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THE INFLUENCE OF PATERNAL AGE ON DOWN SYNDROME

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ABSTRACT

Purpose: Children born to older parents are at greater risk for genetic abnormalities, such as Down syndrome. The influence of maternal age on Down syndrome is well established but little is known about the genetic consequences of advanced paternal age.

Materials and Methods: Data on the incidence of Down syndrome from 1983 to 1997 (3,419 cases) were obtained from the New York State Department of Health congenital malformations registry. Parental age was modeled as individual age groups and by a single linear covariate (drift model). The log linear chi-square test and a test of significance of different explanatory variables were used to evaluate these models to determine significance. We compared actual Down syndrome rates by maternal age with the estimated rate corrected for paternal age.

Results: From 1983 to 1997 a dramatic increase in the number of infants born to parents 35 years or older was observed. During the 15-year study period there was an increase of 111% and 60% in the number of mothers and fathers 35 years old or older, respectively. There was no parental age influence on Down syndrome until age 35 years and older. A paternal age effect was seen in association with a maternal age of 35 years and older, and it was most pronounced when maternal age was 40 years and older ($p = 0.0004$). In this later maternal age group the paternal contribution to Down syndrome was 50%.

Conclusions: Advanced paternal age combined with maternal age significantly influences the incidence of Down syndrome. This effect may represent a paradigm for other genetic abnormalities in children of older fathers.

KEY WORDS: paternal age, Down syndrome, abnormalities, risk factors, genetics

Demographic studies in the United States have shown that the number of births to parents older than 35 years has more than doubled in the past 20 years.[1] This increase in parental age is a public health concern because more infants are being born who are at high risk for genetic abnormalities. Determining the potential risks associated with advanced parental age is now more relevant than ever.

Trisomy 21 or Down syndrome is a common congenital abnormality affecting 1/800 to 1,000 newborns.[2] As the most common nonlethal trisomy disorder, it is the focus of genetic screening and testing protocols. Multiple investigations have been done to identify possible risk factors, of which the most common has been parental age. The effect of maternal age as a risk factor for Down syndrome was described as early as 1933.[3] By examining amniocentesis data the European collaborative study of Ferguson-Smith and Yates determined maternal age specific rates for various chromosomal aberrations, the most common being trisomy 21.[4] They concluded that the rate of trisomy 21 increases dramatically from maternal age of 35 years. Unlike maternal age, the role of paternal age on Down syndrome has not been clearly defined. Some studies suggest no influence,[5–7] while other, smaller studies suggest a positive paternal effect.[8,9] The increasing number of older couples having children has resulted in a renewed interest in determining the genetic risk to children born to these couples. We defined the parental age effect on Down syndrome and clarified whether a paternal age effect exists as a risk factor.

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MATERIALS AND METHODS

Down syndrome data were available from the New York State Department of Health congenital malformations registry, which was initiated in 1982 and represents the entire state. Cases are generally ascertained through medical records departments and are reported to the congenital malformations registry by hospitals and physicians. Although New York State law mandates reporting, monitoring of data and hospital audits are performed to ensure more complete and accurate reporting. The registry includes only live born cases.

Table 1 shows Down syndrome births grouped by 5-year periods for maternal age and paternal age. In addition to simple trend analysis, Poisson regression models were used to fit the data, which were then analyzed using maternal age-paternal age analysis (table 2). The dependent variable was the number of cases and the denominator (or offset term) was the number of live births. The link function was merely $\ln(\mu)$. To increase the number of degrees of freedom in the analysis a drift function was used for father age. The function used was 1, 2, . . ., 5 corresponding to <25, $25 < 30$, . . ., >40 for father age. The number of cases was a variable with a Poisson distribution that is a function of maternal age and paternal age. Paternal age was modeled as individual age groups and by a single linear covariate (drift model). The drift model assumes that there is a linear change in rate for each paternal age group for a fixed maternal age group. The different estimates were determined from maximum likelihood models using a commercially available, generalized, log linear model package. The log linear chi-square test was used to evaluate these models (table 3). Table 4 shows the results of the test of significance for different explanatory variables

TABLE 1. *Rate of Down syndrome per 100,000 births by maternal and paternal age in New York State, 1983 to 1997*

Paternal Age	No./100,000 Births (total No.)				
	Maternal Age 24 or Younger	Maternal Age 25–29	Maternal Age 30–34	Maternal Age 35–39	Maternal Age 40 or Older
24 or Younger	64 (290)	80 (50)	87 (10)	131 (3)	314 (1)
25–29	59 (182)	72 (369)	100 (103)	158 (26)	395 (7)
30–34	57 (53)	58 (227)	105 (502)	174 (120)	578 (35)
35–39	90 (24)	78 (81)	104 (269)	189 (338)	427 (62)
40 or Older	48 (6)	66 (27)	99 (91)	222 (257)	632 (286)

TABLE 2. *Results of Poisson regression*

Parameter	Estimate ± SE	Z Value	Asymptotic 95% CI
Constant	−5.85 ± 0.3	−17.9	(−6.5–−5.2)
Maternal age:			
24 or Younger	−1.54 ± 0.3	−4.7	(−2.2–−0.9)
25–29	−1.45 ± 0.3	−4.4	(−2.1–−0.8)
30–34	−1.03 ± 0.3	−3.1	(−1.7–−0.4)
35–39	−0.89 ± 0.4	−2.4	(−1.6–−0.2)
40 or Older	0*		
Paternal age trend for maternal age:			
35–39	0.12 ± 0.0	2.7	(0.03–0.21)
40 or Older	0.15 ± 0.1	2.2	(0.01–0.29)

* Automatically set to 0.

of paternal age. An F statistic was calculated to determine significance.

RESULTS

The total number of Down syndrome cases in the 15-year study period in New York State was 4,387. Complete data on maternal and paternal age were available on 3,419 cases. The average rate of Down syndrome from 1983 to 1997 was 9.9/10,000 births (range 9.1 in 1989 to 11.6 in 1985) (fig. 1). The rate of Down syndrome has remained relatively stable throughout the study years. Figure 2 shows the demographic change in total births for all parental ages grouped by 5-year intervals between 1983 and 1997. A positive change was observed for mothers and fathers older than 30 years with a negative change for mothers and fathers younger than 30 years. Overall more children were born to couples older than 30 years and fewer were born to couples younger than 30 years. In 1983, 8% of all births were to women 35 years old or older compared with 17% in 1997. Births to mothers older than 40 years increased approximately 2.5 times between 1983 and 1997. The greatest change in this period occurred in maternal and paternal ages greater than 40 years with a 178% and 73% increase from 1983 to 1997, respectively.

Figure 3 shows the number of Down syndrome cases by maternal and paternal age (table 1). The rate of Down syndrome steadily increased for the maternal age group of 35 to 39 years with increasing paternal age. The greatest increase was seen in the maternal age group of 40 years and older with increasing paternal age. The rate of Down syndrome for maternal and paternal age greater than 40 years was approximately 60/10,000 births, which was a 6-fold increase compared with maternal and paternal ages less than 35 years. For paternal age 40 years and greater there was a 2-fold increase in the rate of Down syndrome compared with men 24 years and younger, when combined with maternal age 35 years and greater. Note that there was no increase in the Down syndrome rate with maternal age below 35 years. In these women there was also no paternal age effect.

TABLE 3. *Goodness of fit statistics*

Parameters	Chi-Square	df	p Value
Model 1:			
Maternal age X			
Paternal age X			
Paternal age drift for maternal age 35 or older	18.6	15	0.23
Model 2:			
Maternal age X			
Paternal age drift for maternal age 35 or older	20.8	19	0.35
Model 3:			
Maternal age	33.2	20	0.03
Model 4:			
Maternal age			
Paternal age drift for maternal age 35–39			
Paternal age drift for maternal age 40 or older	20.7	18	0.30

TABLE 4. *Test of significance of different explanatory variables*

Variables	F Statistic	df	Significance
Paternal age	2.2	4	0.1124 (not significant)
Paternal age drift for maternal age:			
35 or Older	12.4	1	0.0023 (significant)
35–39			
40 or Older	12.5	2	0.0004 (significant)

Table 3 lists the results of goodness of fit statistics. Models 1, 2 and 4 each had at least 1 explanatory variable for paternal age. Only model 3 assumed no paternal component and it was the only model that did not significantly explain the variation in data ($p = 0.03$). In other words, when maternal age was considered without the interaction of paternal age (and vice versa), no relationship between parental age and Down syndrome was apparent. Three types of paternal age explanatory variables were used. In particular, 3 drift variables were used, namely 1) a drift variable for paternal age and maternal age older than 35 years, 2) a drift variable for paternal age and maternal age 35 to 39 years and 3) a drift variable for paternal age and maternal age 40 years or greater. The maternal age-paternal age drift model offered substantial improvement over a maternal age adjusted model because the age drift model used only 1 additional df,

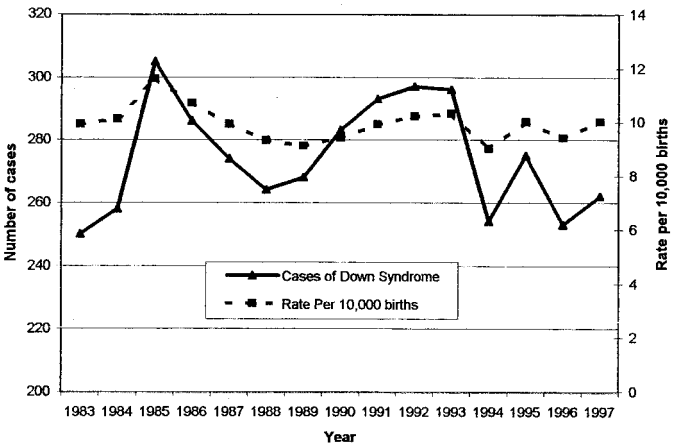

FIG. 1. Cases of Down syndrome and rate per 10,000 births in New York State, 1983 to 1997.

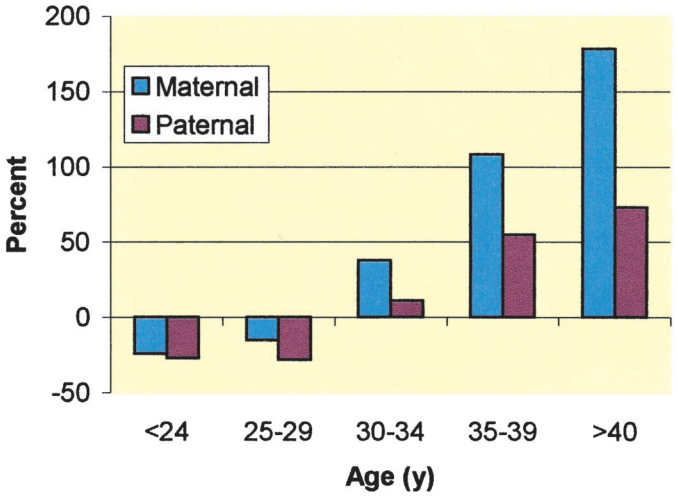

FIG. 2. Percent change in number of births based on maternal and paternal age, 1997 versus 1983.

while accounting for a much larger percent of variation ($p = 0.35$).

Table 4 shows the results of the test of significance for different explanatory variables of paternal age. An F statistic was calculated to determine significance. All drift variables for paternal age were significant. However, individual age groups for paternal age were not. This apparent anomaly can be understood by an examination of the number of cases of Down syndrome for paternal and maternal age (fig. 3, *A*). Note that only for maternal age greater than 35 years was an apparent increase in the rate of Down syndrome by paternal age appreciated. The most marked increase in the rate of Down syndrome occurred in the maternal age group older than 40 years with increasing paternal age.

As expected, there was a strong positive correlation between maternal and paternal age with a correlation of 0.67 ($p < 0.001$). That is, young women tend to have children with young men and older women tend to have children with older men. Figure 3, *B* shows the actual rates by maternal age versus the estimated rates for maternal age using maternal age coefficients for the model (table 2). For maternal age 40 or older an increase from 287 to 575/100,000 births was noted or an increase of 50% due to the paternal effect. Similarly in the maternal age group 35 to 39 years old the increase of 39% can be attributed to paternal effects.

The results imply that for women 35 to 39 years old there is only a modest increase in the rate over that for women 30 to 35 years old. This result is consistent with the data in figure 3. For women 35 to 39 years old and older than 40 years there was about a doubling of the rate as paternal age increased. The increase in Down syndrome births to women 35 to 39 years old is largely due to paternal factors.

DISCUSSION

The existence of a paternal age effect on Down syndrome is controversial. Various large United States and European epidemiological studies of Down syndrome show no influence between paternal age and Down syndrome.[4,10–12] For example, in one of the largest American studies Regal et al analyzed birth certificate reports in upstate New York from 1963 to 1974 and reported no correlation between 853 cases of Down syndrome and paternal age.[13] In contrast, in a study from Canada an examination of 997 cases of Down syndrome revealed a general pattern of increasing relative rate estimates with increasing paternal age.[14]

Smaller studies examining Down syndrome data from prenatal diagnosis conflict with regard to a paternal age effect. After evaluating 158 cases of prenatally diagnosed trisomy 21, including 60 from the Federal Republic of Germany[8] and 98 from the New York State chromosome registry, Stene et al described a paternal age effect.[9] However, in a separate analysis of the same 98 prenatally diagnosed cases in New York State, Hook and Cross found no paternal effect.[15] The contrast between these 2 conclusions is the result of different methods of statistical analysis and possibly of the small sample size.

In our study we were able to examine a larger number of cases than have previously been studied. We evaluated 3,419 cases of Down syndrome in a 15-year period and found that the incidence of Down syndrome is influenced by paternal age. Paternal age has an effect on Down syndrome but only in mothers 35 years old and older. In younger women, in whom maternal age was not a risk factor for Down syndrome, there was no paternal effect. The paternal effect was greatest in couples older than 40 years, where the risk of Down syndrome was 6 times the rate in couples younger than 35 years.

When paternal age is considered without the interaction of increased maternal age (and vice versa), no relationship between parental age and Down syndrome is apparent. Since it seems reasonable to assume a positive correlation between maternal age and paternal age (that is older women tend to have children with older men), the typically identified increase in the rate of Down syndrome for women 35 years and older may in fact be the result of a combination effect of maternal and paternal ages. This interaction would explain the dramatic increase in Down syndrome with increasing maternal age.

This novel finding of a combination of maternal and paternal age influencing Down syndrome can be explained in 2 ways. The first explanation is that there is a sperm contribution to the trisomy. Sartorelli et al studied a small population of men and reported a higher frequency of sperm chromosome abnormalities in older men.[16] While it has been

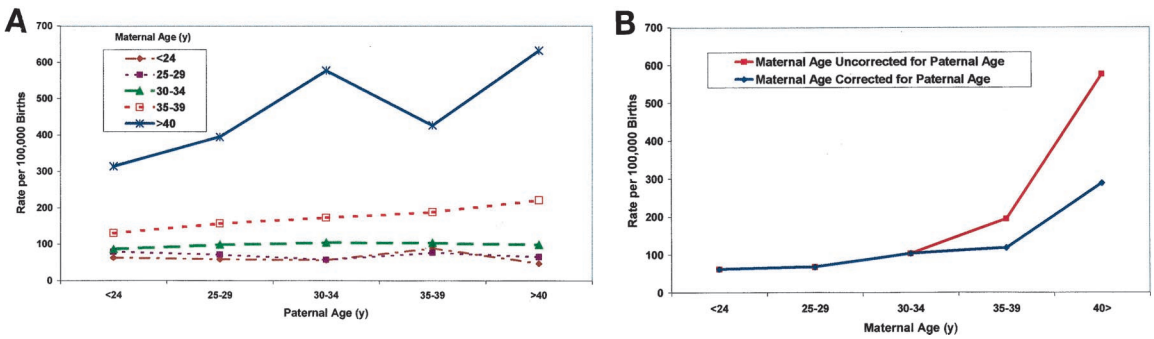

FIG. 3. *A*, rate of Down syndrome births by maternal and paternal age in New York State, 1983 to 1997. *B*, Down syndrome rates by maternal age corrected for paternal age.

estimated that the extra chromosome is of paternal origin 5% to 20% of the time,[17,18] it is possible that older men may contribute the extra chromosome more frequently. To our knowledge studies regarding the sperm contribution related to paternal age are not currently available. The second explanation is that the mechanism controlling spontaneous abortion changes and becomes less efficient with increasing maternal age. That is, with increasing age the mechanisms in the mother that identify and spontaneously abort a chromosomally abnormal fetus may falter. It has been demonstrated that the relative survival of abnormal fetuses compared with normal fetuses increases with increasing maternal age.[9] Our results are most likely explained by a combination of these 2 mechanisms.

A decrease in Down syndrome was observed in the 40 years and older maternal age group when combined with the paternal age group of 34 to 39 years. This finding is in agreement with the data of Stene et al, who reevaluated New York State data and also observed a lower risk in the paternal age group of 34 to 39 years.[9] While the reason for this decrease is unknown, we can speculate that it may represent the effect of voluntary abortions, which may be most pronounced in this age group. Unfortunately we do not know what the abortion rate for Down syndrome is or whether there was an increase during the study period. It is possible that an increase in abortions may explain why the rate of Down syndrome remained relatively stable from 1983 to 1997. Overall stability in the Down syndrome rate may have also been influenced by the fact that most cases of Down syndrome occurred in women younger than 35 years, where parental age did not influence rate.

In addition, our evaluation of data from New York State for the 15-year study period showed a substantial demographic shift in parental age with more mothers and fathers older than 35 years than ever before. This group is at highest risk for children with Down syndrome or other age related genetic abnormalities. A recent study showed that children born to older fathers were at higher risk for schizophrenia.[19] It is known that certain autosomal dominant diseases, such as achondroplasia, neurofibromatosis, Marfan syndrome, osteogenesis imperfecta, Treacher-Collins-Franschetti syndrome, Waardenberg's syndrome, thanatophoric dysplasia and Alport's syndrome, are associated with older fathers, probably via de novo, single gene mutations in sperm that can be passed on to children.[20] Our finding of a paternal contribution to trisomy indicates a larger structural chromosomal risk than had previously been appreciated. It is our belief that increased paternal age as well as maternal age may be responsible for a wide variety of health problems in children. This effect has been underestimated and warrants further research.

CONCLUSIONS

With increasing paternal age an increase in the rate of Down syndrome is seen in women 35 years of age and older. The increase in the rate of Down syndrome for women in this age group is likely a result of a combination affect of maternal and paternal factors. Considering that the population of parents is older than ever before the paternal age affect is significant and should be addressed during counseling. Young couples preparing for family planning must be aware that advanced parental age may not only result in increasing difficulties with fertility for the parents but that children born to older parents may be at higher risk for genetic abnormalities. Lastly, the adverse effect of advanced paternal age on Down syndrome may represent a paradigm for other genetic abnormalities in children of older fathers that must be addressed in future studies.

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