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Inclusion of Early Fetal Deaths in a Birth Defects Surveillance System

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ABSTRACT This investigation evaluated the impact of collecting data on early fetal deaths (less than 20 weeks' gestation) on a birth defects surveillance system. Data were obtained from the Hawaii Birth Defects Program (HBDP), a statewide registry for Hawaii with active case ascertainment methodology. In 1986 through 1997, 257 early fetal deaths with birth defects were identified, representing 2.2% of the total birth defects cases. Two hundred sixteen (84.1%) of the early fetal deaths had chromosomal defects (mainly trisomies, polyploidies, and Turner syndrome) and 59 (23.0%) had structural defects. Most (65.4%) of the early fetal deaths with chromosomal defects occurred at 8–12 weeks' gestation, and 62.3% of the early fetal deaths with structural defects occurred at 16–19 weeks' gestation. For half of the 26 specific birth defects examined, early fetal deaths accounted for at least 4% of all cases. The proportion of total birth defects cases accounted for by early fetal deaths increased over the 12-year period of the study ($p = 0.003$). Most of this secular trend appeared to result from an increase over time in early fetal deaths where a birth defect was prenatally detected ($p = 0.004$). Although ascertainment of early fetal deaths is not believed to be complete, their inclusion in a birth defects registry may be beneficial because of confusion about the pregnancy outcome and/or gestational age reported in the medical record, their importance in cluster investigations, and their contribution to birth defects prevention strategies. *Teratology 64:S20–S25, 2001.*

INTRODUCTION

Approximately 15%–20% of clinically recognized pregnancies are spontaneously lost prior to fetal viability, and the loss is most likely to occur in the first trimester (Warburton and Fraser, '64). An estimated half of all fetal deaths in the first trimester are associated with a chromosomal anomaly (Ford et al., '96). The earlier the gestational age at which the fetal death occurs, the greater the likelihood of an associated chromosomal defect (Ohno et al., '91). Most chromosomal defects reported among fetal deaths are trisomies (particularly trisomy 16), polyploidies, and Turner syndrome (Ford et al., '96; Ohno et al., '91). Structural anomalies such as neural tube defects (NTDs), holoprosencephaly, oral clefts, and limb defects have also been reported to be more common in utero than among live births (Shepard et al., '89; Poland et al., '81; Odent et al., '98).

Much of the information about birth defects among early fetal deaths (fetal deaths at less than 20 weeks' gestation) is derived from facility-based investigations at cytogenetic and pathology facilities. Of the 18 states with birth defects surveillance systems that used active data collection systems, nine (50%) appeared to include early fetal deaths in their case inclusion criteria (CDC, '00).

This investigation examined the contribution of early fetal deaths to a birth defects surveillance system in Hawaii over a recent 12-year period. The study evaluated the impact of early fetal death on the rates of particular birth defect categories. The investigation also examined the influence of prenatal diagnosis on the identification of early fetal deaths with birth defects.

MATERIALS AND METHODS

Data were obtained from the Hawaii Birth Defects Program (HBDP), a statewide birth defects surveillance registry with active case ascertainment methodology (CDC, '00). The HBDP identifies cases through a multiple source ascertainment system that includes all birth and pediatric tertiary care hospitals, facilities that perform terminations secondary to fetal anomaly, cytogenetic laboratories, genetic counseling centers, and most prenatal diagnostic facilities in the state. Trained HBDP staff visit the facilities and review a variety of case finding sources and medical records, then abstract the available medical records for cases meeting the registry's inclusion criteria.

All pregnancy outcomes are included in the HBDP regardless of gestational age at the end of the pregnancy: live births (the intent of the delivery was a live infant and the infant demonstrated signs of life, such

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as respiration or heart beat after delivery), fetal deaths (the embryo or fetus was known to have died before delivery), and medical terminations (delivery was induced with the intent of producing a nonviable infant because a prenatal screen or diagnostic test showed the fetus to have a birth defect). The HBDP collects diagnostic, demographic, and health information about infants/fetuses and their biological parents.

Cases included all pregnancies that ended during 1986–1997 where the pregnancy outcome was an early fetal death. To be classified as an early fetal death, the pregnancy outcome must be a fetal death with a known gestation at the end of the pregnancy of less than 20 weeks, or if the gestational age at the end of the pregnancy was not known (n = 34), then the pregnancy outcome must be reported as a spontaneous abortion, missed abortion, or miscarriage.

Variables included in this investigation for each case were the year of the end of the pregnancy, birth defect diagnoses, gestational age at the end of the pregnancy, and whether there had been prenatal detection of a birth defect.

The total number of early fetal deaths in the HBDP was identified, and the proportion of all HBDP cases represented by early fetal deaths was determined. In Hawaii, fetal deaths of any gestational age can be reported to the Hawaii Department of Health (DOH) on fetal death certificates. Thus the birth defect rate among all reported early fetal deaths was calculated on the basis of denominators provided by the DOH.

The distribution of early fetal deaths by diagnosis category (structural defects and chromosomal defects) was examined and their distribution by gestational age at the end of the pregnancy was determined. The proportion of total cases represented by early fetal deaths was determined for 26 selected birth defect categories. Secular trends in the distribution of all early fetal deaths and in the prenatal detection of birth defects among early fetal deaths was evaluated.

Ninety-five percent confidence intervals (CIs) were calculated by Poisson probability. Secular trends were analyzed by the Chi-square tests for trend.

RESULTS

The HBDP identified 257 early fetal deaths with known or suspected birth defects in 1986–1997. This represents 2.2% (95% confidence interval (CI), 1.9–2.5) of the 11,794 birth defect cases in the HBDP. There were 7,790 early fetal deaths reported to the DOH in 1986–1997, for an identified birth defect rate among reported early fetal deaths of 3.3% (95% CI, 2.9–3.7).

Two hundred sixteen (84.1%, 95% CI 79.0–88.3) of the early fetal deaths had known or suspected chromosomal defects, and 59 (23.0%, 95% CI, 18.0–28.6) had known or suspected structural birth defects. Forty-one (16.0%, 95% CI 11.7–21.0) of the early fetal deaths had known or suspected structural birth defects and no mention of chromosomal defects.

Cytogenetic analysis supported a chromosomal defect in 213 of the early fetal deaths, representing 18.8% (95% CI 16.5–21.2) of the 1,135 cases of all pregnancy outcomes for which chromosomal defects were supported by cytogenetic analysis. One hundred twenty-eight (60.1%, 95% CI 53.2–66.7) of the karyotyped chromosomal defects were trisomies, particularly trisomy 21 (n = 27), trisomy 16 (n = 21), trisomy 15 (n = 13), and trisomy 22 (n = 11). Polyploidies and Turner syndrome accounted for 36 (16.9%, 95% CI 12.1–22.6) and 32 (15.0%, 95% CI 10.5–20.5) of the karyotyped chromosomal defects, respectively.

Table 1 shows the proportion of all pregnancy outcomes represented by early fetal deaths for 26 selected birth defect categories. Seven of the eight birth defects with the highest proportion represented by early fetal deaths were chromosomal defects (triploidy, other autosomal trisomy, other polyploidy, Turner syndrome, trisomy 13, trisomy 18, and trisomy 21) and the eighth was cystic hygroma. For half of the birth defect categories, early fetal deaths accounted for more than 4% of all cases.

The contribution of early fetal deaths to the total number of birth defects increased significantly over the 12-year study period (Table 2). When the proportion of early fetal deaths with prenatal detection of a birth defect is examined by year (Table 2), the prenatal detection rate increased significantly. Because this suggests that prenatal detection of birth defects might account for the increase in the proportion of early fetal deaths, the proportion of all birth defects represented by early fetal deaths where prenatal detection of a birth defect did not occur was calculated (Table 2). An increase was still observed during 1986–1997, but this trend was not statistically significant.

A higher proportion of early fetal deaths with structural defects were found for later gestational ages, particularly 16–19 weeks (62.3% of all structural defects) (Table 3). However, early fetal deaths with chromosomal defects were more common among earlier gestational ages, particularly 8–12 weeks' gestation (65.4% of all chromosomal defects). Among all early fetal deaths with birth defects, the proportion of cases tended to decline after a peak at 8–10 weeks' gestation.

Birth defects in 35 (13.6%, 95% CI 9.7–18.4) of the early fetal death cases were identified solely through hospitals and not through prenatal diagnostic facilities or cytogenetic laboratories. Birth defects in the rest of the cases were identified solely through prenatal diagnostic facilities and cytogenetic laboratories or in combination with hospitals. Seven of the cases in which the birth defect was identified solely through hospitals had a known chromosomal defect.

DISCUSSION

This investigation identified 257 early fetal deaths with birth defects in Hawaii during 1986–1997, representing 3.3% of the early fetal deaths reported to the Hawaii Department of Health. This rate should be considered an approximation, because not all early fe-

TABLE 1. Proportion of selected birth defects where the pregnancy outcome was an early fetal death (<20 weeks' gestation), Hawaii, 1986–1997

Diagnosis	Early fetal deaths (No.)	All pregnancy outcomes (No.)	All pregnancy outcomes represented by early fetal deaths (%)
Ancencephaly	4	89	4.5
Encephalocele	1	45	2.2
Holoprosencephaly	1	25	4.0
Hydrocephaly	3	257	1.2
Cleft palate alone	2	171	1.2
Cleft lip ± cleft palate	3	311	1.0
Anal atresia/stenosis	2	108	1.9
Hypospadias	2	595	0.3
Hydronephrosis	2	262	0.8
Cystic kidney	1	108	0.9
Posterior urethral valves	1	15	6.7
Reduction deformity of upper limb	2	70	2.9
Reduction deformity of lower limb	1	27	3.7
Diaphragmatic hernia	1	69	1.4
Omphalocele	2	68	2.9
Gastroschisis	3	74	4.1
Down syndrome (trisomy 21)	27	363	7.4
Patau syndrome (trisomy 13)	7	47	14.9
Edward syndrome (trisomy 18)	9	116	7.8
Other autosomal trisomy	90	117	76.9
Turner syndrome (45,X)	32	90	35.6
Klinefelter syndrome (47,XXY)	1	103	1.0
Triploidy	30	33	90.9
Other polyploidy	6	9	66.7
Cystic hygroma	16	129	12.4
Amniotic band anomalad	2	49	4.1

TABLE 2. Early fetal deaths (<20 weeks' gestation) by prenatal detection of the birth defect and year, Hawaii, 1986–1997

	Early fetal deaths (defect prenatally detected)		Early fetal deaths (defect not prenatally detected)		Total early fetal deaths		All pregnancy outcomes*
Year	No.	% of total EFDs**	No.	% of total cases	No.	% of total cases	No.
1986	0	0.0	11	1.3	11	1.3	855
1987	2	12.5	14	1.3	16	1.5	1,041
1988	0	0.0	16	1.6	16	1.6	999
1989	1	6.7	14	1.4	15	1.5	980
1990	3	11.1	24	2.4	27	2.6	1,021
1991	2	10.0	18	2.0	20	2.2	923
1992	3	9.7	28	3.2	31	3.6	868
1993	6	24.0	19	2.0	25	2.7	945
1994	0	0.0	16	1.6	16	1.6	1,023
1995	7	30.4	16	1.6	23	2.2	1,028
1996	6	19.4	25	2.1	31	2.7	1,169
1997	6	23.1	20	2.1	26	2.8	942
Total	36	14.0	221	1.9	257	2.2	11,794
P		0.004		0.114		0.005	
Slope per (100)		1.92		0.06		0.11	

*All live births, fetal deaths, and elective termination regardless of gestational age at delivery.
**EFDs, early fetal deaths.

tal deaths identified by the HBDP could be linked with DOH cases, suggesting that not all early fetal deaths are reported to DOH.

Most of the birth defects reported among fetal deaths were chromosomal defects, particularly trisomies, polyploidies, and Turner syndrome. Most of the chromosomal defects were reported among early fetal deaths with a gestational age in the first trimester. These observations are consistent with investigations from cytogenetic and pathology laboratories (Ford et al., '96; Ohno et al., '91). Structural defects were more often observed among early fetal deaths with later gestational ages. This may reflect the relatively greater ease with which structural birth defects can be detected as fetal age increases and the fetus becomes larger and thus easier to examine. Moreover, identify-

TABLE 3. Distribution of gestational age at fetal death by type of birth defect, Hawaii, 1986–1997

Gestational age (weeks)	Structural defects		Chromosomal defects		All cases	
	No.	%	No.	%	No.	%
6	1	1.8	8	4.5	8	3.6
7	0	0.0	11	6.1	13	5.8
8	1	1.8	27	15.1	27	12.1
9	0	0.0	30	16.8	30	13.5
10	1	1.8	24	13.4	25	11.2
11	2	3.6	17	9.5	18	8.1
12	3	5.5	19	10.6	20	9.0
13	3	5.5	13	7.3	14	6.3
14	4	7.3	3	1.7	7	3.1
15	3	5.5	5	2.8	9	4.0
16	8	14.6	8	4.5	15	6.7
17	5	9.1	4	2.2	8	3.6
18	8	14.5	7	3.9	11	4.9
19	16	29.1	3	1.7	18	8.1
Total	55	100.0	179	100.0	223	100.0
P		<0.000		<0.000		<0.000
Slope		1.56		−0.75		−0.28

ing structural birth defects may be difficult in organ systems when fetal development is not complete (Shepard et al., '89).

The 3.3% birth defect rate among early fetal deaths is much lower than might be expected because half of first trimester fetal deaths are estimated to have an associated chromosomal defect (Ford et al., '96). Various problems are inherent in identifying birth defects among early fetal deaths. Not all early fetal deaths are recognized as such by women and health care providers, particularly if they occur very early in gestation. Even if an early fetal death is recognized, not all early fetal deaths occur in a health care setting. In such instances, a fetus may not be available for examination. Even if a fetus is available for examination, identifying structural defects in fetuses with early gestational ages, particularly if maceration has occurred, is often difficult (Shepard et al., '89). Not all early fetal deaths may be sent for cytogenetic analysis, especially if it is the woman's first reported early fetal death. Even if the fetus is sent for cytogenetic analysis, lack of cell growth may prevent karyotyping.

Few identifiable early fetal deaths with identified birth defects are believed to have been missed by the HBDP. The HBDP includes as ascertainment sources all birth hospitals and cytogenetic laboratories and all except one of the genetic counseling and prenatal diagnostic facilities. Thus the registry includes almost all facilities where the early fetal deaths are most likely to be evaluated for birth defects or where a birth defect is most likely to be diagnosed.

The HBDP does not include any case finding sources such as logs or diagnostic codes that are unique to early fetal deaths. For several years the HBDP systematically reviewed all medical records with hospital discharge diagnosis codes indicating early fetal deaths. Several thousand medical records were reviewed, and no early fetal deaths with birth defects were identified that would not have been identified through the other case finding sources already in place. Moreover, the observation that most (86.4%) early fetal deaths in this study were identified through prenatal diagnostic and/or cytogenetic facilities suggests that other case finding sources such as hospital medical record departments are less likely to contribute significantly to the identification of early fetal deaths with birth defects. This is particularly true of chromosomal defects, where birth defect diagnoses for only 3% of the early fetal deaths with known or suspected chromosomal defects were identified solely through hospitals.

Even if ascertainment of early fetal deaths with birth defects is not likely to be as complete as it is for birth defects among live births, later fetal deaths (gestational age of 20 weeks or greater at delivery), or elective terminations, various reasons exist for a birth defects surveillance system to include early fetal deaths in its case criteria.

In this study, early fetal deaths accounted for only a small fraction (2.2%) of all cases with birth defects. Usually an infant's medical record will not be available for review, and a large number of postnatal diagnostic procedures will not be performed. Usually only the mother's medical record will be reviewed, and frequently this record will have little information about the pregnancy that ended in early fetal death. (The relative paucity of information about early fetal deaths may also be considered a reason for excluding of such pregnancy outcomes from surveillance systems. However, this relative lack of information would also possibly apply to elective terminations and later fetal deaths.)

Inclusion of certain pregnancy outcomes and/or gestational ages and exclusion of others by a birth defects surveillance system may confuse data collection staff about whether they should abstract a particular medical record. This can occur even if the surveillance system's inclusion criteria is explicit. If a surveillance system included all pregnancy outcomes except for fetal deaths of a particular gestational age, data collec-

tors may mistakenly also fail to include elective terminations of a similar gestational age.

Confusion also can exist about whether a given pregnancy outcome is a fetal death or elective termination. The same procedures are often used for elective terminations and for removal of a fetus that spontaneously died in utero. In addition, the medical record may not clearly indicate whether the fetus had spontaneously died before the procedure. Moreover, the medical record may classify a fetal death as an elective termination because a procedure was used to remove the fetus. Likewise, an elective termination may be reported in a medical record as a fetal death because the fetus died during or as a result of the delivery procedure or because of political or family reasons.

Confusion also can exist about the gestational age at which the fetal death occurred. Gestational age can be based on the last menstrual period date, prenatal ultrasound, and/or direct examination of the fetus or infant after delivery. The gestational age for a particular fetus may vary depending on the measure upon which the gestational age is based. When different measures give different gestational ages, deciding the most accurate gestational age may be difficult. Ascertainment of gestational age can be particularly important when some of the calculated ages are less than 20 weeks and others are 20 weeks or greater for the same fetal death. Moreover, a gestational age may not be available for some fetal deaths. In this investigation, 34 (13.2%) of the cases were labeled as miscarriages, missed abortions, and spontaneous abortions and had no reported measure of gestational age.

In some instances, examination of a fetus indicates that it died weeks before it was spontaneously expelled or delivered, or a prenatal ultrasound may identify a fetal demise and yet the delivery may occur weeks later. In such situations the criteria on which to base the gestational age of the fetal death may be unclear. This decision becomes important where gestational age is used to determine inclusion of a fetal death in a birth defects registry.

In the past several decades, much of the prenatal screening for and detection of birth defects occurred in the second trimester or later. The main exception was chorionic villus sampling. However, recent advances in prenatal screening using maternal serum markers and nuchal translucency measurement (Canick and Kellner, '99; Devine and Malone, '99) and detection by ultrasonography and embryofetoscopy (D'Ottavio et al., '98; Whitlow et al., '99; Reece, '99) allow birth defects to be detected at earlier gestational ages. As a result, more birth defects may be detected in fetuses at earlier gestational ages, and some of these fetuses can be expected to result in early fetal deaths. In fact, this investigation found that prenatal detection of birth defects among cases that resulted in early fetal deaths increased significantly over the 12-year study period and accounted in large part for the significant increase in the contribution of early fetal deaths made to the registry during 1986–1997.

An increasing proportion of early fetal deaths with birth defects probably would be identified in the future if earlier prenatal screening and detection procedures become more common. Moreover, a proportion of pregnancies in which birth defects are detected early will result in elective termination (Whitlow et al., '99). Thus tracking the proportion of early fetal deaths with birth defects may be useful to evaluate the impact of these elective terminations on birth defect rates among later fetal deaths and live births. Studies have already demonstrated that a portion of fetuses with chromosomal defects identified through amniocentesis do not survive to term (Hook, '83). These fetal losses are often taken into account when the impact of elective terminations secondary to chromosomal defects identified through amniocentesis on live birth rates are calculated.

Even if ascertainment of early fetal deaths is not complete, identification of as many infants and fetuses with birth defects as possible regardless of pregnancy outcome may be useful for birth defects activities other than surveillance. Cluster investigations may involve birth defects that have a strong association with fetal death or are more common among fetuses than among live births. Additionally, the individuals most concerned about a potential cluster may not be interested in fine distinctions between pregnancy outcomes and gestational ages. Failure to include in a surveillance system any identified early fetal deaths with birth defects may hinder certain cluster investigations.

In additional to surveillance, birth defects programs may be involved in prevention activities, particularly the prevention of NTDs through folic acid use. This may involve monitoring NTD rates to evaluate NTD occurrence prevention activities such as folic acid awareness, supplementation, and fortification strategies and/or identifying women who have had an NTD-affected pregnancy so that they can be enrolled in NTD recurrence prevention programs. Failure to identify early fetal deaths with NTDs may impair evaluation of occurrence prevention strategies and exclude women who could benefit from recurrence prevention activities.

In conclusion, this study found that the type and pattern of birth defects among early fetal deaths identified through a birth defects surveillance system was similar to that reported by investigations from cytogenetic and pathology facilities. Although ascertainment is not likely to be complete, birth defect cases among early fetal deaths may prove useful for purposes beyond surveillance.

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