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Chromosome Abnormalities and Spontaneous Fetal Death following Amniocentesis: Further Data and Associations with Maternal Age

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SUMMARY

The pooled results are presented of two North American surveys concerning spontaneous fetal deaths of conceptuses with cytogenetic abnormalities diagnosed prenatally whose mothers had declined elective abortion. The rate of fetal death of those with nonmosaic genotypes associated with Down syndrome was 30.1% (95% confidence interval of 19.0%–42.0%), which is almost identical with the difference of 30% previously estimated between rates observed at amniocentesis and in live births. The fetal death rate for (nonmosaic) 47,+18 was 68.0% (95% confidence interval of 46.5%–85.1%), close to the estimated difference of 75% between rates at amniocentesis and in live births for this genotype. For other nonmosaic genotypes, the rates (and 95% confidence intervals) were: 47,+13, 42.9% (9.9%–81.6%); 47,XXX, 0% (0%–9.0%); 47,XXY, 8.1% (0.8%–11.0%); 47,XYY, 3.0% (.08%–15.8%); for balanced translocations and inversions, 2.8% (0.3%–9.8%); and for markers, variants, and fragments, 0% (0%–12.8%). For 45,X, the rate was 75.0% (42.8%–94.5%), in contrast to the rate for 46,XX/45,X of 10.5% (1.3%–33.1%) and for structural X abnormalities associated with Turner syndrome of 0% (0%–60.2%). The rate for nonmosaic 45,X is significantly different from that for either of the other two categories associated with Turner syndrome. The maternal age of nonmosaic 47,+21 fetuses that survived to live birth was 39.1 ± 6.2, not significantly different from the rate for fetal deaths: 39.5 ± 3.8. The observations provide no support for opposing hypotheses by other groups that maternal age is positively or negatively associated with fetal death of 47,+21 conceptuses. For other chromosome abnormalities, maternal ages of fetal deaths are slightly lower than for live births, but none of the differences are significant. The rates of spontaneous fetal deaths derived here are likely to be pertinent to

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genetic counseling. Their use in adjusting the rates of abnormalities diagnosed at amniocentesis will enable derivation of predicted contemporary live-birth prevalence rates of abnormalities that would be observed in absence of selective abortion.

INTRODUCTION

A perplexing observation following the introduction of amniocentesis for prenatal diagnosis was the difference between maternal-age specific rates of Down syndrome diagnosed prenatally and rates in studies of live births. After appropriate statistical adjustments, it was suggested that the rate was about 30% higher at amniocentesis than in live births [1]. One suggestion for the difference was that there was a high spontaneous fetal death rate associated with Down syndrome after 16–18 weeks of gestation, an effect masked by the selective termination of most cytogenetically abnormal fetuses diagnosed prenatally [1, 2]. A similar explanation was suggested for the high rate of 47,+18 diagnosed at amniocentesis compared with rates in live births [3]. The results of a 1978 survey concerning women in whom a cytogenetically abnormal fetus was diagnosed but who did not elect abortion was consistent with this explanation [4]. The spontaneous rate of fetal loss of Down syndrome in singletons in this group was about 20%, but because of the small numbers involved, the 95% confidence interval was quite wide, from 6% to 46%. For trisomy 18, the rate of loss was 67%, and the estimate had an even larger sampling error. Here I report the results of a further survey, the results of which enable more precise estimates of late spontaneous fetal death rates for these and other cytogenetic abnormalities. In addition, the relationship of maternal age to fetal death rate for these conditions is also examined.

MATERIALS AND METHODS

In March and April, 1981, letters were sent to individuals at 207 centers in North America listed in two directories as providing prenatal cytogenetic diagnostic services [5, 6]. They were asked to provide information on outcomes of all instances in which a cytogenetic abnormality was diagnosed prenatally but the mother did not elect abortion. If a spontaneous fetal death occurred, centers were requested to indicate if this had occurred prior to or after the cytogenetic diagnosis had been reached. The date of diagnosis, maternal age, reason for study, and the presence of twins were also queried. To diminish the possibility of response bias, the letter indicated that there was as much interest in pregnancies resulting in live births as in spontaneous fetal deaths. (A second part of this survey also asked centers to list the total number of specific cytogenetic abnormalities diagnosed prenatally by the laboratory. The data from this part of the survey were used to analyze the proportions of women with a specific diagnosis who did not elect abortion and will be reported separately.) A second letter was sent in June 1981 to 101 centers from which no reply had been received after 10 weeks. A third letter was sent in September 1981 to 53 centers which had not answered by then. By December 1, 1981, replies had been received from 174 out of the 207 centers to which letters had been sent. Some of the centers not replying apparently did not provide diagnostic cytogenetic services despite their listing in the directories used or else worked collaboratively with other centers that had already replied. All replies received were

reviewed to exclude the possibility of duplicate reporting of cases from the same institution by individuals at different centers within these institutions or at different institutions within the same city.

In the earlier analysis [1], all fetal deaths reported by the centers were grouped together. In the analysis here, I distinguish (1) fetal deaths that occurred after amniocentesis but before the diagnosis had been reached, or just after the diagnosis was reached while the mother was deciding whether to have an induced abortion, from (2) spontaneous fetal deaths that occurred after the mother had decided not to have an elective abortion. These may be denoted roughly as "earlier" and "later" fetal deaths, respectively, although precise information on the specific gestational ages at the time of death are not available.

RESULTS

The data on proportions of fetal deaths among cases reported to this survey are presented in table 1. In the earlier study [1], a mild but unexpected bias was encountered because of selective inclusion of twins among affected fetuses not electively aborted—probably to protect a normal cotwin—and the higher fetal death rate of twins. In the present study, the fetal death rate of affected twins was not markedly different from that for singletons for any condition except 47,XXY. (Two affected cotwins were both stillborn.) With this exception, proportions including or excluding twins were roughly the same. The data on twins appear in table 1, footnote[‖].

In table 2 are presented data on singletons and on all outcomes for those reported both to the earlier survey and the present one. As the earlier study did not subdivide fetal deaths by temporal period, no such division is presented here. Table 3 presents data on maternal ages of those in both surveys for whom such information was reported. Table 4 presents the data on maternal age for 47,+21 and 47,+18 from the second survey subdivided by temporal interval of fetal death. (Data on other outcomes are too sparse for analysis.)

DISCUSSION

The observed spontaneous fetal death rate after amniocentesis for all cases of Down syndrome reported to both surveys of 30.1% (95% confidence interval of 19.9%–42.0%) is practically identical with the difference previously estimated between rates reported at amniocentesis and in live births [1]. This does not imply that spontaneous fetal deaths necessarily account for all of this difference; putative cryptic risk factors as proposed by Polani et al. may also contribute [7]. Moreover, the live-birth rates of Down syndrome used in the comparison may not be entirely appropriate because of the possibility of temporal changes occurring since the time of collection of the data on the live-birth rates used for this comparison [8]. Nevertheless, as discussed below, the observations reported here on spontaneous fetal death may be useful for contemporary estimation of risks of affected live births in the absence of selective abortion.

The observed rate of spontaneous fetal death for 47,+18, 68.0% (with a 95% confidence interval of 46.5%–86.1%) is compatible with an estimate of 75% discrepancy (confidence interval of 40%–90%) between rates in live births and at amniocentesis for this abnormality. Spontaneous fetal death likely accounts for

TABLE 1

FETAL DEATHS AND LIVE BIRTHS BY CYTOGENETIC ABNORMALITY

ABNORMALITY	"EARLIER" FETAL DEATHS		"LATER" FETAL DEATHS		ALL FETAL DEATHS		LIVE BIRTHS		TOTAL
	No.	%	No.	%	No.	%	No.	%	No.
47,+21*	6	11.5%	11	21.2%	17	32.7%	35	67.3%	52
47,+18†	7	33.3%	7	33.3%	14	66.7%	7	33.3%	21
47,+13	1	25.0%	1	25.0%	2	50.0%	2	50.0%	4
Mosaic autosomal trisomies‡	2	33.3%	...	...	2	33.3%	4	67%	6
47,XXX	...	...	...	...	...	...	31	100%	31
47,XXX/46,XX	...	...	...	...	...	...	7	100%	7
45X	9	81.8%	...	...	9	81.8%	2	18.8%	11
46,XX/45,X	1	5.9%	1	5.9%	2	11.8%	15	88.2%	17
Other variants with Turner genotype	...	...	...	...	...	...	4§	100%	4
46,XY/45,X	...	...	2	40.0%	2	40.0%	3	60.0%	5
47,XXY‖	...	...	2	8.0%	2	8.0%	23	92.0%	25
47,XXY/46,XX	...	...	...	...	...	...	2	100%	2
47,XYY#	2	7.4%	...	...	2	7.4%	25	92.6%	27
Triploidy	...	...	...	...	3	100%	...	...	3
Balanced Robertsonian translocations	...	...	...	...	...	...	18	100%	18
Other balanced translocations	...	...	...	...	...	...	21	100%	2
Inversions	...	...	1	5.3%	1	5.3%	18	94.7%	19
Markers, variants, fragments	...	...	...	...	...	...	11	100%	11
Unbalanced structural abnormalities aside from those listed above	1	8.3%	1	8.3%	2	16.7%	10	83.3%	12

* Includes three live births and one early fetal death in individuals from four separate twin pregnancies. Also includes two singleton live-birth translocation cases.

† Includes one live birth and one late fetal death in individuals from two separate twin pregnancies.

‡ Includes four live births in trisomy 21 (two cases), 18, and 22 mosaics, and early fetal deaths in trisomy 8 and 22 mosaics.

§ Genotypes were: 46XXp−, 46X,del(X)q25, 46,XX/46,Xi(Xq), 45,X/46,Xi(Xq).

‖ Includes two late fetal deaths in cotwins from the same pregnancy.

Includes one mosaic that was an early fetal death.

TABLE 2

PROPORTIONS OF FETAL DEATHS AFTER AMNIOCENTESIS IN BOTH SURVEYS

	ALL PREGNANCIES			SINGLETONS ONLY		
	FETAL DEATHS			FETAL DEATHS		
	No.	Proportion	(95% confidence interval)	No.	Proportion	(95% confidence interval)
Trisomies (nonmosaic):						
47,+21	73	30.1%	(19.0%–42.0%)	65	30.8%	(19.9%–43.5%)
47,+18	25	68.0%	(46.5%–85.1%)	22	68.2%	(45.1%–86.1%)
47,+13	7	42.9%	(9.9%–81.6%)	...	...	...
47,XXX	39	0%	(0%–9.0%)	...	...	...
47,XXY	37	8.1%	(0.8%–11.0%)	35	1.3%	(0.3%–7.2%)
47,XYY	33	3.0%	(.08%–15.8%)	32	3.1%	(.08%–16.2%)
45,X	12	75.0%	(42.8%–94.5%)	...	...	...
46,XX/45,X	19	10.5%	(1.3%–33.1%)	...	...	...
Balanced translocations and inversions	71	2.8%	(0.3%–9.8%)	...	...	...
Markers, variants, fragments	27	0%	(0%–12.8%)	...	...	...

most if not all of the difference in 47,+18 rates, but again putative risk factors as discussed above may contribute somewhat.

Although the spontaneous fetal death rate after amniocentesis for 47,+13, 42.9%, has a rather wide 95% confidence interval (9.9%–81.6%), the lower limit is still higher than the upper 95% confidence limit of 9.8% for balanced translocations and inversions and markedly greater than the rate of 3% found in those with normal genotype [4]. These data provide the first statistically significant evidence for an increased late spontaneous fetal death rate associated with this genotype.

TABLE 3

MATERNAL AGE, CHROMOSOME ABNORMALITIES, AND VIABILITY DURING GESTATION

	LIVE BIRTHS			FETAL DEATHS		
		MATERNAL AGE			MATERNAL AGE	
OUTCOME	No.	Mean	SD	No.	Mean	SD
47,+21*	46	39.1	6.2	19	39.5	3.8
47,+18*	8	39.0	4.2	16	37.6	6.5
47,+13*	4	40.0	3.5	3	38.0	2.7
47,XXX	42	37.8	4.1	0	...	...
(Nonmosaic)	(34)	(38.2)	(2.9)	(0)	(...)	(...)
(With XX mosaicism)	(8)	(36.1)	(7.4)	(0)	(...)	(...)
47,XXY	41	36.9	6.3	3	34.0	1.7
(Nonmosaic)	(34)	(36.8)	(6.7)	(3)	(34.0)	(1.7)
(With XY mosaicism)	(7)	(37.7)	(3.6)	(0)	...	...
45,X	17	35.1	5.2	10	34.0	6.6
(Nonmosaic)	(3)	(36.7)	(5.8)	(8)	(32.4)	(5.9)
(With XX mosaicism)	(14)	(34.7)	(5.2)	(2)	(40.5)	(6.4)
Balanced Robertsonian translocation and inversions	40	35.1	5.7	1	33.0	...

* Nonmosaics only.

TABLE 4

MATERNAL AGE, CHROMOSOME ABNORMALITY, AND STAGE OF VIABILITY

	LIVE BIRTHS			EARLIER FETAL DEATHS			LATER FETAL DEATHS		
		MATERNAL AGE			MATERNAL AGE			MATERNAL AGE	
OUTCOME	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD
47,+21	31	39.7	4.6	5	39.2	4.1	8	39.0	3.9
47,+18	7	39.0	4.6	7	37.1	3.7	6	35.8	8.6

NOTE: Data are from second survey only. The first survey did not distinguish "earlier" from "later" fetal deaths.

The data on the genotypes associated with Turner syndrome are particularly striking. It has been known for some time that the 45,X genotype is associated with a very high rate of spontaneous embryonic and fetal death, particularly in the first trimester [9]. These data indicate that the high fetal death rate continues into the second trimester, with spontaneous fetal death after amniocentesis of nine out of 12 nonmosaic cases, all of these occurring before a cytogenetic diagnosis was reached. The contrast to the results on the 46,XX/45,X mosaic cases is striking: only 2/19 = 10.5% of the latter underwent spontaneous fetal death, a highly significant difference ($\chi^2_c = 10.7, P \sim .001$). Also, all four fetuses with structural abnormalities of the X chromosome, including long-arm isochromosomes, have survived, a difference from the result for 45,X nonmosaics that is also statistically significant ($P = .02$, Fisher's exact test, two-tailed). This suggests that some material on the long arm of the X chromosome is particularly responsible for fetal survival.

The data on maternal age (table 3) show no marked difference between Down syndrome fetuses that did or did not survive gestation. Previously, some suggested that the proportion of spontaneous fetal deaths among Down syndrome cases was positively correlated with maternal age [10, 11], whereas others suggested a negative association [12]. There is, however, no evidence for either effect in this study, either among the cases lost earlier or later in gestation (table 4) or in the data from both surveys pooled (table 3). The results are consistent with the interpretation that maternal age has little if any association with Down syndrome survival after the time of amniocentesis in midtrimester. For trisomy 18, there is a lower maternal age among fetal deaths than among those surviving to live birth but the difference is not statistically significant.

Regarding the cases with 45,X or 45,X/46,XX genotype, it is possible that sampling fluctuation is responsible for the reverse trends in maternal age seen in these two conditions. If both groups are pooled, the mean ages are close to each other.

The data provided here are pertinent to genetic counseling for the maternal-age specific risks of Down syndrome and other cytogenetic abnormalities. Because of the widespread adoption of prenatal diagnosis and selective abortion of abnormal

fetuses, accurate contemporary studies of live-birth prevalence in many developed countries for purposes of such counseling are now particularly difficult to obtain [8]. But appropriate adjustment of the observed and regression-derived rates from amniocentesis studies using the results on spontaneous fetal deaths derived here will enable indirect estimates to be made of the rates of affected live births that would have been born to mothers at older ages in such studies if selective abortion had not occurred [8].

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