Am. J. Hum. Genet. 58:628–633, 1996

Advanced Maternal Age and the Risk of Down Syndrome Characterized by the Meiotic Stage of the Chromosomal Error: A Population-Based Study

Paula W. Yoon,[1] Sallie B. Freeman,[2,3] Stephanie L. Sherman,[2,3] Lisa F. Taft,[2] Yuanchao Gu,[2] Dorothy Pettay,[2] W. Dana Flanders,[4] Muin J. Khoury,[1] and Terry J. Hassold[5]

[1]Birth Defects and Genetic Diseases Branch, Division of Birth Defects and Developmental Disabilities, National Center for Environmental Health, Centers for Disease Control and Prevention, [2]Department of Genetics and Molecular Medicine and [3]Division of Medical Genetics, Department of Pediatrics, Emory University School of Medicine, and [4]Department of Epidemiology, School of Public Health, Emory University, Atlanta; and [5]Department of Human Genetics and the Center for Human Genetics, Case Western Reserve University School of Medicine and the University Hospitals of Cleveland, Cleveland

Summary

The identification of DNA polymorphisms makes it possible to classify trisomy 21 according to the parental origin and stage (meiosis I [MI], meiosis II [MII], or postzygotic mitotic) of the chromosomal error. Studying the effect of parental age on these subgroups could shed light on parental exposures and their timing. From 1989 through 1993, 170 infants with trisomy 21 and 267 randomly selected control infants were ascertained in a population-based, case-control study in metropolitan Atlanta. Blood samples for genetic studies were obtained from case infants and their parents. Using logistic regression, we independently examined the association between maternal and paternal age and subgroups of trisomy 21 defined by parental origin and meiotic stage. The distribution of trisomy 21 by origin was 86% maternal (75% MI and 25% MII), 9% paternal (50% MI and 50% MII), and 5% mitotic. Compared with women <25 years of age, women ≥40 years old had an odds ratio of 5.2 (95% confidence interval, 1.0–27.4) for maternal MI (MMI) errors and 51.4 (95% confidence interval, 2.3–999.0) for maternal MII (MMII) errors. Birth-prevalence rates for women ≥40 years old were 4.2/1,000 births for MMI errors and 1.9/1,000 births for MMII errors. These results support an association between advanced maternal age and both MMI and MMII errors. The association with MI does not pinpoint the timing of the error; however, the association with MII implies that there is at least one maternal age–related mechanism acting around the time of conception.

Introduction

Down syndrome, one of the most common congenital anomalies, affects ~1 of every 1,000 newborns (International Clearinghouse for Birth Defects Monitoring Systems 1991). It is the most intensively studied human chromosome abnormality, yet little is known about its cause, and only advanced maternal age has been confirmed as a risk factor (Janerich and Bracken 1986). Birth-prevalence rates of Down syndrome, plotted by maternal age, form a J-shaped curve, with women 20–24 years of age having the lowest prevalence rate (1/1,400 births) (Erickson 1978; Hook and Lamson 1990). For women 35 years old, the rate is ~1/350 births, and for women ≥45 years the rate rises to 1/25 births (Hook et al. 1983, 1988).

As many as 95% of Down syndrome cases are caused by trisomy 21, which typically results from nondisjunction during meiosis. Nondisjunction can occur during meiosis I (MI) when the chromosome pairs fail to separate or during meiosis II (MII) when the chromatids fail to separate. Studying the effect of maternal age on the meiotic origin of trisomy 21 could shed light on maternal exposures and their timing because maternal MII (MMII) errors occur around conception, whereas maternal MI (MMI) errors could arise as early as during the mother's fetal life when meiosis is initiated.

Molecular techniques make it is possible to identify DNA polymorphisms on chromosome 21 and more accurately determine the parent and meiotic stage of origin of the extra chromosome. Earlier studies of parental origin relied on cytogenetic analyses, which are more subjective and more likely to result in misclassification. In 1984, Hassold and Jacobs summarized the results of the major cytogenetic studies and concluded that the extra chromosome was of maternal origin ~80% of the time and paternal origin 20% of the time. More recent studies using DNA polymorphisms to identify parental origin estimate the frequency of maternal and paternal nondisjunction at 90%–95% and 5%–10%, respectively (Antonarakis and the Down Syndrome Collaborative Group 1991; Sherman et al. 1991; Antonarakis et al. 1992). The analysis of chromosome 21 pericentromeric DNA polymorphisms has also made it possible to infer the meiotic stage of the chromosomal error. Evidence

Received September 11, 1995; accepted for publication December 14, 1995.

Address for correspondence and reprints: Dr. Stephanie L. Sherman, Department of Genetics and Molecular Medicine, Emory University, 1462 Clifton Road, Atlanta, GA 30322.

0002-9297/96/5803-0021$02.00

to date suggests that the majority of maternal nondisjunction is due to MI errors, whereas paternal nondisjunction is more often due to MII errors (Sherman et al. 1991; Antonarakis et al. 1992).

Recent studies of maternally derived trisomy 21 reported a higher mean maternal age for both MI and MII errors compared to controls (Sherman et al. 1994), and higher mean maternal age for MII errors compared to MI errors (Antonarakis et al. 1992). These studies were not population based and included trisomy 21 cases from diverse sources, including therapeutic abortions, live births from different countries, and other convenient samples. Studies of trisomy 21 that are not population based may be biased with respect to the parental origin of the extra chromosome and the age distribution of the parents. The studies were also limited in that they compared only mean parental ages and most did not adjust for spouse's age. Mean age does not account for differences in the age distribution of populations, nor does it describe the J-shaped nature of the risk curve for maternal age and trisomy 21. Adjusting for spouse's age is necessary in order to show the independent effects of maternal and paternal age. Our population-based, case-control study, which estimates the relative risk of maternally derived trisomy 21 due to advanced maternal age, addresses these limitations and is the first to combine an epidemiological analysis with molecular studies of the parent and meiotic/mitotic origin of nondisjunction.

Material and Methods

This investigation was part of a population-based, case-control study of trisomy 21 in the five-county area of metropolitan Atlanta. From 1989 through 1993, 170 infants with trisomy 21 were ascertained by use of the Metropolitan Atlanta Congenital Defects Program (MACDP), a birth-defect surveillance system that uses active-case ascertainment from multiple sources. Case finding and the criteria for inclusion in MACDP have been described in detail elsewhere (Lynberg and Edmonds 1992). From the same metropolitan Atlanta population, 267 unaffected control infants were randomly selected from hospitals in proportion to the expected number of total births at each hospital. Mothers and fathers of case and control infants were interviewed, and blood samples were obtained from the case infants and their parents in order to study the origin of the chromosomal error. During the 5-year study period (1989–1993), 192,597 infants were born to metropolitan Atlanta–area residents. We obtained information on the ages of the infants' parents from vital records.

Laboratory Methods

Case infants and their parents were genotyped for markers located on chromosome 21. DNA was extracted from peripheral blood samples and/or lymphoblastoid cell lines, and Southern blotting techniques or PCR were used to detect chromosome 21 polymorphisms. Twenty-nine markers were identified and grouped into 17 chromosome regions as described by Sherman et al. (1994). Each region was defined as a group of markers known to be tightly linked in normal individuals. Parental origin of the extra chromosome was determined by examining the contribution of alleles from each parent to the chromosomes 21 of their offspring. Meiotic stage of origin was determined by comparing chromosome 21 pericentromeric markers of the parent who contributed the extra chromosome with those of the offspring. If parental heterozygosity was retained in the trisomic offspring (nonreduction), an MI error was concluded. If parental heterozygosity was reduced to homozygosity (reduction), an MII or mitotic error was concluded. MII and mitotic errors were distinguished by evaluating other nonpericentromeric loci. Those cases with markers that were reduced to homozygosity along the entire chromosome were considered mitotic errors, whereas the remaining were considered MII errors. Further details about the DNA analysis have been described elsewhere (Sherman et al. 1994).

Statistical Analysis

On the basis of the results of the DNA analysis, we grouped the cases according to the parental origin (maternal or paternal) and stage of origin (MI, MII, or mitotic) of the chromosomal error. We used logistic regression to study the effect of advanced maternal and paternal age on the risk of the MI and MII errors. The ages of the parents of case infants were compared with the ages of the parents of control infants and with the ages of the parents of all infants in the Atlanta population. This investigation, therefore, has two components: a case-control analysis and a case-population analysis.

For the analysis of maternally derived trisomy 21, we divided parental age into five groups (<25 years of age, 25–29 years of age, 30–34 years of age, 35–39 years of age, and ≥40 years of age), and the <25-year-old group was used as the referent category for estimating relative risk. Both maternal and paternal ages were included in the regression models to adjust for spouse's age. Results from the case-control analysis are presented as odds ratios (OR) with 95% confidence limits, and results from the case-population analysis are presented as rate ratios (RR) with 95% confidence limits.

Using the RRs from the case-population analysis, we estimated birth-prevalence rates for the meiotic subgroups of maternally derived trisomy 21 by maternal and paternal age. The information required to estimate the birth-prevalence rates was (1) the estimated population rate for the trisomy 21 subgroups, (2) the proportion of mothers and fathers in each age group for the birth population, and (3) the RRs for each parental age

group. The population rates for maternally derived trisomy 21, MMI, and MMII were calculated by dividing the estimated number of cases of each subgroup (proportion of 170 cases ascertained as determined by results of the DNA analysis) by the total birth population. The proportion of mothers and fathers by age group was obtained from vital records, and the RRs were obtained from the case-population analysis. For example, we used the following formula to calculate the age-group specific birth-prevalence rates for MMI,

$$\frac{\text{Estimated No. Cases MMI}}{\text{Total No. Births}} = (\text{proportion}_{<25})(1)X + (\text{proportion}_{25-29})(\text{RR}_{25-29})X + (\text{proportion}_{30-34})(\text{RR}_{30-34})X + (\text{proportion}_{35-39})(\text{RR}_{35-39})X + (\text{proportion}_{\geq 40})(\text{RR}_{\geq 40})X,$$

where X = the absolute risk in the referent group. The equation was solved for X, and X was multiplied by each RR to obtain a birth-prevalence rate for each age group.

Results

Of the 170 infants with trisomy 21 ascertained for the study, 15 died or were adopted before they could be included in the study. The families of 130 of the remaining 155 infants (84%) agreed to participate in the study. The parental origin of the extra chromosome 21 could not be determined for 17 case infants; eight infants required repeat blood samples, and the loci studied for 9 case infants were uninformative. This meant 113 cases were informative with respect to parental origin. Of the 267 control infants identified, 179 (67%) agreed to participate in the study. Of the total birth population (192,597), 0.04% of the mothers' ages were missing from vital records, and 19% of the fathers' ages were missing.

Results of the DNA analysis revealed that 86% of the trisomy 21 cases were maternally derived, 9% were paternally derived, and 5% were due to mitotic nondisjunction (table 1). Of the maternally derived cases, 75% of the errors occurred during MI, and 25% occurred during MII. Eight of the maternally derived cases were uninformative with respect to meiotic stage of origin. Of the paternally derived cases, 50% were MI errors, and 50% were MII errors. Two of the paternally derived cases were uninformative with respect to meiotic stage.

Mean maternal and paternal ages were determined for the trisomy 21 subgroups (parent and meiotic stage of origin), the control infants, and the birth population (table 1). Compared with the mean age of control mothers, the mean age of case mothers was significantly higher for all maternally derived cases (t test, $P < .001$), MMI cases ($P < .02$), and MMII cases ($P < .008$). The mean age of mothers for MMII cases was 2.5 years higher than the mean age of mothers for MMI cases but was not statistically significant ($P = .18$). Although the differences were not statistically significant, compared with the mean age of control fathers, the mean age of case fathers was lower for all paternally derived cases ($P = .76$), paternal MI cases ($P = .27$), and paternal MII cases ($P = .60$). Mothers and fathers of the infants with mitotic errors had higher mean ages than the control parents, but these differences were not statistically significant.

Table 1

Parental Origin and Meiotic Stage of Trisomy 21 Cases and Mean Parental Age of Case Infants, Control Infants, and Birth Population, Atlanta, Georgia, 1989–1993

Parental and Meiotic Origin	Frequency	Proportion	Mean Maternal Age ± SD (years)	Mean Paternal Age ± SD (years)
Maternal:				
Meiosis I (MI)	67	MI/(MI + MII) = 67/89 = 75.3%	29.5 ± 6.8	30.9 ± 6.1
Meiosis II (MII)	22	MII/(MI + MII) = 22/89 = 24.7%	32.0 ± 7.3	34.1 ± 7.9
Meiosis error unknown	8		27.9 ± 5.9	27.7 ± 4.6
Subtotal	97	Mat/All = 97/113 = 85.8%	29.9 ± 6.8	31.4 ± 6.6
Paternal:				
Meiosis I (PI)	4	PI/(PI + PII) = 4/8 = 50.0%	21.0 ± 5.5	24.8 ± 7.1
Meiosis II (PII)	4	PII/(PI + PII) = 4/8 = 50.0%	25.0 ± 4.5	27.8 ± 6.2
Meiosis error unknown	2		29.0 ± 4.2	39.0 ± 5.7
Subtotal	10	Pat/All = 10/113 = 8.8%	24.2 ± 5.4	28.8 ± 8.0
Mitotic errors	6	Mitotic/All = 6/113 = 5.3%	29.5 ± 6.2	31.3 ± 5.6
Total informative cases	113		29.4 ± 6.9	31.2 ± 6.7
Controls	179		27.2 ± 6.0	29.6 ± 6.4
Atlanta population	192,597		26.9 ± 5.9	30.3 ± 6.4

For the analysis of maternally derived trisomy 21, relative risk was estimated for five groups of maternal and paternal ages by use of logistic regression. For comparison, the ORs from the case-control analysis are presented alongside the RRs from the case-population analysis (table 2). Risk tended to increase with increasing maternal age for all maternally derived cases. This trend was also seen when the MMI and MMII cases were considered separately. According to the case-control analysis, compared with women <25 years old, women aged 35–39 years had a 3.7-fold increased risk for MI errors and a 62.8-fold increased risk for MII errors. For women ≥40 years of age, the risk increased 5.2-fold for MI errors and remained high but slightly less for MII errors (OR = 51.4). The RRs for the case-population analysis show the same trends as the ORs from the case-control analysis, but the magnitude of the risks in the older-age groups is slightly higher. From the ORs and RRs, it is evident that paternal age has no effect on the risk of maternally derived trisomy 21. We were not able to estimate the risk of paternally derived trisomy 21 due to maternal and paternal age because there were too few cases.

Using the RRs from the case-population analysis, we estimated the birth-prevalence rates for all maternally derived trisomy 21, MMI, and MMII by maternal and paternal age groups (fig. 1). The graphs show the rates per 1,000 live births. As with the birth-prevalence rates for all Down syndrome, the maternal age curves for both MMI and MMII errors are nearly J-shaped, with a steep increase beginning at 35 years of age. The birth-prevalence rate of MMI is 0.4/1,000 births for women <25 years of age and rises to 1.2/1,000 births for women 35–39 years of age and to 4.2/1,000 births for women ≥40 years old. The birth-prevalence rate of MMII is 0.03/1,000 births for women <25 years of age and rises to 0.6/1,000 births for women 35–39 years of age and to 1.9/1,000 births for women ≥40 years of age. The rates are greater for MI errors than for MII errors, even though the estimated relative risks were higher for MII errors, reflecting the greater frequency of MI errors in the population. The birth-prevalence rates of MMI and II by paternal age (fig. 1) show that paternal age has no effect on the population rates of maternally derived trisomy 21.

Discussion

Using a population-based, case-control study, we have determined the proportion of parental and meiotic subgroups of trisomy 21 and have estimated the effect of maternal and paternal age on the risk of maternally derived trisomy 21. In this population, nearly 90% of the trisomy 21 cases were maternally derived, and the majority of these cases resulted from MI errors. Nine percent of the cases were paternally derived, with an equal number due to meiosis I and II errors. These results are consistent with those reported by others (Antonarakis et al. 1991, 1992; Sherman et al. 1991), although ours is the first such study to be population based.

Table 2

Estimated Relative Risk (Adjusted for Spouse's Age) for Maternally Derived Trisomy 21 Associated with Maternal and Paternal Age for the Case-Control Analysis and the Case-Population Analysis, Atlanta, Georgia, 1989–1993

		Case-Control Analysis				Case-Population Analysis			
		Maternal Age		Paternal Age		Maternal Age		Paternal Age	
Trisomy 21 Subgroup	Age Groups	OR	95% CI	OR	95% CI	RR	95% CI	RR	95% CI
All maternal (N = 92)[a]	<25	Ref.	...	Ref.	...	Ref.	...	Ref.	...
	25–29	1.29	(.5–3.2)	.58	(.2–1.4)	1.02	(.5–2.2)	.61	(.3–1.3)
	30–34	2.22	(.8–6.1)	.46	(.2–1.3)	2.09	(.9–4.7)	.51	(.2–1.2)
	35–39	5.29	(1.6–17.8)	.28	(.1–1.0)	4.11	(1.7–10.2)	.34	(.1–.9)
	≥40	6.54	(1.4–29.5)	.59	(.2–2.3)	12.68	(4.3–37.8)	.45	(.2–1.2)
Maternal meiosis I (N = 66)[a]	<25	Ref.	...	Ref.	...	Ref.	...	Ref.	...
	25–29	1.20	(.5–3.2)	.69	(.3–1.8)	0.95	(.4–2.2)	.71	(.3–1.7)
	30–34	1.80	(.6–5.4)	.50	(.2–1.6)	1.73	(.7–4.4)	.52	(.2–1.4)
	35–39	3.70	(1.0–14.0)	.42	(.1–1.6)	3.06	(1.1–8.9)	.48	(.2–1.5)
	≥40	5.19	(1.0–27.4)	.56	(.1–2.5)	10.21	(2.8–37.7)	.40	(.1–1.4)
Maternal meiosis II (N = 20)[a]	<25	Ref.	...	Ref.	...	Ref.	...	Ref.	...
	25–29	5.14	(.5–50.6)	.10	(.0–1.2)	3.46	(.4–28.5)	.18	(.0–1.4)
	30–34	16.42	(1.1–240.5)	.18	(.0–1.9)	10.56	(1.2–91.4)	.28	(.0–1.7)
	35–39	62.81	(3.4–999.4)	.04	(.0–.6)	21.63	(2.2–213.2)	.09	(.0–.8)
	≥40	51.42	(2.3–999.0)	.29	(.0–4.1)	64.83	(5.5–764.8)	.38	(.1–2.8)

NOTE.—OR = odds ratio; RR = rate ratio; CI = confidence interval; Ref. = reference group.

[a] Number of cases included in regression models is less than totals from table 1 because of missing paternal ages.

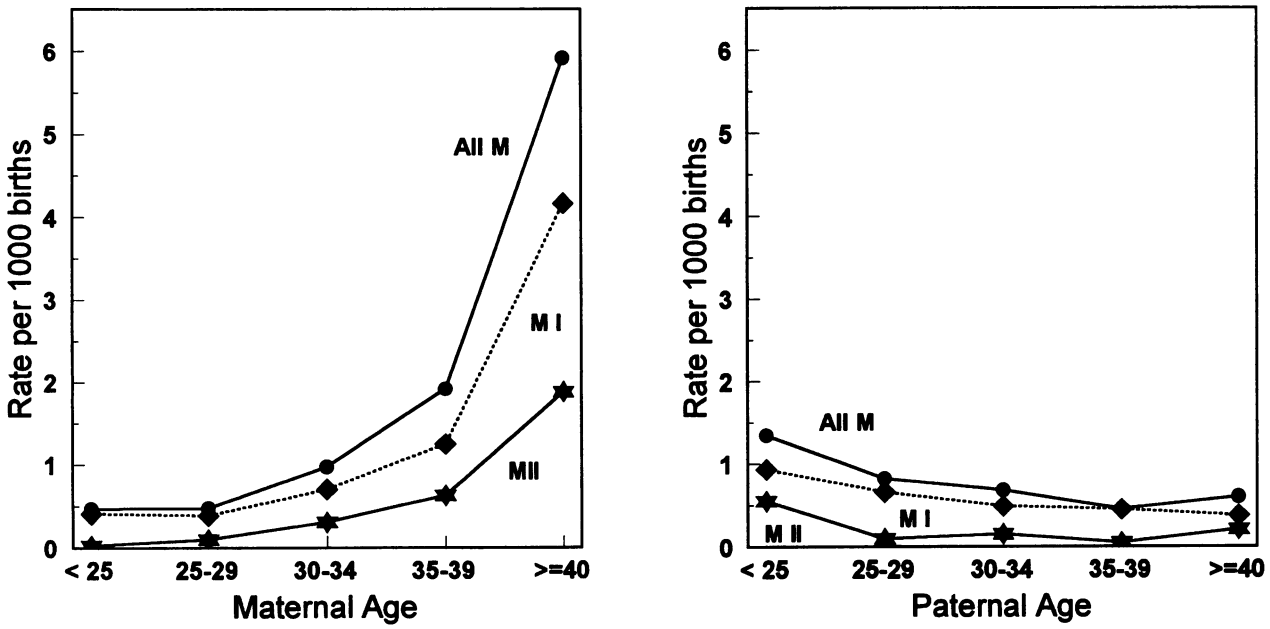

Figure 1 Estimated birth-prevalence rates (adjusted for spouse's age) of maternally derived trisomy 21 by maternal and paternal age, Atlanta, Georgia, 1989–1993. All M = maternally derived cases; MI = maternal meiosis I cases; MII = maternal meiosis II cases.

The results of the logistic regression analysis showed that advanced maternal age was a risk factor for both MMI and MMII errors. The estimated relative risks due to advanced maternal age were greater for MII errors than for MI errors, but the birth-prevalence rates were greater for MI errors. MMI errors were approximately three times more prevalent in the population than were MII errors. Although we did not study the parental age effect on the mitotic errors, research to date suggests that mitotic errors are not associated with advanced maternal age (Antonarakis et al. 1993).

Prior studies of trisomy 21 were limited by comparing only mean parental ages. Mean age does not account for differences in the age distribution of populations, nor does it describe the J-shaped nature of the risk curve for maternal age and trisomy 21. By estimating the relative risk for specific age intervals and adjusting for spouses'ages, we were able to estimate the independent effects of maternal and paternal age. One of the strengths of this population-based study was having two comparison groups—the randomly selected control group and the birth population for the five-county area of metropolitan Atlanta. Although the participation rate for the control group was only 67%, we were able to compare the age distribution of parents in the control group with the age distribution of parents in the birth population and were reassured that the distributions were similar. More important, we were able to reproduce our estimated relative risks in both the case-control and case-population analyses. Although the case-population analysis yielded higher relative-risk estimates overall than did the case-control analysis, the trends were similar, and, in light of the number of cases studied and the resulting 95% confidence limits, the estimates were within the same range, thus confirming our findings.

Another unique aspect of this study, because it was population based, was the use of the RRs to estimate birth-prevalence rates. Although the ORs derived from the case-control analysis are a good approximation of risk (because trisomy 21 is such a rare event), the birth-prevalence rates derived from the population rates depict the actual prevalence of trisomy 21 for each parental age group on an absolute rather than a relative scale.

A limiting factor in this study was the impact of prenatal diagnosis. In this population, it has been estimated that $\geq$56% of women $\geq$35 years of age have prenatal testing done (C. A. Huether, S. Karam, J. H. Priest, S. Guckenberger, L. D. Edmonds, E. L. Krivchenia, J. A. Moskovitz, and D. May, unpublished information), and, if the fetus is found to have trisomy 21, ~90% of the women choose to terminate the pregnancy (Drugan et al. 1990). The impact of this on our study is an underestimation of risk for advanced maternal ages and lower birth-prevalence rates of trisomy 21 for women >35 years of age. In fact, our birth-prevalence rates of trisomy 21 for women >35 years of age are about half the prevalence rates that were reported before prenatal diagnosis was common practice (Adams et al. 1981). A recent study of the epidemiology of Down syndrome in metropolitan Atlanta found that terminations of pregnancies involving trisomic fetuses dramatically lowered

the birth-prevalence rates of Down syndrome enough to offset the increase in birth prevalence that would have resulted from higher average maternal age at birth (Krivchenia et al. 1993). If prenatal diagnoses were not a factor in this population, we would expect steeper birth-prevalence curves for women beginning at 35 years of age.

The mechanisms by which advanced maternal age is associated with trisomy 21 are still unclear, but findings from this study provide further clues to the association between advanced maternal age and the timing of the meiotic errors. The association with meiosis I does not pinpoint the timing of the error; however, the association with meiosis II implies that there is at least one maternal age–related mechanism acting around the time of conception. To determine whether advanced maternal age has a differential effect on meiosis I and II errors and to determine whether there is a paternal age effect, more data are needed on the frequency of trisomy 21 among women $\geq$35 years, paternally derived trisomy 21, and the biological mechanisms that result in nondisjunction. Our study of trisomy 21 in metropolitan Atlanta is ongoing, and, with the collection of more data, we will continue to study parental age effects as well as their associations with risk factors and other exposures both at conception and before.

Acknowledgments

This work was supported by National Institutes of Health (NIH) contract NO1 HD92707 and NIH grants PO1 HD32111 and R01 HD21341.

References

Adams MM, Finley S, Hansen H, Jahiel RI, Oakley GP Jr, Sanger W, Wells G (1981) Utilization of prenatal genetic diagnosis in women 35 years of age and older in the United States, 1977 to 1978. Am J Obstet Gynecol 139:673–677

Antonarakis SE, Avramopoulos D, Blouin JL, Talbot CC, Schinzel AA (1993) Mitotic errors in somatic cells cause trisomy 21 in about 4.5% of cases and are not associated with advanced maternal age. Nat Genet 3:146–149

Antonarakis SE, Down Syndrome Collaborative Group (1991) Parental origin of the extra chromosome in trisomy 21 as indicated by analysis of DNA polymorphisms. N Engl J Med 324:872–876

Antonarakis SE, Petersen MB, McInnis MG, Adelsberger PA, Schinzel AA, Binkert F, Pangalos C, et al (1992) The meiotic stage of nondisjunction in trisomy 21: determination by using DNA polymorphisms. Am J Hum Genet 50:544–550

Drugan A, Greb A, Johnson MP, Krivchenia EL, Uhlmann WR, Moghissi KS, Evans MI (1990) Determinants of parental decisions to abort for chromosome abnormalities. Prenat Diagn 10:483–490

Erickson JD (1978) Down syndrome, paternal age, maternal age, and birth order. Ann Hum Genet 41:289–298

Hassold TJ, Jacobs PA (1984) Trisomy in man. Annu Rev Genet 18:69–97

Hook EB, Cross PK, Jackson L, Pergament E, Brambati B (1988) Maternal age–specific rates of 47,+21 and other cytogenetic abnormalities diagnosed in the first trimester of pregnancy in chorionic villus biopsy specimens: comparison with rates expected from observations at amniocentesis. Am J Hum Genet 42:797–807

Hook EB, Cross PK, Schreinenmachers DM (1983) Chromosomal abnormality rates at amniocentesis and in live-born infants. JAMA 249:2034–2038

Hook EB, Lamson SH (1990) Rates of Down's syndrome at the upper extreme of maternal age: absence of a "leveling" effect and evidence for artifacts resulting from analyses of rates by five-year maternal age intervals. Am J Epidemiol 111:75–80

International Clearinghouse for Birth Defects Monitoring Systems (1991) Congenital malformations worldwide. Elsevier Science, New York, pp 157–159

Janerich DT, Bracken MB (1986) Epidemiology of trisomy 21: a review and theoretical analysis. J Chron Dis 39:1079–1093

Krivchenia E, Huether CA, Edmonds LD, May DS, Guckenberger S (1993) Comparative epidemiology of Down syndrome in two United States populations, 1970–1989. Am J Epidemiol 137:815–828

Lynberg MC, Edmonds LD (1992) Surveillance of birth defects. In: Halperin W, Baker EL (eds) Public health surveillance. Van Nostrand Reinhold, New York, pp 157–177

Sherman SL, Petersen MB, Freeman SB, Hersey J, Pettay D, Taft L, Frantzen M, et al (1994) Non-disjunction of chromosome 21 in maternal meiosis I: evidence for a maternal age-dependent mechanism involving reduced recombination. Hum Mol Genet 3:1529–1535

Sherman SL, Takaesu N, Freeman SB, Grantham M, Phillips C, Blackston RD, Jacobs PA, et al (1991) Trisomy 21: association between reduced recombination and nondisjunction. Am J Hum Genet 49:608–620