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The Natural History of Cytogenetically Abnormal Fetuses Detected at Midtrimester Amniocentesis Which Are Not Terminated Electively: New Data and Estimates of the Excess and Relative Risk of Late Fetal Death Associated with 47,+21 and Some Other Abnormal Karyotypes

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Summary

We report the results of an ongoing survey of rates of spontaenous death of fetuses with chromosome abnormalities detected at second-trimester amniocentesis in which the mother did not elect abortion. Estimated excess risks (and conservative 90% confidence intervals) of spontaneous fetal death for various cytogenetic abnormalities are as follows: 47,+21, 25.6% (18.0%–34.0%); 47,+18, 63.8% (49.3%–79.8%); 47,+13, 36.5% (11%–69.7%); 45,X, 65.3% (41.0%–84.2%); and mosaic 45,X/46,XX, 10.8% (1.0%–26.8%). There is little evidence for an excess risk of fetal death, at least following amniocentesis, for 47,XXX, 47,XXY, or 47,XYY. The excess risks of fetal death were adjusted for the likelihood that a fetus of normal karyotype would undergo spontaneous fetal death in a population of older maternal age similar to that in which prenatal cytogenetic diagnosis is undertaken. The absolute fetal death rates when this factor is ignored are about 3.5% higher (i.e., may be derived by adding 3.5% to the values given). The excess risks are those which are most appropriate for use in estimating the contribution of chromosome abnormalities to spontaneous fetal death.

Introduction

Most cytogenetically abnormal fetuses detected at amniocentesis have a higher rate of spontaneous abortion and/or stillbirth than cytogenetically normal fetuses. A previous survey estimated, for instance, the loss for 47,+21, at 30.0% in fetuses after midtrimester amniocentesis (Hook 1983). There are, however, still relatively few published data, and it appears worthwhile for all which are pertinent to appear. We report here the results of a further survey that brings information up to over 100 fetuses with 47,+21 and expands materially the results on other outcomes. We also report for the first time estimates of the excess and relative risks of fetal death in comparison with the background rate in a group with normal karyotypes.

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Material and Methods

We replicated the methods of data acqusition used in a previous study (Hook 1983) which we denote below as the "second survey." (The first survey [Hook 1978] did not query information on stage of fetal life.) Letters were sent on October 24, 1986, to all laboratories known to us in North America which undertook prenatal cytogenetic diagnosis. Laboratories were asked to send information on the outcomes of pregnancies since the time of the previous survey in which a cytogenetic abnormality was diagnosed at amniocentesis but in which the mother did not have elective termination. We asked laboratories to distinguish, if they could, (1) spontaneous fetal deaths that occurred after amniocentesis but before the diagnosis had been reached (or

just afterward, while the mother was deciding whether to have an elective abortion), from (2) spontaneous fetal deaths that occurred after the mother had learned of the abnormal diagnosis but had decided, nevertheless, not to have an elective abortion. We denote these as "early" and "late" fetal deaths, respectively, although precise gestational ages were not available in most cases. To diminish the probability of bias, our letters noted that we were as much interested in pregnancies resulting in live births as in spontaneous fetal deaths.

Our data here also include late responses to the second survey which had been closed out in December, 1981, and which had not been included in the subsequent publication in 1983.

The letter for the third survey differed in one small respect from that used in the second in that we specifically requested information on all abnormalities whether balanced or unbalanced. (Previously, some laboratories in their response had elected only to send results on unbalanced abnormalities.) Thus the results of the third survey include proportionally more data on "balanced" rearrangements and on "normals" (those with variants) than did the earlier surveys.

Results

Table 1 presents the results specifically from the last (third) survey only. Table 2 summarizes the results in all surveys combined. Earlier summaries did not distinguish the markers and fragments from variants, so these are all pooled together in this table. (See below for discussion on this point.)

Most laboratories reporting balanced rearrangements did not indicate whether they were de novo or inherited, so we are unable to distinguish these categories. In the experience of the New York State Chromosome Registry, 18.0%–20.0% of balanced structural rearrangements detected for any reason at midtrimester amniocentesis were de novo (Hook and Cross 1987). If the New York State Chromosome Registry experience

Table 1

Fetal Deaths and Live Births by Cytogenetic Abnormality (latest survey only, raw data)

Abnormality	"Earlier" Fetal Deaths		"Later" Fetal Deaths		All Fetal Deaths		Live Births		Total
	No.	%	No.	%	No.	%	No.	%	No.
47,+21[a]	7	18.9	3	8.1	10	27.0	27	73.0	37
47,+18	7	46.7	3	20.0	10	66.7	5	33.3	15
47,+13	...	...	1	33.3	1	33.3	2	66.7	3
Mosaic autosomal trisomies[b]	1	10.0	...		1	10.0	9	90.0	10
47,XXX	...		...		...		26	100.0	26
Mosaic 46,XX/47,XXX	...		...		...		2	100.0	2
45,X	...		2	50.0	2	50.0	2	50.0	4
Mosaic 45,X/46,XX	...		...		...		9	100.0	9
Other variants with Turner genotype	...		...		...		3	100.0	3
Mosaic 45,X/46,XY	...		2	20.0	2	20.0	8	80.0	10
47,XXY	...		...				30	100.0	30
Mosaic 46,XX/47,XXY	...		...		...		14	100.0	14
47,XYY[c]	...		1	4.0	1	4.0	24	96.0	25
Triploidy	1	100.0	...		1	100.0	...		1
Balanced Robertsonian translocations[d]	...		1	1.5	1	1.5	64	98.5	65
Other balanced translocations	...		4	3.7	4	3.7	104	96.3	108
Inversions	1	1.9	2	3.7	3	5.6	51	94.4	54
Markers	...		...		...		11	100.0	11
Unbalanced/structural	...	...	1	14.3	1	14.3	6	85.7	7
Normal							23	100.0	23

[a] One twin, outcome live birth (the outcome of the cotwin was a live birth; it is not included in the tabulation here).

[b] The abnormal lines in these mosaics were 47,+7 (early death), 47,+20 (five live births), 47,+12 (two live births), 47,+17 (live birth), and +t(13q14q)+t(13q,14q) (live birth).

[c] Includes two mosaic live-birth outcomes.

[d] Includes two twin live births (cotwin outcomes are live births but are not included).

Table 2

Proportions of Fetal Deaths after Amniocentesis (all surveys combined, raw data)

Abnormality	*N*	No. of Fetal Deaths	All Pregnancies Fetal Deaths	
			Proportion (%)	90% Confidence Interval (%)
Trisomies (nonmosaic):				
47,+21	110	32	29.1	22.0–37.0
47,+18	40	27	67.5	53.3–79.8
47,+13	10	4	40.0	15.0–69.7
47,XXX	65	0	.0	0–4.5
47,XXY	67	3	4.5[a]	1.2–11.2
47,XYY	56	2	3.6	.6–10.8
45,X	16	11	68.8	46.0–87.2
Mos 45,X/46,XX	28	4	14.3	5.0–29.8
Balanced translocations and inversions	298	10	3.4	1.2–6.1
Markers, variants, and fragments	38	0	.0	.0–9.3

[a] If twins are excluded, the fetal death proportion is 1/65 = 1.5%, with 95% confidence interval 0%–8.3%.

is representative of those from all over North America responding to the survey, then 20.0% is a plausible estimate of the proportion of de novo events among the 298 balanced rearrangements considered here.

Table 3 presents data on the stage of fetal death.

Table 4 presents data on maternal age of those cases resulting in live births and those cases ending in fetal death.

Table 5 presents data on the relationship of maternal age to the stage of fetal death in those cases on which data on both variables were available.

Table 6 presents data on the sex proportions by spontaneous fetal death.

Table 7 presents data on chromosome abnormalities found in fetuses of mothers age 35 years or older.

Discussion

The data in the above tables give the proportion P of spontaneous deaths among fetuses diagnosed at amniocentesis. Two other variables are also of interest. One is the *excess death rate* or *excess risk* of affected fetuses. This may be defined as $P_e = P - P_c$, where P_c is the rate of spontaneous death among appropriate control or reference fetuses of normal karyotype. The excess fetal death rate associated with a chromosome abnormality is thus the increase in fetal death rate attributable to the presence of a karyotypic abnormality. The other variable of interest is the *relative risk* of fetal death or $r = P/P_c$, i.e., the proportional increase in the fetal death rate because of the presence of a chromosome abnormality.

The question arises as to what to use for a reference or control rate, P_c.

One possible source of control or reference data are those cases with normal or balanced rearrangements reported to the survey. As noted in table 2, there were 298 balanced rearrangements and 38 markers, variants, and fragments, for a total of 336 cases without apparent major unbalanced aneuploidy. (The markers and fragments should have been distinguished from the variants in the earlier studies; the available data no longer allow us to make this distinction. But the fact that the fetal death proportion is 0% in these 19 cases indicates no bias upward because of their inclusion.) The overall proportion of fetal loss in all 336 cases is 3.0%.

This figure is, however, subject to two biases in opposite directions. The first results from the inclusion of our estimated 20% de novo rearrangements among the balanced abnormalities. There is known to be a significant increase in morbidity in live births with de novo non-Robertsonian balanced rearrangements. For related reasons the proportion with spontaneous fetal death might also be increased relative to the proportion of those with normal karyotypes. The inclusion of de novo balanced rearrangements could thus tend to result in falsely high spontaneous fetal death rates in this putative reference control group.

Table 3

Stage of Fetal Death by Cytogenetic Abnormality Reported in Later Surveys

Abnormality	"Earlier" Fetal Deaths		"Later" Fetal Deaths		All Fetal Deaths (including unstated stage)		Live Births		Total
	No.	Proportion	No.	Proportion	No.	Proportion	No.	Proportion	No.
47,+21[a]	13	14.6	14	15.7	27	30.3	62	69.7	89
47,+18[b]	14	38.9	10	27.8	24	66.7	12	33.3	36
47,+13	1	14.3	2	28.6	3	42.9	4	57.1	7
Mosaic[c] autosomal trisomies	3	18.8	...		3	18.8	13	81.2	16
47,XXX	...		...		...		57	100.0	57
Mosaic 46,XX/47,XXX	...		...		...		9	100.0	9
45,X	9	60.0	2	13.3	11	73.3	4	26.7	15
Mosaic 45,X/46,XX	1	3.8	1	3.8	2	7.6	24	92.4	26
Other variants with Turner genotype	...		...		...		7[d]	100.0	7
Mosaic 45,X/46,XY	...		4	26.7	4	26.7	11	73.3	15
47,XXY[e]	...		2	3.6	2	3.6	53	96.4	55
Mosaic 46,XX/47,XXY	...		...		...		9	100.0	9
47,XYY[f]	2	3.9	1	1.9	3	5.8	49	94.2	52
Polyploidy[g]	1	20.0			4[h]	100.0	...		4
Balanced Robertsonian translocations	...		1	1.2	1	1.2	82	98.8	83
Other balanced translocations	...		4	3.1	4	3.1	125	96.9	129
Inversions	1	1.4	3	4.1	4	5.5	69	94.5	73
Markers (e.s.a.c.)	...		...		...		22	100.0	22
Unbalanced/structural	1	5.3	2	10.5	3	15.8	16	84.2	19
Normal	...		...		...		23	100.0	23

Note.—The total here is restricted to the results of the second survey (Hook 1983) and the new data. The first survey did not query stage. Note that for the polyploidy three cases were of unstated stage.

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

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

[c] Includes 13 live births in mosaics with 47,+21 (two cases), 47,+18, 47,+22, 22 mosaics, 47,+20 (five cases), 47,+12 (two cases), 47,+17, and t(13q14q)+t(13q14q) and early fetal deaths in 47,+7, 47,+8, and 47,+22 mosaics.

[d] Genotypes were 46,XXp−, 46,X,del(X)q25, 46,XX/46,Xi(Xq), and 45,X/46,Xi(Xq).

[e] Includes two late fetal deaths in cotwins from the same pregnancy.

[f] Includes one mosaic that was an early fetal death and two live births.

[g] Includes two twin live births (cotwin outcomes are live births but are not included).

The bias in the other direction results from the fact that (*a*) at amniocentesis, balanced rearrangements are detected in fetuses of mothers whose average age is lower than that in mothers of fetuses with numerical abnormalities and (*b*) maternal age is known to be associated with a higher probability of spontaneous death of fetuses, even in those with normal karyotypes; for instance, in the U.S. collaborative follow-up survey of amniocentesis, among fetuses with normal karyotype the fetal death rate was 14/480 = 2.9% in those with mothers under age 35 years and was 22/541 = 4.1% in those with mothers 35 years or older (Lowe et al. 1978; D. Bryla, personal communciation). Thus, because of age differences in a comparison with mothers of fetuses with numerical abnormalities, this factor would tend to produce an inappropriately low reference control rate.

If we were to restrict our analysis to those cases with maternal age known to be 35 years or older (e.g., see table 7), we would tend to eliminate this latter bias, but the bias from de novo rearrangements would still be present and probably would be stronger, because the ratio of de novo to inherited balanced structural rearrangements is higher among fetuses of mothers age 35 years or older having amniocentesis than it is in younger mothers having the procedure. (The latter trend

Table 4

Maternal Age, Chromosome Abnormalities, and Viability During Gestation (data of all surveys combined)

Outcome	Live Births			Fetal Deaths		
		Maternal Age			Maternal Age	
	N	Mean	SD	*N*	Mean	SD
47,+21[a]	70	39.0	5.9	29	38.7	3.3
47,+18	13	36.8	5.1	26	38.1	5.4
47,+13	6	36.2	6.9	4	39.0	14.8
47,XXX:	70	37.6	4.4	0		
Nonmosaic	60	37.8	3.9	0		
With XX mosaicism	10	36.7	9.1	0		
47,XXY:	78	36.9	5.6	3	34.0	1.7
Nonmosaic	64	37.0	5.9	3	34.0	1.7
With XY mosaicism	14	36.6	3.5	0		
45,X:	36	35.5	4.5	14	34.6	5.6
Nonmosaic	5	33.8	5.8	12	33.7	5.1
With XX mosaicism	31	35.7	4.1	2	40.5	.7
Balanced translocations and inversions	264	34.1	5.3	9	36.2	2.4

Note.—Maternal age was not reported in all instances.
[a] Nonmosaics only.

results from an ascertainment bias, not from a higher mutation rate in older mothers [Hook and Cross 1987].) Thus the use of the reference data from table 7 is likely to result in a falsely high control rate and in falsely low excess and relative risks.

In this regard it is of interest that in all four candidate control categories listed in table 7 the proportion of fetal death is 7/164 = 4.3% (90% interval = 2.0%–7.9%). Among the subgroups with balanced Robertsonian translocations or of normal karyotype, the proportion with fetal death is lower, 1/67 = 1.8% (90% confidence interval 0.1%–6.9%), whereas in the other two subgroups (inversions and "other" balanced rearrangements) the proportion with fetal death is higher, 6/107 = 5.6% (90% confidence interval 2.5%–10.8%). The latter are those balanced rearrangements in which de novo events may be expected to contribute to an increased likelihood of fetal death, so the trends are at least consistent with the direction of the presumed bias. In any event, on the basis of the results in the entire group, 4.3% would appear a plausible *maximum* upper limit of an appropriate reference rate.

Another possible reference source for control data is in the U.S. collaborative study (Lowe et al. 1978) cited above, in which the proportion of fetal deaths among fetuses with normal karyotype was 22/541 = 4.1% in all those fetuses of mothers age 35 years or older.

Table 5

Maternal Age, Chromosome Abnormality, and Stage of Viability

Outcome	Earlier Fetal Deaths			Later Fetal Deaths			Live Births		
		Maternal Age			Maternal Age			Maternal Age	
	N	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
47,+21	12	37.7	3.1	11	38.8	5.0	55	39.3	5.3
47,+18	14	37.8	2.9	9	37.2	8.2	12	36.7	5.3

This reference group of course came from a selected group of laboratories early in the use of amniocentesis before the widespread use of ultrasound. Some diagnoses were done on nonviable fetuses, and some spontaneous fetal deaths almost certainly resulted from use of methods that have since been generally abandoned, in part because of the results of this study itself. If we eliminate fetuses that almost certainly would be judged today as nonviable at the time of amniocentesis–about 4–6 in those mothers age 35 years or older and in 1 in those under age 35 years, (a judgment made by E.B.H. from review of details in the appendixes of Lowe et al. [1978])—then the proportion of spontaneous fetal death in those of normal karyotype is about 2.9%–3.3% among those of mothers age 35 years or older.

Thus a plausible reference control rate of spontaneous fetal death for the karyotypic abnormalities in our own series is about 3.0%–4.0%.

We estimate excess and relative risks by using the mid-

Table 6

Sex Proportions and Spontaneous Fetal Death

Outcome	Proportion (%) Spontaneous Fetal Death
47,+21:	
XY	12/36 (33.3)
XX	9/31 (29.0)
47,+18:	
XY	9/11 (81.8)
XX	7/12 (58.3)
47,+13:	
XY	1/4 (25.0)
XX	1/3 (33.3)

Note.—Only those cases in which sex was specified and for which data are still available are included.

Table 7

Results of Survey 3 in Mothers Known to Be Age 35 Years or Older

Abnormality	Fetal Death		Live Birth		Total		Fetal Death Proportion
	N	Maternal Age (mean ± SD)	N	Maternal Age (mean ± SD)	N	Maternal Age (mean ± SD)	
47,+21	10	37.2 ± 1.8	23	40.6 ± 2.5	33	39.5 ± 2.8	.303
47,+18	10	39.0 ± 3.0	3	38.0 ± 1.7	13	38.8 ± 2.7	.769
Other inversions	3	37.7 ± 3.1	40	37.4 ± 1.9	43	37.5 ± 2.0	.070
Other balanced rearrangements	3	36.0 ± 1.0	61	36.7 ± 1.8	64	36.7 ± 1.8	.047
Balanced Robertsonian translocations	1	38.0	37	37.2 ± 2.3	38	37.3 ± 2.3	.026
Normals	0	...	19	37.4 ± 1.7	19	37.4 ± 1.7	0

point of this range, 3.5%. In estimation of confidence intervals about these excess and relative risks, we calculated the lower 90% confidence limit by assuming that the lower risk estimate was correct (i.e., that the rate of fetal deaths in controls was 4.0%), and we calculated the upper 90% confidence limit by assuming that the higher estimated risk was correct (i.e., that the rate of fetal deaths in controls was 3.0%). The derived values are thus plausible upper and lower *limits* on the true 90.0% confidence intervals of the excess and relative risks, which lie within the calculated intervals. Thus they provide a conservatively wide estimate of the true 90.0% confidence intervals. These results appear in table 8.

As may be noted, the *excess* risk for a 47,+21 fetus over and above that for a fetus of normal karyotype is estimated at about 25.6%, and the true value lies within a range of 18.0%–34.0% with *at least* 90.0% "confidence." Another way of expressing the latter condition is that the probability is *less* than .05 that the true value is greater than 34.0% and *also* is less than .05 that the true value is less than 18.0%. There is no strong evidence of an excess risk for 47,XXX or 47,XYY in these data; the results for 47,XXY which are nonsignificant in any event may be biased by the chance occurrence of twins with fetal death among them.

The excess risks are, in most instances, the more ap-

Table 8

Excess and Relative Risks of Spontaneous Fetal Deaths Following Amniocentesis

	Excess Risk			Relative Risk		
	Estimate (%)	Limits on 90% Confidence Interval (%)		Estimate (%)	Limits on 90% Confidence Interval (%)	
		Lower	Upper		Lower	Upper
47,+21	25.6	18.0	34.0	8.3	5.5	12.3
47,+18	64.0	49.3	79.8	19.3	13.3	26.6
47,+13	36.5	11.0	69.7	11.4	3.8	23.2
47,XXX	−3.5	−4.0	1.5	0	0	1.5
47,XXY	1.0	−2.8	8.2	1.3	.3	3.7
47,XYY	.1	−3.4	7.8	1.0	.15	3.6
45,X	65.3	41.0	84.2	19.6	11.3	29.1
mos 45,X/46,XX	10.8	1.0	26.8	4.1	1.3	9.9

Note.—See text for derivation. The lower estimate in the ranges assume a true reference value of 4.0% spontaneous fetal death in an appropriate comparison group; the upper value of the ranges assumes a true reference value of 3.0%. Note that for 47,XXX the lower limits are really the null result, so the upper limit is best interpreted as a boundary on the one-tailed upper 95% confidence limit.

propriate proportions to use than are the absolute fetal death rate, in estimating the contribution of chromosome abnormalities to spontaneous fetal death.

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