Am. J. Hum. Genet. 57:875–881, 1995

The Natural History of Down Syndrome Conceptuses Diagnosed Prenatally That Are Not Electively Terminated

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Summary

The pregnancy outcomes on cases of Down syndrome diagnosed prenatally in which the mother did not elect termination were evaluated in data reported to a comprehensive Register of Down syndrome for England and Wales for 1989–94. In the 168 cases in which placental biopsy was not used, the overall rate of spontaneous loss was 35%, but this figure masks considerable heterogeneity by gestational stage at ascertainment. Data on ages at diagnostic procedure and on pregnancy termination enabled a more precise survival analysis. The loss rates were ~50% for those fetuses ascertained at 15–17 completed wk, 43% at 18 wk, 31% at 19 wk, 25% at 20 wk, and then a leveling off at ~20%–25% for fetuses ascertained at 21–28 completed wk. For fetuses ascertained prior to 18 wk, there was no evidence that maternal age was associated with fetal loss, consistent with earlier reports. At 18 wk and after, however, maternal age was on the average ~3 years greater in fetuses that were lost. Comparison of successive gestational birth cohorts provided no evidence in these 168 cases that the diagnostic procedure itself had any effect on loss or that selective ascertainment of mothers in risk of loss had any effect on the results. In contrast, in the 21 cases in which placental biopsy had been undertaken, the overall loss rates were not only higher when appropriate comparisons could be made, but there was some evidence for selective ascertainment and/or procedure-associated losses. The total data here are >1.5-fold the previous number of cases in which the natural history of Down syndrome fetuses has been evaluated directly.

Received March 6, 1995; accepted for publication June 23, 1995.

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0002-9297/95/5704-0019$02.00

Introduction

It has been recognized for >15 years that fetuses with Down syndrome karyotypes diagnosed prenatally at amniocentesis whose mothers do not elect termination have a significantly elevated spontaneous fetal death rate compared to the loss rate in the vastly greater number of those with normal karyotypes (Hook 1978). The most recent synthesis of available data estimated a rate of loss of ~30% among 110 cases ascertained through an international survey (Hook et al. 1989). One unexpected observation in the latter analysis was the lack of any association of maternal age with fetal loss. We present here an analysis of data ascertained recently in a nationwide study in England and Wales (Mutton et al. 1991), which includes >1.5-fold the number of previously ascertained cases in the international series. The trends in this extensive study in a single jurisdiction are somewhat different from those collected previously.

Methods

The methods of data collection and processing have been reported elsewhere (Mutton et al. 1991, 1993). Some details also appear in Morris et al. (1994). The present analysis includes all cases in a register of chromosome abnormalities associated with Down syndrome in England and Wales on which information was reported and processed from the inception of the Register in January 1989–December 31, 1994. The earliest dates of conception of cases included were in late 1988. Excluding those *first ascertained* as spontaneous miscarriages or stillbirths, 6,505 cases were reported. Of these, 6,160 had a nonmosaic +21 karyotype (2,485 diagnosed cytogenetically prenatally and 3,675 first diagnosed at birth or later); 79 had a 46/47,+21 pattern reported (33 diagnosed prenatally and 46 postnatally); 233 had a predisposing Robertsonian translocation or analogous isochromosome (48 diagnosed prenatally and 185 postnatally); 20 had another predisposing unbalanced rearranged chromosome (14 diagnosed prenatally and 6 diagnosed postnatally); and 13 had double aneuploidy, involving the 21 chromosome (of which 7 were diagnosed prenatally and 6 were diagnosed postnatally).

We included in the initial analysis the 193 cases in which a prenatal diagnosis of a karyotype associated with Down syndrome had been made but in which a voluntary termination of the pregnancy had not occurred and in which the outcome of pregnancy was known. We exclude from our main analysis the 21 of these 193 cases in which diagnosis had been made upon placental biopsy and chorionic villus study (CVS) but consider these separately. We also exclude four cases with mosaicism (3 cases) or double aneuploidy (1 case), leaving 168 total.

Because we had in most cases data not only on the reported gestational age at tissue sampling for diagnosis but also on the reported gestational age at the end of the pregnancy, we could also undertake a more refined survival analysis. For any achieved gestational age, we could calculate the number of conceptuses that had been ascertained by that age but that had not yet been reported to terminate. In such analysis, for any gestational age, say x completed wk (i.e., $7 \times$ d), we considered the fate of all fetuses ascertained prior to and not known to have been lost prior to $7 \times$ d. This considerably increased the data pertaining to cases at any gestational age. (Data were not available on age in gestational days.)

The survival analysis also allowed us, where there were sufficient data, to investigate the possibility of selective ascertainment of pregnancies at high risk to be lost at least shortly after the procedure. We did this by comparing the results of what we term "lagging" survival analyses of the same gestational week. For instance, in analysis of the fate of conceptuses from 20 completed wk onward, we considered first all those ascertained by at least 19 wk not known to have been lost by age 20 wk (a "lag" of <1 week), then all those ascertained by at least 18 wk not known to have been lost by age 20 wk (a "lag" of 1 to <2 wk), etc., up to a lag of 3 to <4 wk. Thus, for conceptuses reaching exactly 20 completed wk of gestation, we could determine whether there was any difference in survival and whether they had been ascertained as early as 16 wk or as late as 19 wk. The longer the lag, the fewer the number of cases for analysis but the less likely the observations are to be influenced by selective inclusion of high risk pregnancies, because such pregnancies are likely to have already been lost in the "lagged" period. (Lower rates of loss at the end of the longest lagged interval compared to shorter intervals might also reflect the selective effect of the diagnostic procedure upon spontaneous loss of affected conceptuses in the interim.)

All confidence intervals on proportions with denominators <100 were exact limits given in Documenta Geigy tables (Diem 1966), which are derived from the binomial distribution. Otherwise, the limits were extrapolated from the exact limits in this reference.

Results

Pertinent data were available on 110 live births and 58 fetal deaths among the nonmosaic 47 or translocation trisomies for our primary analysis. The distribution of these cases by grouped intervals of gestational age at ascertainment and the observed maternal ages appear in table 1. Data by single week of gestational interval appear in the appendix. Overall, the rate of loss is ~35%, not too different from the rate of 30% reported in an earlier study of a different group (Hook et al. 1989). But the summary figure of our study masks the considerable heterogeneity in rate of loss by gestational week of diagnosis as illustrated in table 1. As may be noted, the proportion of conceptuses that do not survive declines dramatically with gestational age. Precise trends by 1 wk may be noted in the appendix. The χ^2 test for trend (Armitage 1973) indicates that the overall drop in fetal death proportion with advancing gestational age is highly significant. (If one pools the data by gestational week in the appendix into 10 groups such that the minimum expected number in each cell is no less than 4.0, then the χ^2 for trend is 37.0 with 8 df; $P < .001$.) Differences between adjacent weeks are not significant, despite this, because of relatively small numbers.

The most extensive evidence is on those ascertained between 12 and 23 wk of gestation. In the first half of this range, 12–17 wk, the proportion of fetuses lost is ~50%, and there is suggestive evidence that this loss proportion is even higher in the first 2 wk of this interval. There is little difference in maternal ages between the live births and fetal deaths ascertained in 12–17 wk. In the second half of the range, 18–23 wk, the proportion lost drops to ~35%, closer to but still higher than the ~30% loss rate of the earlier series. (For this difference in this series between the two intervals [12–17 wk: 34/59 = .52 loss proportion versus 18–23 wk: 15/42 = .36 loss proportion] $P < .10$; $\chi^2 = 2.8$ with 1 df.) The maternal age difference between the live births and fetal deaths in the 18–23-wk interval is not nominally significant ($.15 < P < .2$), nor is it for the group >27 wk ($.05 < P < .10$), but for the entire group it is highly significant ($P < .001$), all by t-test.

The results of the survival analysis, which markedly increases the numbers for analysis at any gestational stage, appear in table 2. These are consistent with the trends exhibited in the cruder analysis, which indicated a marked drop in spontaneous proportion lost as gestational age increases and a change in the maternal age association at 18–19 wk. The survival analysis in table 2 tends to smooth trends because there is an overlap between adjacent intervals of analysis. This explains why the trends to, say, diminished fetal death proportion or diminished maternal age in live births with advancing gestational age are more notable in table 2 than in the appendix, in which data in disjointed intervals appear.

Table 1

Number and Maternal Age (Mean and SD) of Nonmosaic Cases, by Gestational-Age Interval at Time of Diagnostic Procedure

Gestational Age Interval (wk)	Fetal Deaths			Live Births			Proportion of Fetal Deaths (%)	95% Confidence Interval	
		Maternal Age (years)			Maternal Age (years)				
	No.	Mean	SD	No.	Mean	SD		Lower	Upper
<14	4	39.25	4.50	0	...	...	4/4 (1.00)	.4	1.00
14–17	30	37.87	3.99	31	38.10	6.02	30/61 (.49)	.36	.62
16–23	37[a]	37.30	5.40	54	36.07	6.42	37/91 (.41)	.30	.51
18–23	15[a]	36.21	6.77	27	34.07	6.46	15/42 (.36)	.22	.52
24–27	1	40.00	...	5	28.60	8.96	1/6 (.17)	.004	.64
>27	7	31.86	7.17	38	29.55	7.08	7/45 (.16)	.06	.29
Unknown	1	45.00	...	9	34.11	5.44	1/10 (.10)	.003	.45
Overall	58[a]	36.98	5.57	110	33.40	7.40	58/168 (.35)	.28	.42

NOTE.—Includes three "translocation" cases: two fetal deaths, one t(14;21) diagnosed at 18 wk, maternal age 27 years; one i(21q) at 15 wk, maternal age 40 years; and one livebirth at t(14;21) diagnosed at 34 wk, maternal age 27 years. There were also three mosaic cases and one case with an extra structurally abnormal chromosome (esac), not included in this tabulation. One mosaic case, a fetal death, was diagnosed at 26 gestational wk to a mother aged 26 years; one live-birth mosaic was diagnosed at 13 gestational wk to a mother aged 41 years; and the other live-birth mosaic at 19 wk to a mother aged 28 years. The case with the esac was a live birth diagnosed at 16 wk to a 49-year-old mother.

[a] Includes one case of unknown maternal age diagnosed at 20 wk (note that intervals overlap).

Table 2

Survival Analysis

For Fetuses Ascertained No Later Than 6 d Plus	Outcomes in Those Not Known Lost Before 0 d Plus	Fetal Deaths			Live Births			Fetal Deaths Proportion (%)	95% Confidence Limits	
			Maternal Age (years)			Maternal Age (years)				
		No.	Mean	SD	No.	Mean	SD		Lower	Upper
14 wk	15 wk	2	39.00	1.41	2	43.00	5.66	2/4 (50)	.07	.93
15 wk	16 wk	6	37.17	2.23	4	38.25	8.30	6/10 (60)	.26	.88
16 wk	17 wk	18	37.72	4.66	18	38.00	4.73	18/36 (50)	.33	.67
17 wk	18 wk	23	37.65	4.44	31	38.10	6.02	23/54 (43)	.29	.57
18 wk	19 wk	18	39.94	3.28	41	37.15	6.24	18/59 (31)	.19	.44
19 wk	20 wk	16	39.94	4.17	48	36.88	6.11	16/64 (25)	.15	.37
20 wk	21 wk	14	39.21	4.84	52	36.63	5.97	14/66 (21)	.12	.32
21 wk	22 wk	18	38.28	5.67	54	36.39	6.01	18/72 (25)	.16	.37
22 wk	23 wk	18	38.28	5.67	56	36.61	6.01	18/74 (24)	.15	.36
23 wk	24 wk	20	37.85	5.53	58	36.22	6.50	20/78 (26)	.16	.37
24 wk	25 wk	18	38.44	5.54	62	35.65	7.01	18/80 (23)	.14	.33
25 wk	26 wk	16	38.06	5.78	62	35.65	7.01	16/78 (21)	.12	.30
26 wk	27 wk	16	38.06	5.78	63	35.62	6.95	16/79 (20)	.12	.31
27 wk	28 wk	14	39.00	4.72	63	35.62	6.95	14/77 (18)	.10	.29

In the analysis of the lagged survival analyses, where sufficient data were available there was no evidence for earlier loss in those more recently ascertained. Thus, for those reaching 20 completed wk, the rates of loss were 16/64 (25%) in the lag of <1 wk, 13/54 (24%), in the lag from 1 to <2 wk, 11/42 (26%) in the lag of 2 to <3 wk, and 6/24 (25%) in the 3- to <4-wk lag. For 19 wk, the results for the same lag intervals were, respectively, 18/59 (31%), 15/46 (33%), 10/28 (36%), and 3/7 (43%). (The nonsignificant trend here is actually contrary to the hypothesized effect.) For 18 wk, the results were respectively, 23/54 (43%), 16/34 (47%), 4/8 (50%), and 0/2 (0%). The maternal age trends at any gestational age were unaffected by the length of the lag in the analysis.

Table 3

Results of (Nonmosaic) Cases Diagnosed on Placental Biopsy Specimens

Gestational Interval at Diagnosis (wk)	Fetal Deaths			Live Births		
	No.	Mean	SD	No.	Mean	SD
<14	6	36.83	4.26	2	32.00	12.73
17–23	3	34.33	4.04	2	25.50	4.95
≥28	3	31.00	9.17	4	32.25	12.15
Unknown	1	47.00	...	...	...	...
Total	13	34.75	5.75	8	30.50	9.97

There were only three mosaic trisomy 21 cases in this series, two live births and one fetal death. The details of these cases, which are excluded from the main analysis in table 1, because they would be expected to have less lethality, appear in the footnotes, as do those on one case with double aneuploidy, also excluded.

In addition to these 168 cases reported from nonplacental biopsies, there were 21 cases reported on diagnoses made on placental biopsies (CVS). While this procedure was introduced originally for early cytogenetic diagnosis, in fact in these 21 cases the procedure of placental biopsy was reported on five midtrimester diagnoses and seven third-trimester diagnoses, in addition to one case of unreported gestational age, and eight cases at 13 completed wk or younger. The results in these 21 cases appear in table 3. The fetal death proportion is greater at midtrimester and in the third trimester in this group than in those studied at amniocentesis. There is greater mean maternal age in all three gestational intervals among the fetal deaths.

Discussion

Several aspects of the results of this study are unexpected. The first is the overall observed rate of loss. The estimates of the earlier international surveys assumed unbiased reporting by the participating laboratories. Although steps were taken in the requests for data to diminish such bias, one can not exclude the possibility that spontaneous fetal loss, especially in instances shortly after the invasive procedure, may have come to the attention of the laboratory preferentially. This would result in a falsely high estimate of the loss rate in these earlier studies. The present study considers data in a register that attempted to ascertain all cases of Down syndrome, however and wherever diagnosed at any stage of life within a particular jurisdiction. Ascertainment of live births has been estimated to have been almost complete in the entire study. If anything, affected spontaneous fetal deaths were underascertained, compared to live births. The difference might well be expected to lead to an underestimate of fetal loss. Thus, if the expected biases were present, one would predict the observed proportion of fetal loss to be lower in this study than the previous one (Hook et al. 1989). Unexpectedly, if anything it is somewhat higher. Nevertheless, it is still possible there was a bias to selective reporting of fetal death in those declining termination.

Second, in the previous study there was no evidence for a maternal age difference between live births or fetal deaths. This was despite the expectation that maternal age should be associated with such loss. In the present study, maternal age is found to be of significance but unexpectedly in somewhat different directions at different gestational stages. There is a weak trend to lower maternal age among live births <18 wk and a stronger effect in the other direction at ≥18 wk. The earlier study, using a cruder gestational age interval because of the limitations of available data, nevertheless found no maternal age difference in fetuses ascertained through amniocentesis whether "earlier" or "later" in gestation (Hook et al. 1989).

Third, since the collection of the data of the international series, there have been marked changes in the evaluation and management of pregnancies, in particular the greater routine use of diagnostic ultrasound in midtrimester. This factor might result not only in greater prenatal ascertainment of affected pregnancies (as would, of course, the increasing use of biochemical screening) but selectively pregnancies at higher risk to be spontaneously lost. Such pregnancies one would expect to be lost relatively shortly after ascertainment. Yet, contrary to the latter expectation, the lagged survival analysis provides no evidence for such an effect. In this series, for instance, an affected fetus who reaches 20 wk of gestation is as likely to be lost subsequently, whether it was ascertained at 16 wk or 19 completed wk, and analysis at other stages are consistent with this.

One incidental consequence of the lagged analysis as well is that there is no evidence for any markedly increased spontaneous mortality of Down syndrome fetuses as a consequence of the diagnostic procedure, at least from an average of 1–4 wk after the procedure,

when one would expect to observe excess mortality and morbidity if such was associated with the procedure. Estimates of the associated loss rate as a consequence of amniocentesis have varied from ~1/100–1/400. Certainly one would not expect to observe such an increase in the relatively small numbers analyzed here. But the earlier risk estimates of the consequences of amniocentesis were only pertinent to those of normal karyotype, and prior to this study there was no evidence to our knowledge pertinent to cytogenetically abnormal fetuses. The results here suggest no major effect, at least of amniocentesis, on the spontaneous mortality of Down syndrome fetuses from an average of 1–4 wk after the procedure.

Finally, there appear to be somewhat different trends with regard to loss after the procedure in those in whom placental biopsies were carried out (CVS). The data here are sparse, with only 21 such cases, so inferences here must be guarded. Of the eight cases ascertained at <14 wk, six died spontaneously. Four of the six losses were within <2 wk of the diagnostic procedure, suggesting these women were either at particularly high risk of loss and/or the procedure itself may have had some effect. This group appears less likely than those ascertained at midtrimester amniocentesis to provide representative data on the natural history of fetuses with the Down syndrome karyotype.

In those ascertained at the second trimester or later, placental biopsy is sometimes used in preference to amniocentesis, at least in part to enable a quick diagnosis. Again, after adjustment for gestational age of ascertainment women in this study undergoing placental biopsy had a higher rate of spontaneous loss than those undergoing other procedures. The differences however, are not significant, because of the small numbers. In those ascertained at ≥28 wk who had placental biopsy, 43% (3/7) resulted in spontaneous fetal death compared with an expected rate of ≤20% from the survival analysis of results in the main group. While the details of case management were not reported to the Register, we believe the perceived need for placental biopsy, especially after 28 wk, has occurred in cases in which fetal life appears in jeopardy and a Cesarean section is being considered. Clinicians might well be reluctant to undertake such a procedure if the fetus has a cytogenetic abnormality and would seek a quick fetal diagnosis such as that available from a direct preparation of a chorion tissue. This bias of ascertainment, we suspect, has contributed to the higher fetal death proportion in this small group of cases.

One striking observation in the present series is how much difference gestational age at ascertainment makes to the results, at least before 20 wk. Between 18–19 achieved wk in the survival analysis, for instance, the observed proportion lost drops from 43% to 31%. Yet, from 21–27 wk there appears to be little change, and the proportion lost is ~20%–25%. It is also noteworthy that at the 18–19-wk junction, at which there is such a large change in the loss proportion, the live birth–fetal death–maternal age difference changes direction. The data suggest that the maternal-fetal unit involving a Down syndrome conceptus is undergoing some abrupt transitional change at this interval.

These data are, of course, pertinent only to the loss proportion of Down syndrome conceptuses. Without similar data from the same jurisdiction on fetuses of normal karyotype (or all karyotypes), we cannot estimate the *excess* loss of the Down syndrome conceptuses, a variable of independent interest. Among older mothers, the background rate of loss in those with normal karyotype has been estimated as ~3.5% (Hook et al. 1989), which, if correct, should be subtracted from the estimated loss proportion for Down syndrome to calculate this excess. But this background value will vary with age of the mother and with the precise gestational age of the conceptus of normal karyotype, even among those diagnosed from 16–22 wk. Nevertheless, it appears likely that the excess loss is ≤4% lower than the observed loss proportions estimated here at each gestational interval.

The excess proportion, lost at least in those of maternal age 35–40 years, may be crudely independently estimated by comparing the reported maternal specific prevalence rates of Down syndrome diagnosed at amniocentesis and at live birth (reference data are summarized in Hook 1992; see also Hecht and Hook 1994). after adjustment for the mean average difference of ~0.4 years in exact maternal ages of those of the same truncated age. (Mothers of truncated age 35 years, say, at amniocentesis are on the average ~0.4 years older in exact age at the time of expected live birth than are the mothers of live births with truncated age 35 years, a difference requiring adjustment before any comparison of the rates at the two stages.) Such an analysis predicts a likely excess loss proportion of ~20%–25%, almost certainly lower than that implied by the observations in this data set, even in the absence of extensive reference data on the loss rate in those of normal karyotype. (Halliday et al. [1995] estimate, in a similar indirect analysis of data from a small series, an 18% loss after amniocentesis, 13% before 20 wk and 5% thereafter.) Several explanations are possible for the apparent discrepancy. First, the data here suggest that there is a very dramatic change in the loss proportion of Down syndrome with gestational age, even within the relatively narrow 16–20-wk or 16–22-wk interval in which amniocentesis is carried out. The earlier summary data on maternal age–specific prevalence rates at amniocentesis may have included disproportionately more women ascertained later in midtrimester

so that observed loss proportion at 20 wk in the study reported here may be more appropriate to the comparison of prevalence rates at amniocentesis and live birth than are the higher loss rates in those ascertained earlier. Second, factors such as maternal cigarette smoking may have significant differential impact on loss of midtrimester Down syndrome fetuses compared to normal fetuses, and levels of such exposure may have been quite different in the population studied here than in those summarized in the earlier amniocentesis and live-birth data. (For references and discussion on this point, see also Hecht and Hook 1994.) Finally, of course, statistical fluctuation alone may contribute to the apparent difference.

Appendix

Table 1A

Numbers and Maternal Ages (Mean and SD) by Gestational Age at Time of Initial Sampling Procedure of Prenatally Diagnosed Cases without Elective Termination

Completed Weeks of Gestation at Ascertainment	Fetal Death			Live Births		
	No.	Mean	SD	No.	Mean	SD
<10	0	...	...	0	...	...
10	0	...	...	0	...	...
11	0	...	...	0	...	...
12	3	38.00	4.58	0	...	...
13	1	43.00	...	0	...	...
14	2	39.00	1.41	2	43.00	5.66
15	5	37.00	2.45	2	33.50	9.19
16	15	37.93	5.04	14	37.93	3.65
17	8	38.00	3.25	13	38.23	7.68
18	4	39.50	8.96	10	34.20	6.27
19	3	36.33	6.43	7	35.29	5.44
20[a]	3	33.50	3.54	4	33.75	3.10
21	4	35.00	7.87	2	30.00	2.83
22	0	...	...	2	42.50	2.12
23	1	33.00	...	2	25.50	13.44
24	0	...	...	4	27.25	9.74
25	0	...	...	0	...	...
26	1	40.00	...	1	34.00	...
27	0	...	...	0	...	...
28	0	...	...	2	33.50	2.12
29	0	...	...	2	34.50	4.95
30	0	...	...	3	32.67	6.11
31	2	34.50	4.95	3	25.67	6.43
32	3	29.33	10.97	5	27.20	6.65
33	1	31.00	...	3	32.00	4.58
34	1	35.00	...	7	31.14	9.81
35	0	...	...	8	28.38	8.78
36	0	...	...	1	22.00	...
37	0	...	...	2	29.00	5.66
38	0	...	...	2	27.50	2.12
39	0	...	...	0	...	...
40	0	...	...	0	...	...
41	0	...	...	0	...	...
42	0	...	...	0	...	...
>42	0	...	...	0	...	...
Subtotal	57	36.81	5.47	101	33.45	7.52
Unknown	1	45.00	...	9	34.11	5.44
Total	58	36.98	5.57	110	33.4	7.40

Note.—Nonmosaic cases not ascertained through placental biopsy.

[a] One fetal death of unknown maternal age ascertained at 20 wk.

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