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Paternal Age and Down Syndrome

J. DAVID ERICKSON[1]

SUMMARY

The frequency of Down syndrome (DS) in infants of older fathers has been examined in two sets of data. The effect of maternal age was controlled by single years of age. Lack of tight control has been an important weakness of other studies on this subject. Data obtained in metropolitan Atlanta by an intensive case-ascertainment program showed no overall excess of DS infants born to older fathers. Nor was there evidence of such an effect in recent birth certificate data made available by the National Center for Health Statistics. The Atlanta data suggest an increased number of DS infants born to older fathers who had children by women $\leq$ 34 years. However, there was a small deficiency of DS infants born to older fathers by women $\geq$ 35 years. The possibility of a paternal-age effect remains open, but the available data suggest that, if it exists, it is quite small.

The incidence of Down syndrome (DS) rises dramatically with maternal age. The increased risk for older women has generated an interest in providing them with an opportunity for prenatal diagnosis through amniocentesis, fetal cell culture, and karyotyping. What about the risk for older fathers? To be sure, the incidence of DS increases with increasing paternal age, but conventional wisdom has held that there is no independent effect of fathers' age. In other words, it has been held that the increased risk for older fathers is simply a reflection of the maternal-age effect and the high correlation between mothers' and fathers' ages. Conventional wisdom notwithstanding, the correct interpretation of the available data was that if there were an effect, it was too small to be detected [1], either because of relatively small sample sizes or weak statistical methods.

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[1] Birth Defects Branch, Bureau of Epidemiology, Center for Disease Control, Public Health Service, United States Department of Health, Education, and Welfare, Atlanta, GA 30333.

In the last decade it has become clear that the extra chromosome 21 can arise from the father [2–4]. Indeed, it appears that between one-fourth and one-third of contemporary cases of DS are the result of an extra paternal chromosome. These cytogenetic data piqued the curiosity of several workers, including myself. Was it possible that previous statistical studies of paternal age had missed an effect? At the time of this writing there have been at least three recent studies on the subject. Stene and Stene [5] suggested that the statistical methods used in the older studies were weak. In a companion paper in the same journal [6], this Danish group used more powerful statistical methods and seemingly demonstrated an excessive number of DS infants born to older fathers. Another recent study, from Japan, [7] is in some ways supportive of the Danish findings. Unfortunately there is a major inconsistency in the Japanese data which prevents a clear interpretation: there was an excess of DS infants born to fathers $\geq$ 55 years of age, but a deficit of DS infants born to fathers aged 40 to 44. I reported on the subject using a very large sample of DS infants and could demonstrate no independent paternal-age effect [8]. However, these cases were ascertained from birth certificates—a notoriously poor source of ascertainment, missing roughly half of all cases. This underascertainment itself is not important, but the possibility that the available data are biased in some way is. In a subsequent paper, Stene and Stene [9] stated that the data I used were biased and therefore unsuitable for an investigation of the paternal-age effect.

The purpose of this paper is to present new data on DS and fathers' age and to discuss some of the relevant methodological issues.

METHODS AND MATERIALS

The data presented here were derived from two sources: the Metropolitan Atlanta Congenital Defects Surveillance Program and the National Center for Health Statistics (NCHS).

Metropolitan Atlanta Data

Since October 1967, these data have been gathered in a program sponsored by the Center for Disease Control, Emory University, and the Georgia Mental Health Institute. An attempt is made to ascertain all live- and stillborn babies with congenital defects born to mothers resident in a five-county area, including and surrounding the city of Atlanta. Multiple case-finding techniques are used. The Department of Human Resources of Georgia provides data on live births for computing rates and for use as controls; these data were available for 1968–1976. DS cases and births from 1968 through 1976 were used as the basis for all incidence rates presented in this report. However, for statistical testing, DS infants born from October 1967 through December 1977 were compared with births from 1968 through 1976.

National Center for Health Statistics Data

The Center collects vital statistics for the United States, and for the years 1973–1975 has coded congenital malformations reported on live-birth certificates. Data on all live births are available for the same years, but because of the enormity of the files, only the data from the central year, 1974, have been used for computing rates and as control material for statistical testing.

Statistical Methods

Stene and Stene [5] reviewed some of the problems inherent in attempting to separate the effects of maternal and paternal age on the incidence of DS. Problems arise because of the high correlation between maternal and paternal age and because of the very strong independent effect

of maternal age. They proposed the simple technique of dividing fathers into two groups, young and old. They also proposed that a paternal-age effect, if present, might be like the maternal-age effect: relatively constant up to a certain age and then increasing sharply. Such a proposal seems reasonable, and thus the approach of dividing paternal ages into two categories would be quite powerful, if the right definition of young and old is chosen. To maximize the chance of finding a paternal-age effect, I have used several definitions of young and old paternal ages: ≤ 39 and ≥ 40, ≤ 44 and ≥ 45, and ≤ 49 and ≥ 50 years. Because the effects of maternal age are so strong, control has been made by single years of age. This is an important feature. If control is crude (e.g., 5-year age groups or even coarser) then one can expect to have some residual effect of maternal age mixed with the presumed paternal-age effect.

The data categorized in this way result in a number of 2×2 tables, one for each year of maternal age. On one axis of each table the classification is DS–not DS, and on the other axis, young paternal age–old paternal age. Stene and Stene's [5] data for each of their maternal age categories were set out in the same way, and they computed an exact probability for each table. Then they summarized the association between DS and paternal age over tables, also by computing an exact probability. Because of the large numbers involved in the present report, and also because stratification by individual years of maternal age yields a large number of tables, the derivation of exact probabilities is computationally infeasible. Therefore a large sample approximation to the approach of Stene and Stene [5] was used here, the Mantel-Haenszel (MH) test [10–12]. This test was among those used in my previous report [8]. The MH test yields a chi-square statistic for each 2×2 table and a summary chi-square which measures the association between DS and paternal age free of the effect of maternal age. The MH procedure is a typical chi-square test, comparing an observed number with an expected number. The data are presented here in the form of observed and expected numbers of DS cases, and the expected numbers were computed as a part of the MH procedure. Thus the expected values are similar to those which would be computed during the process of indirect standardization [12].

RESULTS

Metropolitan Atlanta Data

Figure 1 shows the incidence of DS by single years of maternal and paternal age. Whites and blacks have very different maternal age distributions, but there are no marked differences in the maternal age-specific rates (table 1). Therefore, all Atlanta data presented are for whites and blacks combined. The age-specific rates plotted in figure 1 were smoothed by taking a 5-year moving average. This smoothing was done so that trends would not be obscured by the visual effects of fluctuations caused by the small number of cases at the individual years of parental age. It should also be noted that the plots are truncated at the higher ages, 45 years for females and 49 for males.

The top part of table 2 shows the result of the statistical analysis of the Atlanta data for evidence of an independent paternal-age effect. When summarized over all maternal ages, there are no significant effects attributable to paternal age, and the observed and expected numbers of DS infants are very close for each of the three divisions of father's age into "young" and "old." The data have also been tabulated in two groupings of mother's age, ≤ 34 and ≥ 35 years.* The expected number of cases for each of these groupings was computed while taking account of the effects of maternal age (within the coarse groupings) by single years of age. For mothers ≥ 35 years, there is no independent effect of paternal age apparent. However, for mothers $\leq$

* Raw data tables may be obtained by writing directly to the author.

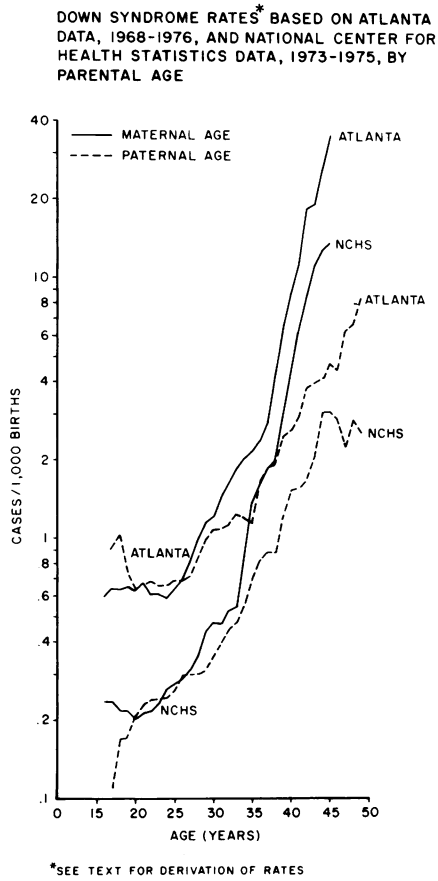

FIGURE 1

34 years the observed numbers of DS infants for "old" fathers exceed the expected numbers.

National Center for Health Statistics Data

The maternal and paternal age-specific DS rates (smoothed by a 3-year moving average) for whites *only* are shown in figure 1. The level of ascertainment of DS seems to be particularly poor for blacks in this data set, and there are marked differences in the maternal-age distribution of whites and blacks. It was therefore considered prudent to consider only whites. The underascertainment of these white DS infants is also readily apparent (table 3, fig. 1). There is also evidence of relatively poorer ascertainment at young maternal ages than at the older ages: for ages ≤ 35 the Atlanta rates are 2.5 to 3 times the NCHS rates, whereas for maternal ages ≥ 35 the Atlanta rates only exceed those from the NCHS by about twofold.

TABLE 1

DOWN SYNDROME RATES BY MATERNAL AGE AND RACE

MATERNAL AGE	WHITES			BLACKS		
	Cases	Births	Rate/1,000	Cases	Births	Rate/1,000
≤ 19	19	25,414	0.75	14	22,837	0.61
20–24	35	55,437	0.63	14	24,429	0.57
25–29	40	52,058	0.77	12	14,286	0.84
30–34	31	20,915	1.48	11	6,329	1.74
35–39	15	5,879	2.55	7	2,475	2.83
40–44	18	1,253	14.37	9	636	14.15
≥ 45	4	73	54.79	0	36	0.0
Unknown	0	423	0.0	0	165	0.0
Total	162	161,452	1.00	67	71,193	0.94

NOTE.—Metropolitan Atlanta data, 1968–1976; rates/1,000 live births.

TABLE 2

OBSERVED AND EXPECTED CASES OF DOWN SYNDROME BY PATERNAL AND MATERNAL AGE

PATERNAL AGE	MATERNAL AGE						
	≤ 34		≥ 35		Total		
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	χ^2
Metropolitan Atlanta data:							
≤ 39	161	165.2	23	20.7	184	185.9	0.24
≥ 40	10	5.8	32	34.3	42	40.1	
≤ 44	167	169.2	39	38.4	206	207.7	0.26
≥ 45	4	1.8	16	16.6	20	18.3	
≤ 49	168	170.4	51	49.5	219	219.9	0.18
≥ 50	3	0.6	4	5.5	7	6.1	
NCHS data:							
≤ 39	1212	1212.5	210	216.0	1422	1428.5	0.29
≥ 40	46	45.5	390	384.0	436	429.5	
≤ 44	1245	1242.3	428	423.5	1673	1665.8	0.45
≥ 45	13	15.7	172	176.5	185	192.2	
≤ 49	1252	1252.7	561	546.7	1813	1799.4	3.70
≥ 50	6	5.3	39	53.3	45	58.6	

NOTE.—See text for derivation of expected no. cases and Chi-square statistics.

Neither the overall underascertainment nor the more severe underascertainment at younger maternal ages necessarily makes these data unsuitable for testing for an independent paternal-age effect. The pertinent question is whether there is a differential ascertainment for young and old fathers at specific maternal ages.

The results of the analysis of the NCHS data for evidence of a higher risk among older fathers can be found in the lower part of table 2. For none of the three paternal age dichotomies is there such evidence. There is substantial agreement between the

TABLE 3

DOWN SYNDROME RATES BY MATERNAL AGE, WHITES ONLY

Maternal age	Cases	Births	Rate/1,000
≤ 19	168	746,850	0.22
20–24	383	1,634,310	0.23
25–29	471	1,438,065	0.33
30–34	296	564,834	0.52
35–39	309	171,045	1.81
40–44	285	39,759	7.17
≥ 45	31	2,442	12.69
Total	1,943	4,597,305	0.42

NOTE.—National Center for Health Statistics data. Cases from 1973–1975; births for 1973–1975 estimated by multiplying the no. 1974 births in each maternal age category by 3.

observed and expected number of cases for the paternal age divisions of ≤ 39 and ≥ 40, and ≤ 44 and ≥ 45. However, the observed number of cases for fathers ≥ 50 is lower than would be expected; this overall deficiency derives from mothers ≥ 35 (table 2).

DISCUSSION

If there is an increased risk of DS for older fathers, as suggested by Stene et al. [6], and by Matsunaga et al. [7], then it must be rather modest. The overall negative finding from the two data sets used here are of course not proof that there is no effect. They merely suggest that, if it exists, if must be rather small. In arriving at this conclusion, there are a number of points which need to be considered.

First, the high correlation between maternal age and paternal age and the strong independent effect of maternal age [8] make it very difficult to detect an effect of paternal age which is not simply secondary to an association with maternal age. This is the question which Stene and Stene [5] addressed, and their technique of dividing fathers' ages into two groups was used here. However, in my approach, I controlled for maternal age by single years. Stene et al. [6] grouped mothers into three age categories: ≤ 34, 35–39, and ≥ 40. In my opinion, such broad control will not provide incontrovertible evidence in favor of a paternal-age effect. Consider the maternal age category ≤ 34 years. The ages of mothers within this grouping who have children by older fathers tend to be clustered around the upper limit of the category, while those who have children by younger fathers tend to be in the lower range of the group. To be specific, consider the NCHS mothers ≤ 34 years of age. The mean maternal age was 24.2 for those whose mates were ≤ 39 years, while the mean for those mothers whose mates were ≥ 40 years was 29.2 years, a difference of 5 years. Figure 1 shows that while the rates for maternal age ≤ 34 are *relatively* constant, they increase about 50% between ages 24 and 29. The expected number of cases for fathers ≥ 40 derived while accounting for maternal age by single years is 45.5 (table 2). On the other hand, the expected number is 30.7 when computed from the maternal age rate for the whole ≤ 34 years group. In other words, the expected number of cases is spuriously reduced by

crude control of maternal age, and it is reduced markedly. Thus a crude control of maternal age as Stene et al. used [5, 6] and subsequently advocated [9] does not remove all the effects of maternal age. It has also been argued that stratification by single years of maternal age causes a loss of power. Overstratification might have undesirable results if the stratification is done over a range of maternal ages where the incidence is constant. But the data in figure 1 suggest that the age-specific rates increase with every increase in maternal age. In any case, there can be no question of a loss of statistical power when that power can be gained only at the risk of losing validity.

The Atlanta data are well ascertained, and the maternal age-specific rates are as high as those reported in any study in which DS infants have been ascertained among live- and stillborn babies. As was noted before, this is not true of the NCHS data. There are many factors which influence the recording of a diagnosis of DS on birth certificates. However, we need only be concerned if the ascertainment is biased with respect to paternal age at specific maternal ages. If they are not, then the NCHS data are for all intents and purposes like a random sample comprising one-third to one-half of cases at each level of maternal age. It was suggested [9] that such bias was present in my own previous report [8] where cases were also ascertained through birth certificates. In those data there was a deficiency of DS infants born to old fathers and young mothers. No such deficiency was found in the NCHS data. Instead, there appears to be a deficiency of DS infants born to the fathers ≥ 50 and mothers ≥ 35 years of age. Either of these deficiencies could be considered as evidence of biases or of moderately unusual sampling fluctuations. Unfortunately, it is not possible to know which of these hypotheses is true. The obvious advantage of using birth certificate data is that they provide a ready source of large numbers of cases. If they are unbiased or if the bias is small, then they provide useful information on what the upper limits of a potential paternal-age effect might be. As a possible source of bias, it has been suggested that the likelihood of diagnosis of DS is lower for persons of lower socioeconomic status, and that the average difference in maternal and paternal ages increases with decreasing socioeconomic status [9]. I have used education as an indicator of socioeconomic class, dividing the NCHS data into 2 groups: one for fathers with ≥ 13 years of education and one for those with ≤ 12 years. The level of ascertainment was generally higher for mothers whose mates had more education. However, there was no evidence of a paternal-age effect among the better educated or among those with poorer education. My current opinion is that if these data are biased, the bias is probably quite weak and would only obscure the most modest of independent paternal-age effects.

The Atlanta data suggest that there may be an effect detectable in mothers ≤ 34 years, but the numbers are very small. The strongest evidence here is the fact that three DS infants were born to fathers ≥ 50 and mothers ≤ 34. The expected number was 0.6 (table 2). However, it should also be noted that there is a small deficiency of DS infants for fathers ≥ 50 and mothers ≥ 35 (4 observed vs. 5.5 expected). These data are not, in my opinion, clear evidence of a paternal-age effect as was stated by Stene and Stene [9].

The DS infants born to mothers ≤ 34 and fathers ≥ 50 in Atlanta suggest an important avenue of research into this problem. The ages of the three fathers were 50,

52, and 53; the ages of the mothers were 25, 34, and 24, respectively. If the extra chromosome was found to arise from the father for a majority of DS infants where the maternal and paternal ages are so disparate, it would add some credibility to the theory of an independent paternal-age effect. On the other hand, if such DS infants were found to arise most frequently from maternal nondisjunction, the case would be weakened considerably. This is so since the statistical evidence for a paternal-age effect rests very heavily on these few age-disparate parents.

The paternal-age incidence curves in figure 1 deserve further consideration. The NCHS curve shows a flattening at about age 45. A similar pattern was noted in the birth certificate data which I reported earlier [8]. This seems to be evidence in favor of no paternal-age effect. It is at the older parental ages where the correlation between maternal and paternal ages breaks down: there is an upper limit to maternal age, whereas paternal age is, relatively speaking, unbounded. This provides a natural, rather than a statistical, control of the maternal-age effect. The Atlanta data seem to present a different picture: the rates, as graphed, show no evidence of a flattening, but the graphs are truncated at paternal age 49. This was done because of the extreme fluctuation of the rates for the individual years of age. The Atlanta rates show evidence of a flattening, but not until age 50 is reached. Further, for both the NCHS and the Atlanta data, the observed number of DS infants born to fathers ≥ 45 is very close to what is expected.

Finally, if there is a paternal-age effect, what are the clinical and public health implications? From a clinical viewpoint, the effect might warrant special counseling, particularly when the mother is young and the father is quite old. On the other hand, for older women the effect added by an older father should be trivial. From a public health standpoint, such an effect would be even more insignificant: very old fathers are rare, and children born to these men by younger women are even more infrequent.

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