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Mortality in Fetal Alcohol Spectrum Disorders

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Abstract

Objective: Mortality in FASD has not been well studied. In this paper we review published reports of mortality in FASD. Method: We searched using Pub Med for all years in all languages for reports of all-cause mortality associated with any FASD. Results: We located 26 papers reporting on 57 deaths. Cause of death was reported for 49/57 cases (86%). The two most prevalent potential causes of death were malformations of the heart (37 of 49 cases, 75.5%) which varied from atrial septal defect or patent ductus arteriosus to tetralogy of Fallot, hypoplastic left heart, aortic arch interruption, etc. and brain malformations (25 of 49, 51%) including microcephaly, hydrocephalus, porencephaly, agenesis/absence of the corpus callosum and semilobar holoprosencephaly. In several cases potential causal findings overlapped. The three most frequent other causes of death were sepsis (7 cases, 14.3%), kidney malformations (7 cases, 14.3%), and cancer (4 cases, 8.2%). Over half the deaths (30/55, 54.5%) occurred in the first year of life. Discussion: We found that congenital heart disease was the most common cause of death in people with FASD. This may be due to an ascertainment bias since many of the published studies were focused on congenital heart disease in FASD. We conclude that FASD is frequently undetected in mortality events and could be a common finding in infant, child, adolescent and adult mortality.

Keywords

Fetal Alcohol Spectrum Disorder; Mortality; Birth Defects; Heart Defects; Brain Malformations; Sepsis; Cancer

1. Introduction

In 1899, a prison medical officer reported on the role of maternal alcoholism in infant mortality [1]. The rate of

infant mortality was doubled in alcoholic mothers. Later-born children had increased risk compared to earlier births (1st-born, 33.7%; 6th- to 10th-born, 72%). In the 299 surviving children born to mothers with a previous child death, the rate of epilepsy was 4.1% (10 - 40 times higher than rates reported in the general population at that time). One of the first descriptions of outcomes in children of alcohol-exposed pregnancies was published in 1968 [2]. They reported increased rates of miscarriages, stillbirths, prematurity and birth defects.

World-wide alcohol abuse now accounts for 4% of total worldwide mortality and between 4% and 5% of all disability-adjusted life years [3]. The prevalence of drinking during pregnancy is quite high especially prior to pregnancy recognition when slightly more than 50% of women in the United States report some alcohol use [4] [5]. Since many pregnancies are unplanned, early exposure is common. The prevalence of alcohol exposure decreases from 50% prior to pregnancy recognition to around 10% upon recognition of pregnancy [5]-[7]. About 3% - 5% of women continue to drink throughout pregnancy and many drink heavily, more than five drinks per occasion and often several times per week [4]. Thus, several hundred thousand pregnancies have prenatal alco- hol exposure at levels increasing risk for a fetal alcohol spectrum disorder (FASD). FASD is comprised of four categorical entities summarized in **Table 1** [6]. Current prevalence estimates suggest that 1% of live births may have an FASD and the rate is much higher in some at-risk populations [8].

While prenatal alcohol exposure may result in damage to any of the organ systems, the heart and brain appear to be two most commonly reported organ systems [6] [9]-[13]. However, recently Patel *et al*. [14] have reported that they found no increase in risk for non-syndromic atrioventricular septal defects attributable to maternal alcohol consumption in a large data set from the National Birth defects Prevention Study.

While multiple studies have examined the role of prenatal alcohol exposure on fetal and infant mortality, very limited data are available on mortality in FASD. To improve understanding of mortality events in FASD, we completed a review of published papers reporting on deaths in people with an FASD.

2. Methods

A search strategy was developed and conducted by an expert reference librarian with guidance from the authors. The search was conducted through the following electronic databases and search engines: PubMed, Scopus, Cochrane Database of Systematic Reviews, Quertle, and Google Scholar (**Table 2**). The following key words and subject headings were utilized in the search: prenatal alcohol exposure, fetal alcohol syndrome, mortality and prenatal exposure delayed effects. The reference list for each paper was then hand searched to identify other potential references not identified by our electronic search strategy. We excluded studies that did not report data on FASD.

The search, which was completed to December of 2012, placed no limits on language or publication date. When examining data from the selected articles, we relied on the original authors' report for prenatal alcohol exposure, cause of death and case descriptions (birth defects, infectious illness).

3. Results

We located 26 papers which met our inclusion criteria and reported on 57 deaths (**Table 2**). The reports ranged from single cases to 13 deaths. **Table 2** also summarizes data on prenatal exposure, gestational age at birth, birth weight, growth impairment, abnormal facial features, neurocognitive impairments and FASD ca-

Table 1. Diagnostic criteria for Fetal Alcohol Spectrum Disorders (FASD)[1].

	CNS Microcephaly Malformations Cognitive Impairments Mental Disorders Developmental Delays	**FACE** Thin upper lip Philtrum abnormalities Short palpebral fissures Flat nasal bridge Epicanthal folds Cleft lip and/or palate	**GROWTH** Height < 10th Weight < 10th Head Circumference <10th	**EXPOSURE**
FAS	YES (3 + Domain Deficits)	YES (3 of 3)	YES (≤ 10%)	YES[2]
PFAS	YES (3 + Domains Deficits)	YES (2 of 3)	N/A	YES[2]
ARND	YES (2 + Domain Deficits)	N/A	N/A	YES
ARBD[3]				YES

[1]FAS = Fetal alcohol syndrome; PFAS = Partial fetal alcohol syndrome; ARND = Alcohol related neurodevelopmental disorders; ARBD = Alcohol related birth defects. [2]Diagnosis can be made without confirmation of prenatal alcohol exposure. [3]Birth defects attributed to prenatal alcohol exposure. Defects of the heart and brain are the most prevalent.

Table 2. The search strategies utilized in this review at each sequential step - duplicates were excluded at each subsequent step.

SEARCH STRATEGY & TERM	YIELD (N)
Pub Med Searches	
"Fetal Alcohol Syndrome/mortality"[Mesh]	2
("Fetal Alcohol Syndrome"[Mesh]) AND "Infant Mortality"[Mesh]	3
("Fetal Alcohol Syndrome"[Mesh]) AND "Sudden Infant Death"[Mesh]	3
"Stillbirth"[Mesh] AND "Ethanol"[Mesh]	0
("Sudden Infant Death"[Mesh Terms]) AND "Ethanol"[MeSH Terms]	0
"Survival Analysis" [mesh] AND "Fetal Alcohol Syndrome" [mesh]	1
("Cause of Death"[MeSH Terms]) AND "Fetal Alcohol Syndrome"[Mesh]	1
("Fetal Alcohol Syndrome"[Mesh] OR "Alcoholism"[Mesh]) AND "Cause of Death"[Mesh]	2
("Fetal Alcohol Syndrome"[Mesh]) AND "Fetal Death"[Mesh]	6
("Alcoholism/complications"[MeSH Terms]) AND "Fetal Death/chemically induced"[MeSH Terms]	5
(("Fetal Diseases/chemically induced"[MeSH Terms]) AND (alcohol OR ethanol[Title/Abstract])) AND (autopsy OR death OR fatal* OR mortal*)	7
("Fetal Alcohol Syndrome"[Mesh]) AND autopsy[Title/Abstract]	3
("Fatal Outcome"[Mesh]) AND "Fetal Alcohol Syndrome"[Mesh]	3
(("Death"[Mesh]) And "Fetal Alcohol Syndrome"[Mesh]))	5
Fetal alcohol spectrum disorders mortality	
"fetal alcohol" AND death	4
("fetal alcohol"[Title/Abstract]) AND (death OR mortality[Title/Abstract])	2
(fetal alcohol effects) AND death	1
Foetel alcohol death	5
Embryofetal alcohol syndrome	1
Hand Search of Bibliographies	12
Scopus	4
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	2
Academic Search Premier	53

tegorical diagnosis. The diagnostic criteria for the FASD include growth impairment, abnormal facial features and neurocognitive impairments (**Table 3**).

Data on prenatal alcohol exposure was present for 48 of the 57 cases (84.2%) and all of these women were reported to be heavy drinkers. Drinking was most prevalent in the first trimester. The 57 cases included data on birth weight for 20 cases (35.1%) and gestational age at delivery for 22 cases (38.6%). Of the cases with information on gestational age, 12 of 22 (63.6%) were born preterm (<37 weeks gestation). Data was available on weight for 11 cases (19.3%), on height for 6 (10.5%) and on head circumference for 12 cases (21.1%). Nonspecific growth restriction was reported in 9 cases (15.8%).

The three most frequently reported abnormal facial features in fetal alcohol syndrome are thin upper lip, indistinct or smooth philtrum and short palpebral fissure length (**Table 3**). Abnormal facial features were reported for 32 (56.1%) of the cases. These were highly variable but included short palpebral fissures 13 (22.8%), thin upper lip 9 (15.8%), microganthia 8 (14%), low set ears 7 (12.3%), ptosis 7 (12.3%), absent or indistinct philtral ridge 5 (8.8%), epicanthal folds 5 (8.8%), cleft palate 9 (15.8%), flat nasal bridge 6 (10.5%) and midface hypoplasia 3 (5.3%) (**Table 2**). In addition 10 cases (17.5%) were reported to have unspecified abnormal facial features, including FAS typical facial abnormalities, diagnostic facial features or dysmorphic facial features.

The neurocognitive features commonly reported in FASD are microcephaly, intellectual disability, attention deficit hyperactivity disorder and behavioral impairments. Structural abnormalities of the central nervous system were reported for 25 of the 49 cases (51%). These included microcephaly, agenesis/absence of the corpus callo-

Table 3. Data on exposure, gestational age at birth, birth weight, growth impairments, and abnormal facial features for 57 deaths in people with a fetal alcohol spectrum disorder (HT = height, HC = head circumference, WT = weight, FP = flat philtrum, EP = epicanthal folds, SPL = short palpebral fissures length, CC = chest circumference, TUL = thin upper lip).

Publication	Alcohol Exposure + = reported	Gestational Age/Birth Weight	Growth Impairment	Facial Features	Neurocognitive Impairments	FASD Status
[34]	+	Term 1600 g	WT, HC <10% at birth	SPL, FP, TUL, micrognathia and low set ears	Brain was histologically normal on autopsy	FAS
[35]	+	35 weeks 1360 g	HC, HT, WT <3% at birth	Hypertelorism, broad nasal bridge, inferolateral deviation of right eye, low-set and posteriorly rotated right ear,	Microcephaly and partial agenesis of the corpus callosum	FAS
[36]	+		Reported	Described as abnormal		FAS
[36]	+		Reported	Described as abnormal		FAS
[37]	+	37 weeks 2330 g	WT, HT, HC, CC <3rd %	Long upper lip, cleft palate, hypertelorism, partial ptosis, curved fused eyebrows[1]	Absence of corpus callosum and underdevelopment of cerebellar vermis, areas of necrosis in the brain[2]	FAS
[37]	+	32 weeks 1180 g	WT, HT, HC, and CC <3rd %	Reportedly similar to previous case	Brain was small for developmental age (395 grams at 4 months)[3]	FAS
[37]	+	Term Not reported		Similar to previous cases without cleft palate	Abnormalities of cortical mantle formation[4]	FAS
[37]	+	35 weeks 1525 g	WT (1525 g), HC (28.5) both small for gestational age	Nondiagnostic facial features (flat nasal bridge and recessive mandible)	Brain was heavy (405g) but small[5]	FAS
[37]	+	29 weeks 880 g	WT below 3rd %	Reported facial features to be similar to the other cases in the paper	Brain small for gestational age (124.5 g) and an area of heterotopia white matter of the temporal lobe	FAS
[38]	+	Term 1770 g	Reduced birth weight, growth deficiency at 2 years	Blepharophimosis, SPL, flat nasal bridge, bilateral ptosis, and EF	Microdysplasias (partial fusion of third ventricle), spongiform loosening in the optic nerve and in the hypothalamus, seizures, psychomotor retardation	FAS
[38]	+	Term		Blepharophimosis, hypertelorism, micrognathia, hypoplastic ears, short upturned nose, and cleft palate	Hydrocephalus internus, heterotopic gyri in cerebellar white matter, slowed maturation of cerebral and cerebellar white matter	FAS
[38]	+			SPL, TUL, and low set ears	Seizures, porencephaly, hydrocephaly, agenesis of corpus callosum, multiple other abnormalities	FAS
[26]	+					FAS
[26]	+					FAS
[26]	+					FAS
[26]	+					FAS
[26]	+					FAS
[26]	+					FAS
[26]	+					FAS
[26]	+					FAS
[26]	+					FAS
[26]	+					FAS
[26]	+				Status epilepticus at 18 months, hemiplegia	FAS
[26]	+					FAS
[26]	+					FAS

Continued

[26]	+					FAS
[39]	+	36 to 37 weeks 3100 g	At death growth was 10th % and HC was 5th %	SPL, hypertelorism, midfacial hypoplasia, high arched palate	Microencephaly, small anteriorly fused frontal lobes[6]	FAS
[31]	+	32 weeks 1300 g	None	Microphthalmia, cleft palate	Agenesis of corpus callosum[7]	FAS
[28]	+					FAS
[40]	+	32 weeks	prenatal growth deficiency	SPL, maxillary hypoplasia	Microcephaly[8]	FAS
[40]	+	Term 3200 g	None	SPL, maxillary hypoplasia, EF, and micrognathia	Hydrocephalus at birth, no cranial nerve function, hypotonia, areflexia[9]	FASD/ ARND
[41]	+			“Typical facial anomalies”	Mild hydrocephalus internus, multiple heterotopic gyri of white matter of cerebellum	FAS
[41]	+			“Typical facial anomalies”	Severely mentally disabled, partial fusion of the 3rd ventricle[10]	FAS
[41]	+			“Typical facial anomalies”	Extreme brain malformations, absent corpus callosum[11]	FAS
[42]	+	34 weeks 1640 g	WT and HT at 10th % for 34 weeks, HC 10% - 25th %	SPL, microphthalmia, low nasal bridge with upturned nose, narrow face with triangular chin	None reported	FAS
[43]	+	3600 g	None	SPL, TUL, hypoplastic philtrum, short anteverted nose, and micrognathia	Mental retardation	FAS
[44]	+	40 weeks	prenatal growth deficiency	SPL, EF, small lips, micrognathia, small mandible, posteriorly rotated ears	Microcephaly, occasional glial meningeal heterotopias, cortical cerebellar heterotopias[12]	FAS
[45]	+	34 weeks 1780 g	WT and HT 10th %, HC <3 % at birth	SPL, long, FP, micrognathia, low-set ears, short upturned nose, flat nasal bridge, and high-arched palate	Opisthotonic posturing, increased tone, brisk deep tendon reflexes, absent social smile at 7 weeks	FAS
[46]					Microencephaly, agenesis of corpus callosum[13]	FAS
[46]					Microencephaly, severe glioneuronal heterotopias in over normal cortex	FAS
[47]	+	35 weeks 1450 g	At birth WT, HT, HC <10th %	SPL, FP, TUL, broad nose, low set ears, midface hypoplasia, hypertelorism	Pachygyria, triphyllocephaly semilobar holoprosencephaly	FAS
[48]	+	40 weeks 1970 g	Present	Present	Present	FAS
[48]	+	32 weeks 2110 g	Present	Present	Present	FAS
[48]	+	36 weeks 2420 g	Present	Present	Present	FAS
[49]	+	36 weeks 1500 g	Severe growth impairment	Moderately pronounced cranial dysmorphism	4 mamillary bodies At 4 months brain weight 472 g	FAS
[50]	+	1440 g			Brain hemorrhage	FAS
[51]	+		None reported	Dysmorphic facies	Psychomotor retardation	FAS
[52]	+	28 weeks		Flat nose, cleft lip and palate, hypertelorism	Microcephaly, Hypotonia, recurrent myoclonic seizures, alobar holoprosencephaly[14]	Possible FAS
[53]	+		WT <10th %, HC <50th %	FP, SPL, ptosis	Mental retardation	FAS
[54]	+	1446 g		EF, hypertelorism, facial asymmetry, esotropia	Occipital cavernous hemangioma delayed/speech and development	FAS
[22]						FAS

Continued

[22]					FAS
[22]					PFAS
[22]					ARND
[22]					FAS
[22]					ARND
[22]					FAS
[55]	+	At 21months he was small	Low-set ears, downward slanting eyes, EF, bilateral ptosis,	Microcephaly, mental retardation, hyperactive, delayed motor skills	FAS

(HT = height, HC = head circumference, WT = weight, FP = flat philtrum, EP = epicanthal folds, SPL = short palpebral fissures length, CC = chest circumference, TUL = thin upper lip); [1]Micrognathia, short nose with a broad depressed bridge and anteverted nostrils, posteriorly rotated ears with folded upper helixes; [2]Developmental retardation in all areas (level of 1 month at 7 months of age), reduced mass of cerebral hemispheres; [3]Minor anomalies of cerebral mantle (small sulci and bridges between gyri) seemed to be secondary to heterotopic glial clusters in the meninges leading to gyral fusion; [4]Small submeningeal glial heterotropic protrusions, single heterotopy in white matter of temporal lobe; [5]Necrotic changes were present in the whole brain, most severe in periventricular white matter, one small glioneuronal meningeal heterotopias; [6]Absent olfactory bulbs and tracts, hypoplastic optic nerves, thalamus and caudate nuclei fused across midline, single ventricle with rudimentary lateral horns, unidentified anterior corpus callosum, septum pellucidum, fimbria, and fornices, absent posterior pituitary lobe; [7]Multiple heterotopias throughout the leptomeninges, cerebral mantle, and subependymal regions, cellular disorganization of cerebral mantle; [8]Massive sheet of tissue that covered the left cerebral hemisphere and extended to the right frontal lobe, consisting of neuronal and glial elements, agenesis of anterior corpus callosum, multiple neuroglial heterotopias. The cerebellum was small and there was an absence of a posterior folia; [9]Moderately dilated ventricles, ectopic neurons throughout frontal and temporal white matter, small and misshapen cerebellum, absent pons and medulla, anterior wall of fourth ventricle mainly composed of glial tissue, rudimentary brainstem with a dense leptomeningeal layer obstructing subarachnoid space causing the hydrocephalus; [10]Spongiform loosening in hypothalamus and optic nerve; [11]Olfactory bulbs, and cerebellar vermis, enlarged fourth ventricle, hypoplastic and malformed cerebellar hemispheres, syringomyelia porencephalic cyst over the cortex, and several cysts around the central canal of the spinal cord which were covered by ependymal cells; [12]Uncovered rostral region of insula, and decrease in number of dendritic spines of layer V of pyramidal neurons; [13]Underdeveloped cerebellar vermis, few small glioneuronal heterotopias over normal cortex; [14]Singular square shaped ventricle with midline fusion of basal ganglia and thalami.

sum and multiple severe brain malformations described in **Table 2**.

In **Table 4** we summarize the data on age at death, gender, and cause of death. **Figure 1** is a graphic presentation of the age at death data demonstrating that 12.7% of deaths occurred in the first week, and 54.5% of the deaths occurred by age one year. Only 25.5% of the deaths were reported to occur after 5 years of age (**Figure 1**). Gender was reported for 50 cases; 29 (58%) were male and 21 (42%) were female. The M/F ratio was 1.38 males for each female.

In **Table 5** we summarize the leading causes of death which was available for 49 of the 57 cases (86%). The most common cause of death was congenital heart disease 37/49 (75.5%) with suspected or confirmed congenital heart disease including atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, hypoplastic left heart, aortic arch interruption, etc. (**Table 4**). However, for some cases it was difficult to determine if the heart defect was the cause of death, a complicating condition, or related postmortem finding.

The second leading cause of death was congenital brain malformations which were present in 25/49 (51%). These included microcephaly, abnormalities of the corpus callosum, hydrocephalus, porencephaly and multiple other less severe malformations. Again it was difficult to determine if these defects were the cause of death, a complicating condition, or a postmortem finding of uncertain significance. Sepsis 7/49 cases (14.3%), malformations of the kidney 7/49 cases (14.3%), and cancer 4/49 cases (8.2%) were the other leading causes of death.

4. Discussion

We identified 57 deaths occurring in people with an FASD and identified a potential cause of death for 49 (86%). These 26 studies reported highly variable dosimetry for prenatal alcohol exposure, thus no dose response data were available to estimate mortality risk by duration of exposure, pattern of drinking, or quantity of exposure.

In this review congenital heart defects were reported to be the most prevalent cause of mortality in people with an FASD. We have previously reviewed the published data on the association of FASD and congenital heart defects [15]. In several cases it was difficult to determine if the deaths were due to congenital heart defects which were morbid but not mortal. However, several severe and likely lethal cardiac defects were reported including tetralogy of Fallot, hypoplastic left heart and aortic arch interruption. Another potential reason for the

Table 4. Data on age at death, gender and cause of death for 57 deaths in people with fetal alcohol spectrum disorders.

Publication	Age of Death	Gender	Cause of Death	Comments
[34]	20 hours	Female		Baby was born with phocomelia of upper limbs and amelia of lower limbs
[35]	110 days	Male	Aspiration	Autopsy found a paravertebral neuroblastoma.[1]
[36]			Heart failure due to combined atrial and ventricular septal defects and persistent ductus arteriosus	
[36]			Bowel obstruction from an inguinal hernia	Large ventricular septal defect and a persistent left superior vena cava.
[37]	8 months	Female	Congestive heart failure (ventricular septal defect) with superimposed infection (Yersinia)	Multiple abnormalities: hypoplastic nipples, hypoplasia of the labia majora, clitoral hypertrophy, deep sacral dimple
[37]	4 months	Male	Autopsy - ventricular septal defect, cardiomegaly, and collapse of left lung	
[37]	48 hours	Male	Autopsy - atrial septal defect and cardiomegaly	
[37]	17 days	Male	Cardiac arrest, acidosis	
[37]	4 days	Male	Autopsy - diffuse pulmonary hemorrhage and overdistention of lungs with cyst formation	
[38]	4.5 years	Male	Complete atrioventricular channel with infundibular and valvular stenosis of the pulmonary artery and bicuspid pulmonic valve	Clinodactyly of 5th finger
[38]	6 months	Male	Autopsy found Tetralogy of Fallot, thrombosis of basilar artery, and necrosis of cerebellum and pons	Aplasia of right kidney, hydronephrosis[2]
[38]	9 months	Female	Autopsy showed atrial septal defect, aspiration pneumonia, and multifocal interstitial pneumonia	Hydrocephalus, severe hypotonia[3]
[26]	5 years, 5 months	Female	Tetralogy of Fallot	
[26]	4 years, 4 months	Male	Tetralogy of Fallot	
[26]	5 years, 3 months	Male	Tetralogy of Fallot	
[26]	1 year, 3 months	Male	H. influenzae meningitis	
[26]	5 years 9 months	Male	Tetralogy of Fallot	
[26]	1 year, 11 months	Male	Bronchopneumonia, septicemia	
[26]	10 years, 7 months	Male	Tetralogy of Fallot	Cleft palate
[26]	5 months	Male	Congenital extra hepatic biliary atresia	Ventricular and atrial septal defects, patent ductus arteriosus
[26]	13 days	Female	Hypoplastic left heart syndrome	
[26]	29 years, 10 months	Female	Congenital cirrhosis	Esophageal varices, portocaval shunts, splenectomy
[26]	26 months	Female	Tracheolaryngomalacia, laryngeal webbing	Gastroesophageal reflux, pulmonary aspiration
[39]	2.5 months	Female	Respiratory distress	Choanal stenosis[4]
[31]	5 days	Female	Multiple apneic episodes	2 vessel umbilical cord, left sternal border murmur[5]
[28]	3.5 years	Female	Drowning in bath tub	4/6 systolic murmur interpreted as a ventricular septal defect[6]
[40]	6 weeks	Female	Prolonged apneic spell	Joint and cardiac anomalies
[40]	10 weeks	Male	Cardiopulmonary arrest	
[40]	68 hours		Idiopathic respiratory distress syndrome	
[41]	Either 6 months or 4 years	Male		Tetralogy of Fallot, hypoplasia of one kidney
[41]	Either 6 months or 4 years	Male	Heart failure	Atrioventricular canal
[41]	9 months		Massive hydrocephalus internus and externus	Atrial septal defect

Continued

[42]	7 days	Male	Shock	Interrupted aortic arch with aortopulmonary fenestration
[43]	11 months	Male	Pulmonary Hemorrhage	Severe mitral regurgitation, mild-moderate aortic stenosis and pulmonary stenosis[7]
[44]	4 months	Male	Pneumonia and congestive heart failure	2 cm ventricular septal defect with ventricular hypertrophy
[45]	96 days	Male	Sepsis	Atrial septal defect, pyloric stenosis with failure to thrive, undescended testes, sacral dimple
[46]	8 months		Congenital heart disease causing heart failure	Hydronephrosis
[46]	4 months		Congenital heart disease causing heart failure	Hydronephrosis
[47]	41 days	Female	Cardiopulmonary failure	Pfeiffer-like syndrome[8]
[48]	5 months	Female	Reported as noncardiac	Atrial septal defect
[48]	9 months	Female	Reported as noncardiac	Atrial septal defect
[48]	4 months	Male	Hypoxic spells and respiratory failure	Pulmonary stenosis, ventricular septal defect
[49]	4 months	Male	Unknown, found dead in crib	Ventricular septal defect, radial and ulnar malformation hospitalized for first 3 months life
[50]	10 hours	Male	Brain hemorrhage	Pulmonary hyaline membranes and a left undescended testicle
[51]	27 months	Male	Candida Sepsis	Born with dysplastic kidney and required renal transplant and immunosupressive therapy, developed hepatoblastoma
[52]	8 days		Recurrent Seizures	Patent ductus arteriosus
[53]	21 months	Male	Septicemia	Embryonal rhabdoymasarcoma
[54]	13 years	Female	Adrenal carcinoma	
[22]	17 years	Female	Accident	
[22]	22 years	Female	Complications from cerebral palsy	
[22]	11 years	Female	Respiratory complications	
[22]	17 years	Female	Suicide	
[22]	28 years	Male	Congenital heart disease	
[22]	23 years	Female		
[22]	18 years	Male		
[55]	21 months	Male	Septic complications from rhabdomyosarcoma of the bladder	Kidney-ureter abnormalities, urinary infection[9]

[1]Multiple other defects including multiple atrial septal defects, incomplete rotation of the gut with failure of fixation of the cecum and descending colon, right diaphragmatic hernia and bilateral inguinal hernias, as well as midline cleft palate, cleft lip on the left, wide spaced nipples, prominent right hemithorax, simian creases, hypoplastic nails, long and slender fingers, syndactyly of the second and third toes bilaterally, undescended testes, synostosis of the right radius and ulna; [2]Radial ulnar synostosis, camptodactyly, and anomalies of the palmar creases; [3]Porencephaly diastasis recti, hypertrophy of clitoris, anomalies of palmar creases. Hydramnios, cephalohematoma, and generalized edema noted at birth; [4]Transverse palmar crease, bilateral renal parenchymal duplication with single pelvis, small atrial septal defect, severe thymic and adrenal involution; [5]Hirsutism (especially over forehead), overlapping of 2nd by the 3rd fingers, clinodactyly of the left 5th finger, camptodactyly of right 3rd finger, absence of distal interphalangeal crease; [6]Congenital hip dysplasia, repeated ear infections; [7]Short 5th fingers, palmar transverse creases, congenital heart defect - markedly thickened and rolled up mitral valve, moderately thickened aortic valve leaflets, dysplastic pulmonary valve, markedly dilated left atrium, severe hypertrophy of left ventricle, moderate hypertrophy of right ventricle, patent foramen ovale; [8]Cloverleaf skull, craniosynostosis, bilateral choanal stenosis, bilateral auditory canal bony atresia, hypoplasia of stapes, cleft palate, short neck, cubitus valgus, broad thumbs, bilateral palmar creases, broad and medially deviated halluces, sacral and coccygeal deformities, caudal regression, patent ductus arteriosus, left-sided aortic arch and aberrant retroesophageal right subclavian artery; [9]Broad nose, anteverted nares, marked nasiolabial folds, high palate.

disproportionate numbers of cardiac deaths may be due to the publication of multiple studies specifically focused on cardiac malformations in FASD, primarily fetal alcohol syndrome.

The number and severity of brain malformations was also interesting. These include hydrocephalus, porencephaly, absence of the corpus callosum, semilobar holoprosencephaly, and brain hemorrhage (**Table 2**). These findings suggest that pediatric neurologists and neurologists are likely to encounter and manage cases of FASD with some frequency [16] [17].

Death from sepsis was reported for 7/49 cases (14.3%). Susceptibility to infection and increased risk of sepsis

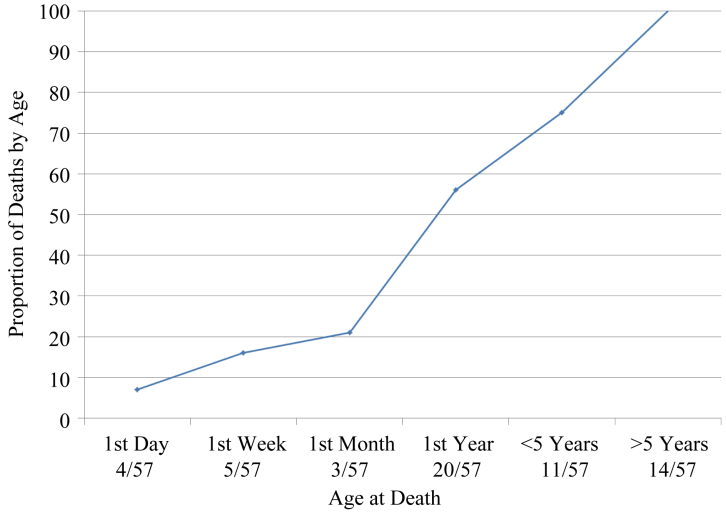

Figure 1. Cumulative mortality by age.

Table 5. Cause of death findings for 45 of the 59 cases included in this review.

	n	%
Congenital Heart Malformations	37/49	75.5
Congenital Brain Malformations	25/49	51
Sepsis	7/49	14.3
Kidney Malformations	7/49	14.3
Cancer	4/49	8.2
Liver Malformations	2/49	4.1

in FASD has been previously reported [10] [18]-[22]. Kidney malformation was found to be the cause of death in 7/49 cases (14.3%). Previous studies have examined malformations of the kidney, however, it is difficult to determine if the reported cases exceed expected rates for the co-occurrence of two conditions or if rates of kidney malformations exceed expected rates in people with an FASD [9] [23] [24]. Cancers were reported to be a cause of death in 4/49 cases (8.2%). However, no particular risk for a specific cancer could be determined from this small sample.

The early age of death distribution was surprising since a diagnosis of FASD is difficult in infancy and early childhood. Given the prevalence of FASD at about 1% of live births case reports and case series studies of mortality should be common rather than limited to 57 cases. It seems likely that most cases of mortality in FASD occur in a context where the FASD (likely even the potential role of prenatal alcohol exposure) is not routinely considered [25]. In previous reports we have suggested that a context of prenatal alcohol exposure should be considered in all infant and childhood deaths [25]. A diagnosis of FASD is associated with increased risk of death for affected people and their siblings (even when the sibling FASD status is unknown) [21] [22]. In populations of children with an FASD, recent reports suggests a 5% - 6% mortality risk [10] [21] [22] [26]. Several reports have also demonstrated increased rates of mortality in mothers of children with FAS [10] [27]-[30].

We present several strategies which might improve the ascertainment of FASD in mortality events. 1) Larger population studies with improved exposure assessments. 2) Studies to develop strategies to routinely configure FASD and PAE into the decisional algorithm for classification of cause of death. 3) Development of risk stratification strategies to identify deaths at risk for having an FASD. Estimation of risk would be improved by a careful review of relevant data from the mothers and child's records. These would include use of information of previous maternal substance abuse treatment of all types (alcohol is often used in combination with other drugs), review of prenatal care records, identification of prenatal alcohol exposure, exposure dosimetry, maternal death, sibling with a diagnosis of FASD, sibling death, and adoption or placement in foster care.

The context of prenatal alcohol exposure and a diagnosis of FASD can offer important information on a va-

riety of multifaceted and interacting risk markers and increase our understanding of the risk for mortality and adverse outcomes. This schema could be considered analogous to the concept of an infant of a diabetic mother where the infants are considered candidates for increased surveillance for a wide range of adverse outcomes. It is also important to clarify that the diagnosis of a chromosomal disorder, genetic abnormality, birth defect, infection, or traumatic cause of death does not exclude alcohol as an important consideration in risk assessment for mortality and other adverse events.

In previous research we have described the mechanisms of expression of neurobehavioral deficits in FASD [13]. Prenatal alcohol exposure modifies risk and phenotype severity by three primary pathways: 1) by lowering thresholds for expression of neurobehavioral deficits; 2) by increasing the number of comorbidities; 3) direct causation of some deficits. The structural deficits associated with prenatal alcohol exposure associated with mortality are large and include effects from exposure over multiple embryonic periods of development likely in concert with other modifiers of exposure. Importantly, non-lethal abnormalities are likely to have implications for subsequent neurobehavioral development and risk for mental disorders. These risks will likely change over time in response to past development and both age and development dependent demands. The potential range of neurobehavioral deficits seems large and in contrast to the typical facial features of FASD (thin upper lip, upturned nose, flat philtrim) many will have significant developmental implications far into the future as neurobehavioral development continues.

Limitations

Several important limitations for diagnosis of FASD are important in interpretation of this study. Firstly, the diagnostic nomenclature has been modified over the 35 year span of time (1974 to 2009) for cases included in this review [6] [31] [32]. Secondly, there is no widely accepted threshold for exposure that is necessary or sufficient to cause an FASD [33]. Thirdly, it is likely that many deaths occur in people with an FASD that is undiagnosed or where a past diagnosis is not available at the time of the death. It seems likely that these 57 cases represent a modest fraction of deaths in people with an FASD. Thus, the cause of death rankings may be incorrect.

Multicenter studies of mortality will likely be required to determine the extent of mortality risk in FASD and to identify the most prevalent causes of mortality. In the United States alone, there are 40,000 new cases of FASD each year and in the population birth through 18 years of age, about 720,000 people have an FASD. In this population several hundred deaths would be expected each year. This suggests that most cases of FASD are missed in mortality reviews. FASD should be considered as a risk marker for all-cause mortality in all family members (except fathers, where no mortality data are currently available).

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