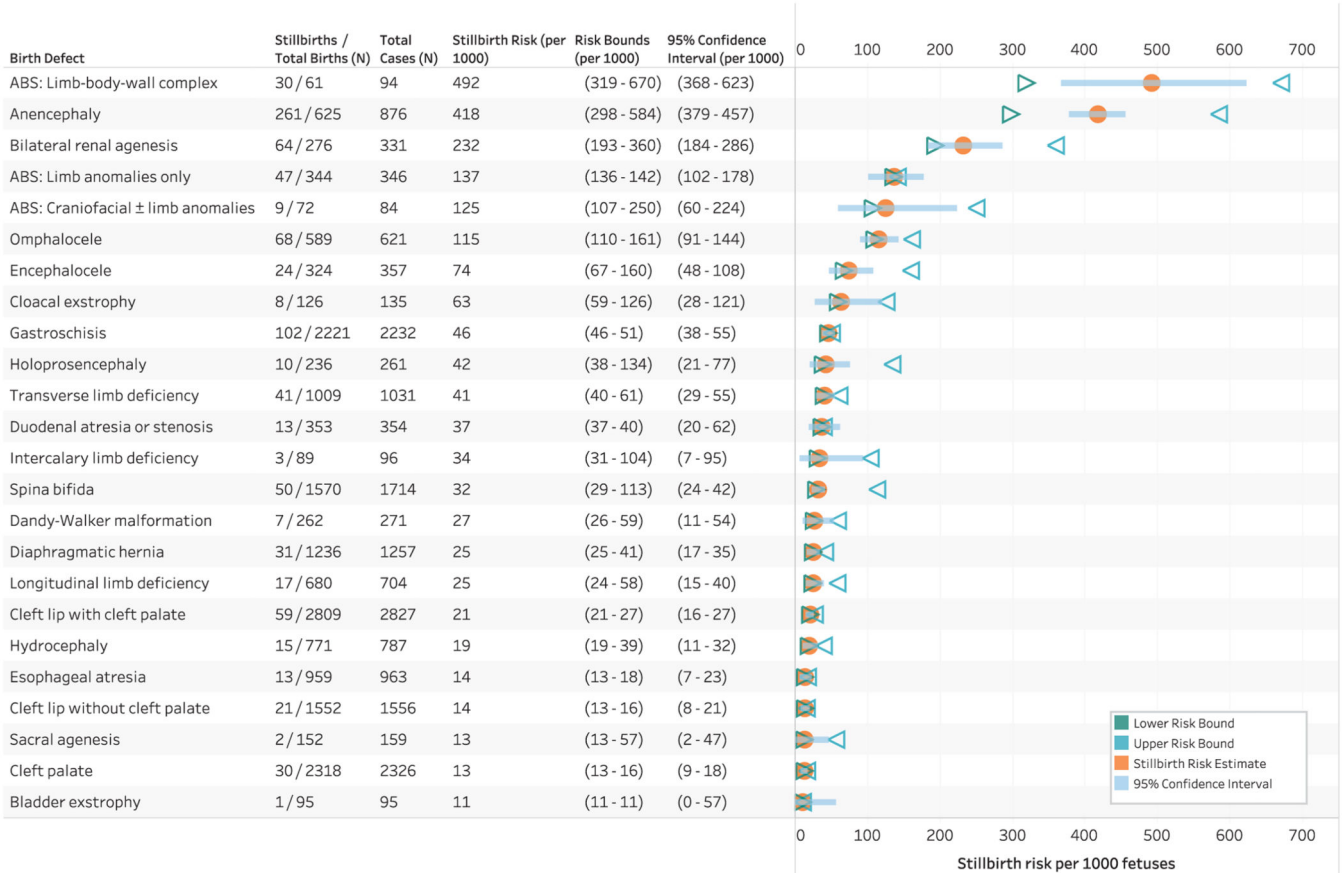


Fig. 1.
Flow diagram of study cohort. *Included in sensitivity analysis.



Birth Defect	Stillbirths / Total Births (N)	Total Cases (N)	Stillbirth Risk (per 1000)	Risk Bounds (per 1000)	95% Confidence Interval (per 1000)
ABS: Limb-body-wall complex	30 / 61	94	492	(319 - 670)	(368 - 623)
Anencephaly	261 / 625	876	418	(298 - 584)	(379 - 457)
Bilateral renal agenesis	64 / 276	331	232	(193 - 360)	(184 - 286)
ABS: Limb anomalies only	47 / 344	346	137	(136 - 142)	(102 - 178)
ABS: Craniofacial ± limb anomalies	9 / 72	84	125	(107 - 250)	(60 - 224)
Omphalocele	68 / 589	621	115	(110 - 161)	(91 - 144)
Encephalocele	24 / 324	357	74	(67 - 160)	(48 - 108)
Cloacal exstrophy	8 / 126	135	63	(59 - 126)	(28 - 121)
Gastroschisis	102 / 2221	2232	46	(46 - 51)	(38 - 55)
Holoprosencephaly	10 / 236	261	42	(38 - 134)	(21 - 77)
Transverse limb deficiency	41 / 1009	1031	41	(40 - 61)	(29 - 55)
Duodenal atresia or stenosis	13 / 353	354	37	(37 - 40)	(20 - 62)
Intercalary limb deficiency	3 / 89	96	34	(31 - 104)	(7 - 95)
Spina bifida	50 / 1570	1714	32	(29 - 113)	(24 - 42)
Dandy-Walker malformation	7 / 262	271	27	(26 - 59)	(11 - 54)
Diaphragmatic hernia	31 / 1236	1257	25	(25 - 41)	(17 - 35)
Longitudinal limb deficiency	17 / 680	704	25	(24 - 58)	(15 - 40)
Cleft lip with cleft palate	59 / 2809	2827	21	(21 - 27)	(16 - 27)
Hydrocephaly	15 / 771	787	19	(19 - 39)	(11 - 32)
Esophageal atresia	13 / 959	963	14	(13 - 18)	(7 - 23)
Cleft lip without cleft palate	21 / 1552	1556	14	(13 - 16)	(8 - 21)
Sacral agenesis	2 / 152	159	13	(13 - 57)	(2 - 47)
Cleft palate	30 / 2318	2326	13	(13 - 16)	(9 - 18)
Bladder exstrophy	1 / 95	95	11	(11 - 11)	(0 - 57)

Fig. 2.

Overall stillbirth risk for specific birth defects. This figure shows the number of stillbirths, births, and total cases, as well as the estimated stillbirth risk (*closed circle*), risk bounds (lower bound, *open right arrow*; upper bound, *open left arrow*), and 95% CIs (*gray bar*); all estimates are reported per 1,000 affected fetuses. Risks were calculated when there were at least 10 births in a specific birth defect category. Two-tailed 95% CIs using the Poisson distribution were used when there were fewer than 20 stillbirths, using the exact binomial method otherwise. Neonates and fetuses with multiple birth defects are included in the analysis for each primary birth defect for which they meet the eligibility criteria. ABS, amniotic band syndrome. Total births5stillbirths+live births; risk of stillbirth5stillbirths/live birth+stillbirths; upper risk bound5stillbirth+terminations/ live births+stillbirths +terminations; lower risk bound5stillbirth/live births+stillbirths+terminations.

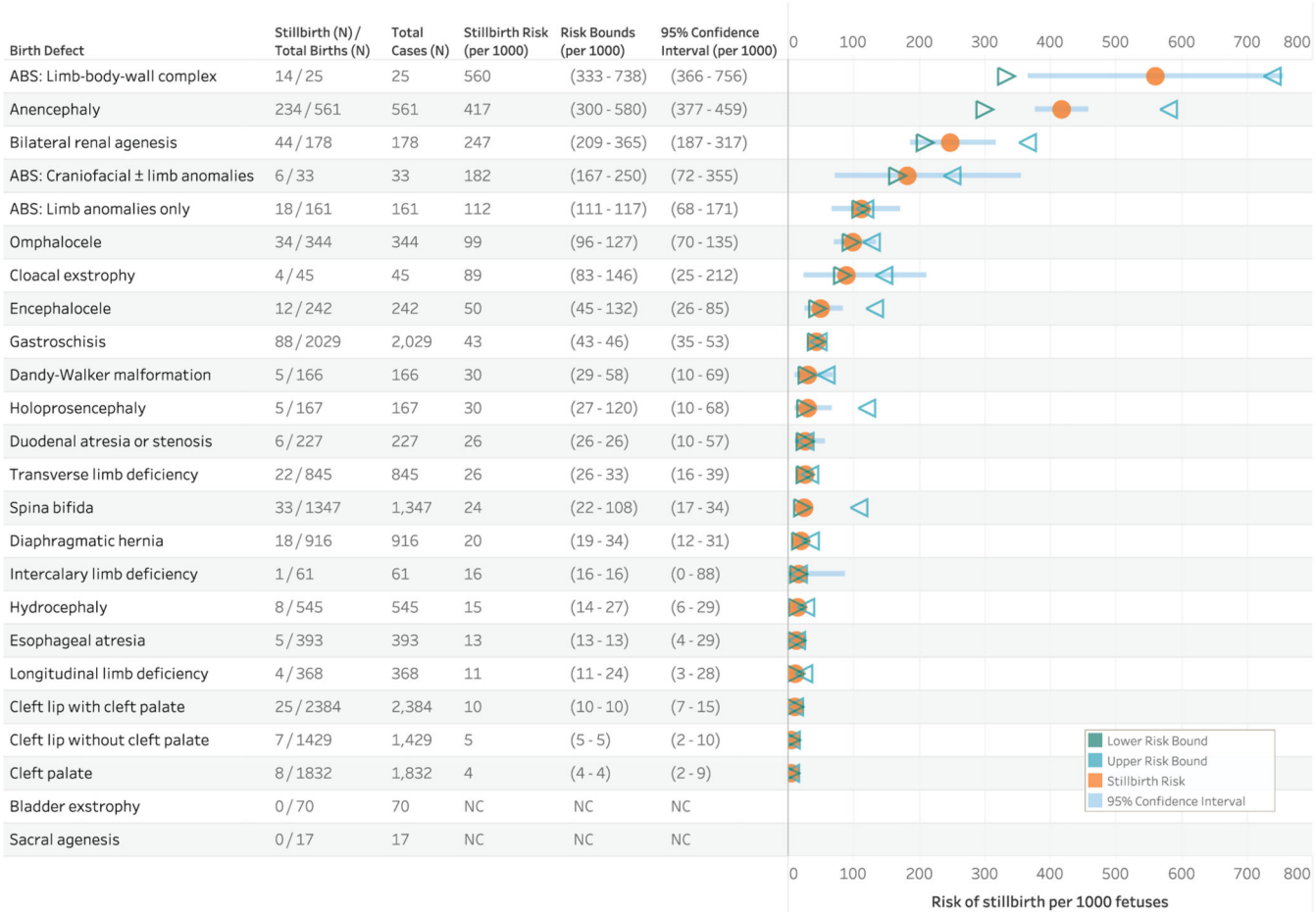


Fig. 3.

Stillbirth risk for isolated cases of specific birth defects. This figure shows the number of stillbirths, births, and total cases, as well as the estimated stillbirth risk (*closed circle*), risk bounds (lower bound, *open right arrow*; upper bound, *open left arrow*), and 95% CIs (*grey bar*); all estimates are reported per 1,000 affected fetuses. Risks were calculated when there were at least 10 births in a specific birth defect category. Two-tailed 95% CIs using the Poisson distribution were used when there were fewer than 20 stillbirths, using the exact binomial method otherwise. Because this analysis is restricted to isolated cases, neonates and fetuses are included only once. ABS, amniotic band syndrome. Total births5stillbirths +live births; risk of stillbirth5stillbirths/live births+stillbirths; upper risk bound5stillbirth +terminations/live births+stillbirths+terminations; lower risk bound5stillbirth/live births +stillbirths+terminations.