Etiology and clinical presentation of birth defects: population based study

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ABSTRACT

OBJECTIVE
To assess causation and clinical presentation of major birth defects.

DESIGN
Population based case cohort.

SETTING
Cases of birth defects in children born 2005-09 to resident women, ascertained through Utah's population based surveillance system. All records underwent clinical re-review.

PARTICIPANTS
5504 cases among 270 878 births (prevalence 2.03%), excluding mild isolated conditions (such as muscular ventricular septal defects, distal hypospadias).

MAIN OUTCOME MEASURES
The primary outcomes were the proportion of birth defects with a known etiology (chromosomal, genetic, human teratogen, twinning) or unknown etiology, by morphology (isolated, multiple, minors only), and by pathogenesis (sequence, developmental field defect, or known pattern of birth defects).

RESULTS
Definite cause was assigned in 20.2% (n=1114) of cases: chromosomal or genetic conditions accounted for 94.4% (n=1052), teratogens for 4.1% (n=46, mostly poorly controlled pregestational diabetes), and twinning for 1.4% (n=16, conjoined or acardiac). The 79.8% (n=4390) remaining were classified as unknown etiology; of these 88.2% (n=3874) were isolated birth defects. Family history (similarly affected first degree relative) was documented in 4.8% (n=266). In this cohort, 92.1% (5067/5504) were live born infants (isolated and non-isolated birth defects): 75.3% (4147/5504) were classified as having an isolated birth defect (unknown or known etiology).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Birth defects are common, costly, and critical

Two hospital based studies have tried to directly assess the proportion of birth defects with or without a known etiology

WHAT THIS STUDY ADDS

In this population based birth defect case cohort, the cause was established in only one in every five infants

The inability to understand etiology in four of five cases highlights the urgent need for better basic and translational research as a basis for primary prevention and care

In addition, many birth defects are associated with fetal loss: estimates of the global burden of birth defects that consider only liveborn infants with isolated conditions will underestimate this burden by at least 25%, and even more for selected conditions

CONCLUSIONS
These findings underscore the gaps in our knowledge regarding the causes of birth defects. For the causes that are known, such as smoking or diabetes, assigning causation in individual cases remains challenging. Nevertheless, the ongoing impact of these exposures on fetal development highlights the urgency and benefits of population based preventive interventions. For the causes that are still unknown, better strategies are needed. These can include greater integration of the key elements of etiology, morphology, and pathogenesis into epidemiologic studies; greater collaboration between researchers (such as developmental biologists), clinicians (such as medical geneticists), and epidemiologists; and better ways to objectively measure fetal exposures (beyond maternal self reports) and closer (prenatally) to the critical period of organogenesis.

Introduction

Birth defects are inborn errors of development. Broadly defined, they include any structural or functional anomaly with measureable effects on physical, intellectual, and social wellbeing.[1] Birth defects represent a considerable and increasing clinical and public health challenge because of their worldwide impact on population health.

Major birth defects are common, costly, and critical. Collectively, they occur in one in 33 births,[2] which in 2006 translated into an estimated 7.9 million babies worldwide.[3] In the US alone, the cost of care during a single year (2004) was estimated at $2.6bn (£2bn, €2.4bn).[4] This estimate does not account for the considerable indirect and lifelong personal and societal costs. Finally, many birth defects critically affect survival. In the US, birth defects are the leading cause of infant mortality[5] and in 2013 were associated with 4778 deaths, one in every five deaths in the first year of life.

The temporal trends are even more concerning. The occurrence of birth defects, with few localized exceptions (such as neural tube defects in countries that implemented folic acid fortification), has not decreased for many decades. Birth defects might indeed increase worldwide, with the alarming increase of known risk factors such as maternal diabetes and obesity. New threats such as the Zika epidemic are emerging. Unless progress is made in identifying and preventing the root causes of birth defects, these conditions will continue to have draining effects on the survival and health of individuals, families, and countries.

Progress in detecting and characterizing risk factors for birth defects has come mainly from epidemiologic studies. In fact, such studies have produced many associations between risk factors and groups of birth

defects. Translating these associations to actual causes, however, has been difficult. As a first step in filling this gap, we evaluated the clinical and etiologic profile of birth defects in a well characterized population based case cohort through systematic review by clinicians, using a multidimensional assessment tool that incorporates etiology, morphology, and pathogenesis.

Methods

Study population

The data source for this study was Utah's statewide population based public health surveillance system (Utah Birth Defect Network, UBDN), housed at the Utah Department of Health. There is no patient involvement or contact as part of this surveillance system. The network monitors birth defects among all pregnancy outcomes (live births, stillbirths, pregnancy terminations) among Utah residents. If a termination occurred, existing medical records were ascertained and reviewed to determine eligibility. To identify potential cases, the program uses multiple reporting sources, both prenatal and postnatal. All reporting sources are mandated to regularly submit any potential diagnosis in infants aged up to 24 months and are legally protected to report if a diagnosis is made after 24 months. The detailed clinical information for each case is based on the abstracted prenatal and postnatal clinical records by trained data abstractors. The presence of a prenatal diagnosis without autopsy or postnatal confirmation is not sufficient for inclusion in the system, with few exceptions, the main one being anencephaly if well described by a perinatologist. For example, hydronephrosis based on only prenatal diagnosis was not eligible for inclusion unless it was confirmed postnatally. Some birth defects have not ever been eligible for inclusion in the surveillance system because it is more challenging to identify and ascertain all cases or they are not considered a birth defect—for example, isolated muscular ventricular septal defects, patent foramen ovale, patent ductus arteriosus, talipes equinovarus, congenital hip dysplasia/dislocation, congenital pulmonary airway malformation, and cryptorchidism. Cases of fetal alcohol syndrome were included only if a major birth defect was diagnosed. Further details of the system's case ascertainment and medical record abstraction have been published elsewhere.[6][7]

Clinical case review

A team of clinicians with training in medical genetics (LDB, JCC, JLBB) reviewed case records, including inpatient and outpatient records, laboratory reports (such as genomic microarray), diagnostic evaluations (such as ultrasound images and echocardiograms), operative notes, and autopsy reports. Once a case was deemed eligible, the clinician generated a list of the major and minor defects and the timing of first diagnosis (prenatal or postnatal). Each defect was coded with the World Health Organization international classification of diseases (version 9) with British Paediatric Association extensions (ICD-9 BPA). In addition, the clinician provided three additional classifications for each case:

known etiology (yes, no); isolated versus multiple (unrelated) birth defect versus syndromic (that is, known etiology: genetic or environmental); and whether the case was familial (yes, no). A case was considered familial if a first degree relative (parent or sib) had a concordant phenotype.

Multidimensional etiologic classification

To systematically capture the clinical presentation and etiology in the study cohort we developed and implemented a multidimensional classification with three axes: etiology (known, unknown), morphology (isolated, multiple majors, minors only), and pathogenesis (sequence, developmental field, or pattern). Table 1 summarizes the system and definitions. Briefly:

- Known etiology was assigned based on specific and conservative criteria and could be either genetic, environmental (teratogenic), or due to twinning:
  - Genetic—cases were classified as having a known genetic etiology if there was documentation of abnormal chromosomal number (trisomy) or structure (insertion, deletion) or a single gene condition (such as Noonan syndrome)
  - Environmental—this required documentation of exposure to a recognized human teratogen[8] (for example, medication, such as valproic acid, or pregestational diabetes with abnormal hemoglobin A_{1c} concentration during the periconceptional period or early pregnancy). Among mothers noted to have diabetes (pregestational or gestational), we reviewed their timing of diagnosis before or during pregnancy, medication use for control of blood sugar, and if listed, the hemoglobin A_{1c} testing date and concentration. Women listed as having gestational diabetes with a diagnosis in the first trimester were reclassified as having pregestational diabetes if their hemoglobin A_{1c} was >5.6. To assign diabetes as a cause, the mother had to have evidence of poorly controlled pregestational diabetes and an infant with selected birth defects that, based on the published literature, were indicative of diabetic embryopathy[9-11]: heterotaxy, holoprosencephaly, multiple vertebral defects, bilateral renal defects, or caudal dysgenesis. Conversely, pregestational diabetes in cases of isolated defects such as anencephaly or a congenital heart defect, or a major with minor defect was not considered as a known cause for those particular infants
  - Twinning—abnormalities in twinning included either acardiac or conjoined twins.
- Morphology: a case with a single major birth defect (with or without a minor birth defect) was considered isolated. This definition includes isolated sequences. Infants without a major birth defect were included if they had a chromosomal anomaly (such as trisomy 21 with no reported major birth defect, normal echocardiogram, and none of the selected list of objective minor defects) or eligible genetic condition (such as skeletal dysplasia). Only a selected list of minor defects was classified and analyzed; these were

Table 1 | Classification groups and definitions for etiologic classification of all cases of birth defects in Utah, 2005-09

Group	Definition
Etiology	
Known	Anomaly of chromosome number (trisomy 21) or structure (del 22q); single gene condition (such as Noonan syndrome); anomaly of gene expression (methylation-related Beckwith-Wiedemann syndrome); established human teratogen (such as pregestational diabetes, valproic acid); specific twinning abnormality (such as acardiac or conjoined twin)
Unknown	No identifiable cause could definitively be established and documented
Morphology	
Isolated	Single major malformation, with or without a non-objective minor defect. Note: a sequence (see below for definition) if isolated is considered an isolated defect, as in the case spina bifida with clubfoot and hydrocephalus
Multiple	Two or more unrelated major malformations
Minor*	Select, distinctive, and objective structural defect that is not clinically or surgically significant
None	No major or distinctive minor defects were detected. Case might still be eligible in the presence of an eligible chromosomal anomaly (such as child with trisomy 21, without a major defect, or one of the selected minor defects in the list of objective minors).
Pathogenesis	
Sequence†	Pattern of related malformations that occur as a result of a single primary malformation. Examples include spina bifida with hydrocephalus and clubfoot (spina bifida sequence, with spina bifida as the primary malformation). A sequence can occur as an isolated defect (spina bifida sequence) or as multiple defect (such as spina bifida sequence and cleft lip)
Developmental field defect‡	Pattern of malformations resulting from the abnormal development of an embryonic unit (developmental field) that develops as a single unit in early embryogenesis (such as during blastogenesis). Etiology of developmental field defects is typically heterogeneous. An example is the DiGeorge anomaly, related to abnormal development and fate of populations of neural crest cells, leading to multiple structural anomalies and potentially caused by different genetic abnormalities (such as deletion 22q11) or environmental factors (such as retinoic acid)
Pattern§	Non-random occurrence or pattern of multiple malformations without a known cause. Examples include the VATER/VACTERL recurrent and variable pattern of anomalies.

*Absent nails, auricular tag/pit, bifid uvula, branchial tag/pit, camptodactyly, cervical ribs, cup ear, cutis aplasia, cystic hygroma, ear lobe crease, ear lobe notch, extra nipples, iris coloboma, lop ear (microtia type 1), natal tooth, neck webbing, overlapping finger, polydactyly type B: tag involves hand or foot (polydactyly is a major defect when involvement includes a full extra digit of hand or foot), preauricular tag/pit, rocker bottom feet, single crease fifth finger, single transverse crease, single umbilical artery, syndactyly (toes), syndactyly (hands, mild, first flexion crease involvement: syndactyly is a major defect when involvement is up to/include second flexion crease (moderate) and severe when it includes distal phalanx).

†Amniotic band, amniotic band with limb-body wall, arthrogryposis, frontonasal malformation, gastroschisis with congenital intestinal atresia, limb-body wall complex, Pierre Robin sequence, Poland anomaly, urethral obstruction (that is, posterior urethral valves, urethral atresia/stenosis), urethral obstruction and renal agenesis (MCDK), renal (agenesis, multicystic dysplastic kidney, infantile autosomal recessive polycystic kidney disease), spina bifida (hydrocephalus, club foot), Sturge-Weber syndrome.

‡Pentalogy of Cantrell, cloacal exstrophy, DiGeorge anomaly, holoprosencephaly, laterality, septo-optic dysplasia, sirenomelia, urorectal septum malformation.

§Caudal dysgenesis, VACTERL: vertebral anomalies, anal atresia, cardiovascular, tracheoesophageal fistula, esophageal atresia, renal and/or radial, limb, MURCS: Müllerian duct aplasia, renal aplasia, and, cervicothoracic somite dysplasia, Goldenhar/OAV (oculo-auricular-vertebral).

selected because they can be considered as objective findings with limited variation in reporting and classification (table 1). This list included mainly discontinuous traits such as preauricular tags or single umbilical artery, rather than continuous traits such as hypertelorism, which require careful measurements and chart based decision criteria

- Pathogenesis: three groups were created and defined by mechanism based on embryology, not ICD-9 BPA codes (sequence, developmental field defect, or known pattern of birth defects, table 1). An example of a "known pattern" is the VATER/VACTERL association. This association was operationally defined as the presence of three or more VACTERL defects (vertebral defects, anal atresia, cardiac anomaly, esophageal atresia or tracheoesophageal (TE) fistula, renal malformation, radial limb malformation) with at least one being either esophageal atresia/TE fistula or anal atresia.[12] To further promote consistency, the same clinical geneticist (JCC) reviewed and classified all cases of potential VACTERL association

Implementation of multidimensional classification

For this study, the clinicians together developed a systematic process for the re-review of all cases. In general, each case was reviewed by one clinician, and the accuracy of the classification was further enhanced by assigning certain phenotypes to the clinician with the greatest expertise in that specialty. We re-reviewed the complete population based resident cohort for five consecutive birth years (1 January 2005 to 31 December 2009). We elected to assess this five year birth cohort because some genetic tests can be ordered well after infancy, changing the classification status. Case classification can also change as knowledge progresses. For example, cases of CHARGE association (coloboma, heart defect, choanal atresia, growth/developmental retardation, genital and ear abnormalities) were changed from "multiple congenital anomaly" to "syndrome/genetic" after mutations in the CHD7 gene were established as a cause in 2004[13]—in this situation, cases that met the established clinical criteria for CHARGE (with or without CHD7 mutation testing) were reclassified as "genetic." The classification was supported by an Access database module that captured both the classifications and comments from the clinical reviewers.

The cohort included 6547 confirmed cases. We excluded 834 cases of isolated birth defect: twin related (n=2); pelviectasis or hydronephrosis without evidence of obstruction (n=47); small (<4 mm) secundum atrial septal defects (n=200); and distal (first degree) or megameatus type hypospadias (n=585). We also excluded spontaneous abortions occurring at <20 weeks' gestation (n=209). After exclusions, the final study cohort included 5504 cases.

Statistical analyses were done with SAS Enterprise Guide version 6.1 software (SAS Institute, Cary, NC, 2013).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in

Table 2 | Number of cases of birth defects, percentage, and prevalence (per 1000 births) stratified by morphology (isolated and non-isolated) and pregnancy outcome in Utah, 2005-09

	Pregnancy outcome		
Morphology	Live birth	Fetal loss	Total
Isolated			
No of infants	4147	204	4351
% total	75.3%	3.7%	79%
Prevalence/1000	15.3	0.8	16.1
Non-isolated*			
No of infants	920	233	1153
% total	16.7%	4.2%	21%
Prevalence/1000	3.4	0.9	4.3
Total			
No of infants	5067	437	5504
% total	92%	7.9%	100%
Prevalence/1000	18.7	1.6	20.3

*Non-isolated: cases with ≥2 majors, minors only, and no major or minor malformations.

the design and implementation of the study. There are no plans to involve patients in the dissemination of results.

Results
The population based study cohort included 5504 infants with major birth defects among 270 878 total births (live births and stillbirths), giving a prevalence of 2.03%. In this cohort, 92.1% (5067/5504) of cases (isolated and non-isolated) occurred in liveborn infants: 75.3% (4147/5504) had an isolated defect (unknown and known etiology combined) (table 2). A positive family history (having a similarly affected first degree relative) was documented in 4.8% cases overall (266/5504). Compared with the underlying birth cohort (births in Utah, 2005-09), the affected cohort included more boys (57.7%, P<0.001), even after we excluded cases known to be sex limited anomalies (such as hypospadias, 47,XXY/XYY/XXX, 45,X).

Unknown etiology
Overall, 79.8% of cases (n=4390) were classified as unknown etiology (table 3), 3.6% were known to be familial (isolated 3.7%; multiple 2.7%). Boys were over-represented in both isolated (59.5%, P<0.001) and multiple (55.4%, P=0.02) case groups.

Among the unknown etiology case group, 344 (7.8% of 4390) were further classified as a sequence (n=242, 70.3%), a developmental field defect (n=71, 20.6%), or a known pattern (n=31, 9.0%) (table 4). Isolated defects accounted for most cases classified as a sequence (n=187, 77.3%) or developmental field defect (n=50, 70.4%), whereas cases classified as a pattern were more likely to have multiple birth defects (n=30, 96.8%). Eighteen of 20 infants with birth defects consistent with VATER/VACTERL association (known pattern) were classified as unknown etiology.

Known etiology
A fifth (20.2%, n=1114) of cases were assigned a known etiology (table 3). As shown in figure 1, 90.4% of the

cases with a known etiology were represented by the three common trisomies (21, 18, 13), Turner syndrome, structural chromosomal abnormalities, and single gene disorders.

For the known etiology case group, 57 (5.1% of 1114) were further classified as a sequence (n=35, 61.4%), a developmental field defect (n=13, 22.8%), or a known pattern (n=10, 17.5%) (data not shown). Of the remaining two cases with VATER/VACTERL association (known pattern), one case occurred with pregestational diabetes (teratogen) and another with partial trisomy (7q11.21 duplication) (chromosomal-structure).

Discussion
In this five year population based birth defect case cohort, systematic clinical review identified known etiology in only one in five—specific etiology could not be conclusively assigned in most (79.8%) cases. We considered the etiology known if there was conclusive evidence of one of four factors: chromosomal abnormalities (structure or number), genetic conditions, twinning, or an established human teratogen. Methods to determine if an environmental exposure is a human teratogen were recently reviewed and applied to the birth defects associated with the Zika virus.[14]

Based on current science, our study revises and updates the historical findings from two well known hospital based studies of infants with birth defects.[15 16] The overall conclusion remains that a specific cause cannot yet be determined for most birth defects, underscoring the current gaps in knowledge and the challenge of primary prevention.

Comparison with other studies
We focused on major birth defects (excluding some common defects), for a prevalence of 2%. If we extrapolate from this conservative estimate, we estimate that each year a minimum of 78 000 infants are born in the US with a serious birth defect. In 63 000, there would be no identifiable etiology. These figures are intended as minimum estimates. With different criteria for inclusion, investigators have reported a prevalence of 2.24% among infants with a birth defect diagnosed before discharge from the maternity ward or before the age of 5 days at Boston Hospital for Women[16] and 5.5%[17] from the Texas Birth Defects Monitoring Program.

Our estimate of a known etiology in just over 20% is conservative. As genetic technology advances and more discoveries made on the genetic causes of birth defects, the proportion with a known cause will increase. For example, estimates of the genetic contribution to congenital heart disease (the most common birth defect) has increased, based on recent data suggesting that copy number variants and de novo mutations together could account for 15% of all cases.[18-20] Also, for some well known risk factors, attribution of an exposure to a birth defect in an individual case remains challenging. The epidemiologic metric of attributable fraction (that is, the proportion of birth defects attributable to the exposure when cause is known) is applicable to populations, not individual cases. In this study, it was not

Table 3 | Etiologic classification of birth defects stratified by morphology and pregnancy outcome in Utah, 2005-09. Figures are numbers (percentage)

| | Morphology | | | | | | | | |
| | None | | Isolated | | ≥2 majors | | Minors only* | | |
	Live birth (n=66, 1.2%)	Fetal loss† (n=43, 0.8%)	Live birth (n=4147, 75.3%)	Fetal loss† (n=204, 3.7%)	Live birth (n=749, 13.6%)	Fetal loss† (n=137, 2.9%)	Live birth (n=105, 1.9%)	Fetal loss† (n=53, 1.0%)	Total (n=5504)
Known etiology									
No (%) total	66 (5.9)	43 (3.9)	407 (36.5)	70 (6.3)	287 (25.8)	83 (7.5)	105 (9.4)	53 (4.8)	1114 (20.2)
Chromosomal abnormality	58	43	285	52	183	67	103	53	844
Number	41	41	216	47	103	63	92	53	656
Structure	17	2	69	5	80	4	11	—	188
Genetic	8	—	106	5	80	7	2	—	208
Expression	—	—	3	—	4	—	—	—	7
Single gene	8	—	103	5	76	7	2	—	201
Teratogen	—	—	15	1	23	7	—	—	46
Diabetes	—	—	8	—	18	7	—	—	33
Infections	—	—	5	1	3	—	—	—	9
Medications	—	—	2	—	2	—	—	—	4
Twinning	—	—	1	12	1	2	—	—	16
Acardiac	—	—	—	8	—	—	—	—	8
Conjoined	—	—	1	4	1	2	—	—	8
Unknown etiology									
No (%) total	—	—	3740 (85.2)	134 (3.1)	462 (10.5)	54 (1.2)	—	—	4390 (79.8)

*Minors only (n=158)—chromosomal (n=156): trisomy 21 97, Turner 29, trisomy 18 10, 45,X mosaic 3, Klinefelter 3, trisomy 21 mosaic 2, microdeletion 5, partial trisomy 3, del/dup 1, del 5p 1, del 22q 1, DiGeorge 1; genetic (n=2): OI type 1 1, fragile X 1.
†Includes stillbirths (≥20 weeks' gestation) and pregnancy terminations (any gestation).

Table 4 | Pathogenesis of 344 cases of birth defects with unknown etiology, stratified by morphology and pregnancy outcome in Utah, 2005-09. Figures are numbers (percentage)

| | Morphology | | | | |
| | Isolated | | ≥ 2 majors | | |
	Live birth	Fetal loss*	Live birth	Fetal loss*	Total
Sequence (n=242, 70.3%)					
Spina bifida, hydrocephalus, clubbed foot	46	5	14	—	65 (26.9)
Renal†	13	16	4	1	34 (14.0)
Arthrogryposis	15	2	10	4	31 (12.8)
Pierre Robin	21	-	8	—	29 (12.0)
Amniotic band	11	8	1	—	20 (8.3)
Urethral obstruction‡	10	4	1	2	17 (7.0)
Limb-body wall with/without amniotic band	2	11	—	2	15 (6.2)
Gastroschisis with atresia§	11	1	1	—	13 (5.4)
Urethral obstruction with renal¶	4	2	5	—	11 (4.5)
Poland anomaly	2	—	1	—	3 (1.2)
Sturge-Weber	3	—	-	—	3 (1.2)
Frontonasal malformation	—	—	1	—	1 (0.4)
Total	138 (57.0)	49 (20.2)	46 (19.0)	9 (3.7)	242
Developmental field defect (n=71, 20.6%)					
Laterality	27	1	8	1	37 (52.1)
Holoprosencepahly	10	2	5	4	21 (29.6)
Septo-optic dysplasia	2	—	2	—	4 (5.6)
Urorectal septum defect	3	—	1	—	4 (5.6)
Pentalogy of Cantrell	2	—	—	—	2 (2.8)
Sirenomelia	2	—	—	—	2 (2.8)
Cloacal exstrophy	1	—	—	—	1 (1.4)
Total	47 (66.2)	3 (4.2)	16 (22.5)	5 (7.0)	71
Pattern (n=31, 9.0%)					
VATER/VACTERL	—	—	16	2	18 (58.1)
Goldenhar/OAV	1	—	8	1	10 (32.3)
Caudal dysgenesis	—	—	3	—	3 (9.8)
Total	1 (3.2)	0	27 (87.1)	3 (9.6)	31

Goldenhar/OAV (oculo-auricular-vertebral); VACTERL: vertebral anomalies, anal atresia, cardiovascular, tracheoesophageal fistula, esophageal atresia, renal and/or radial, limb.
*Includes both stillbirths and pregnancy terminations.
†Renal agenesis, multicystic dysplastic kidneys infantile autosomal recessive polycystic kidney disease.
‡Posterior urethral valves, urethral atresia/stenosis.
§Congenital intestinal atresia (does not include acquired atresia after delivery).
¶Urethral obstruction with renal agenesis, multicystic dysplastic kidneys infantile autosomal recessive polycystic kidney disease.
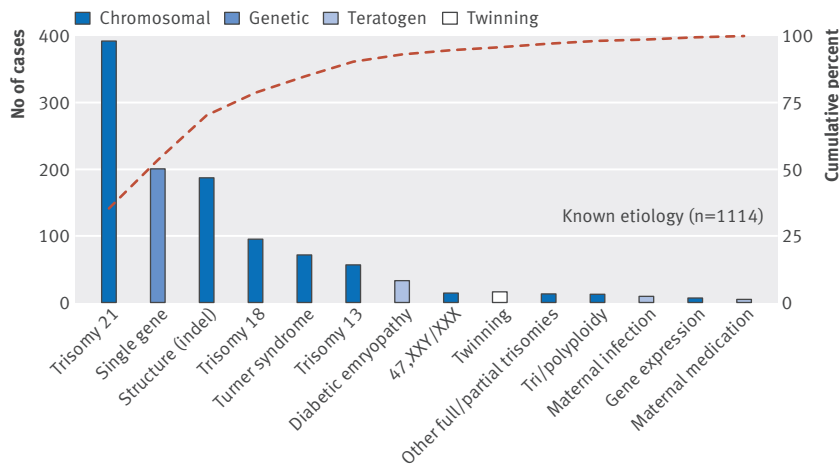
Fig 1 | Number and cumulative percent of cases of birth defects with a known etiology, Utah 2005-09

possible to determine if a woman's history of smoking directly resulted in her infant's oral facial cleft as the modest odds ratio of about 1.3 predicts that many children do not have an oral cleft because of that exposure. For pregestational diabetes, however, we used data on the estimates and attributable fraction of 70% for isolated and 90% for multiple defects[10] to select certain birth defects as related to diabetes.

Determination of etiology is critically important to focus research efforts for reduction of risk or prevention of occurrence (such as preconception folic acid supplementation and neural tube defects). Few studies have tried to directly assess the proportion of birth defects with or without a known etiology. Higurashi and colleagues re-examined infants each month for the first year to identify those with malformation syndromes not diagnosed at birth but did not mention the proportion without a known etiology.[21] Two hospital based cohorts used different methods (such as inclusion criteria and diagnosis within days after birth) to generate estimates of those infants without a known etiology.[15 16] Nelson and Holmes estimated 43.2% of their infants with birth defects born in a single hospital did not have a known etiology.[16] Infants were included if they received a diagnosis on or before the fifth day of life. Notably, cases considered to be familial (14.5%) or "multifactorial" (23%) were considered to be of known etiology; however, definitions were not provided and the inclusion especially of the "multifactorial" conditions is debatable. In contrast, in our study, we defined familial cases only as infants with an affected first degree relative (4.8% overall, 3.6% unknown etiology). Moreover, because of the difficulty in defining and proving multifactorial inheritance, we did not have such a category. Of note, if we add the cases classified by Nelson and Holmes[16] as multifactorial inheritance (23%) and familial (14.5%) to those that they classified originally as unknown (43.2%), the total adds to 80.7%, similar to our finding.

The causes of birth defects currently without known etiology are probably complex and could include interactions between the genetic profiles of parents and embryo and the environmental milieu during preconception and early gestation. For some birth defects, some progress has been made over the past decades, such as the contribution of microdeletions (such as deletion 22q11 in cases of heart defects and cleft palate[22-25]) and novel single gene mutations (such as CHD7 mutations in CHARGE syndrome[13]). While these genetic causes are relatively straightforward, however, it is likely that further research will discover more complex networks accounting for genetic and environmental contributions to birth defects etiology. Accumulating evidence is uncovering developmental networks that when disrupted can cause birth defect syndromes.[26] Some of these networks could also be influenced by environmental exposures, such as the midline patterning network related to the sonic hedgehog gene, which directly involves cholesterol metabolism. For example, the risk for holoprosencephaly could be increased not only by mutations in sonic hedgehog but potentially also by environmental influences (yet undiscovered) that alter the embryonic cholesterol biosynthesis, perhaps interacting with sonic hedgehog variants.[26]

Birth defects know no geographic boundary and occur in every country of the world. Because many countries do not have the capacity to monitor birth defects that occur among all pregnancy outcomes, it is difficult to estimate their true worldwide prevalence and global burden. Based on the findings of this study, however, if we count only those infants live born with an isolated birth defect, 25% of the cases will be missed. The resulting underestimation of the burden of disease can have serious policy implications and hinder the investments in research and interventions to better prevent and treat these major threats to childhood survival and lifelong health.

Research to understand birth defect etiology requires a well defined and clinically characterized case group. Cases with known etiology must be carefully identified and excluded to maximize the chance of discovery.[27] While commonly used birth defect classification schemes (such as ICD-9 or ICD-10) are valuable for general purposes such as studies on morbidity and mortality, they are not ideal in the evaluation of etiologies or trends[28] and could overestimate prevalence.[29-32] These coding systems are typically organized by anatomy or function rather than cause or embryologic process. Few studies have applied classifications specific to birth defects to population based cohorts. One of these, the National Birth Defects Prevention Study, has leveraged the collaboration of clinical geneticists and epidemiologists to pursue discovery of modifiable causes of birth defects.[33-35] Continued progress will require the combined effort and a multidisciplinary approach that incorporates not only the clinical evaluation by dysmorphologists/clinical geneticists and the methodological expertise of epidemiologists but also includes experts in developmental biology, pharmacology, infectious diseases, immunology, and bioinformatics, in addition to a more objective assessment of periconceptional exposures that improve on the typical maternal self

reports. Finally, it would be helpful to integrate etiology, morphology, and pathogenesis assessment into the basic framework of epidemiologic studies. Such integration will improve precision and assist researchers to focus research initiatives and investigate common pathways among birth defects.

Limitations

This study has potential limitations. The birth prevalence of 2.03% reported in this study is lower than the 2.24-5.5% reported elsewhere.[2 16 17] Such lower prevalence estimates could relate to the eligibility criteria of the Utah surveillance system, which exclude some common mostly milder conditions that are variably defined and ascertained (such as muscular ventricular septal defects, clubfoot, cryptorchidism). Also, because cases were classified based on data abstracted from mother and infant medical records, there is a possibility that critical information for appropriate classification was unavailable at the time of medical record abstraction. In addition, we could have underestimated the proportion caused by a teratogen if an exposure (such as maternal pregestational diabetes) was not noted in the medical record or not queried by the physician of record. The information in these medical records comes from different specialists, often including perinatologists, genetic counselors, neonatologists, and/or pediatric geneticists. Whereas some level of etiologic under-ascertainment cannot be excluded, it is unlikely that an established environmental cause of birth defects would be missed by everyone involved in the care of the mother and the child. For a genetic investigation, the laboratory evaluation (such as karyotype, microarray) was determined by the clinician(s) caring for the infant and was tailored to the clinical presentation. We would expect some variation within the practice of medicine.

Conclusion and public health implications

Understanding the etiology of birth defects should be both a public health and research priority. Our findings underscore the large gaps in current knowledge of the causes of birth defects. These gaps in turn represent opportunities for both basic and translational researchers. Such research can be particularly powerful and efficient if done in collaboration with population based birth defect surveillance programs enhanced with clinical expertise and meaningful case classification.[36] Advances in the knowledge of the causal pathway leading to birth defects can be the basis for better primary prevention interventions, resulting in longer and better lives. For clinicians and parents, it is important to understand what can be done today to prevent birth defects, in particular the role of preconception care focusing on optimal women's health (including screening/treating chronic illnesses, attaining folic acid sufficiency, etc). In addition, investigation of potential causes of a birth defect at the time of diagnosis (such as whether a genetic condition is present) can help to better plan management and appropriately counsel families, including the relief of anxiety related to unfounded information and guilt.

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