Ethnic Differences in the Impact of Advanced Maternal Age on Birth Prevalence of Down Syndrome

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A B S T R A C T

Objectives. This study explored whether ethnic differences in the impact of advanced maternal age on the risk of Down syndrome might reflect differences in use of prenatal diagnostic technologies.

Methods. Maternal age-specific odds of Down syndrome and amniocentesis use were compared among African Americans, Mexican Americans, and non-Hispanic Whites via birth data for the years 1989 to 1991.

Results. The odds ratio and population attributable risk of Down syndrome due to maternal age of 35 years or older were highest for Mexican Americans, intermediate for African Americans, and lowest for non-Hispanic Whites.

Conclusions. Advanced maternal age has a greater impact on the risk of Down syndrome for African American and, particularly, Mexican American women than for non-Hispanic White women. This difference in impact might reflect lower availability or use of prenatal diagnostic technologies. (*Am J Public Health.* 2000;90:1778–1781)

Down syndrome is the most commonly recognized human malformation complex and is the foremost known genetic cause of mental retardation.[1,2] The established risk factors for Down syndrome include advancing maternal age and, to a quantitatively lesser degree, family history of trisomy or relevant chromosomal rearrangements.[1] For the past 3 decades, there has been a consistent trend toward delayed childbearing in the United States.[3] This trend in the population's maternal age structure, as expected, has been shown to increase the prevalence of fetuses affected by trisomy 21, or Down syndrome.[4]

Prenatal screening methods and conclusive diagnostic techniques are available for early-pregnancy detection of Down syndrome. Current noninvasive screening strategies include the use of maternal serum biochemical methods[5] and, to an increasing extent, early-pregnancy ultrasound evaluation for anatomic markers associated with aneuploidy.[6,7] Definitive prenatal diagnosis, however, requires invasive fetal testing, most commonly by amniocentesis, occasionally by chorionic villus sampling, and in rare instances by fetal blood sampling.

Traditionally, invasive fetal testing has been offered to empirically "high-risk" groups, including (1) women of "advanced maternal age," defined somewhat arbitrarily as 35 years or older at time of delivery, and (2) selected women with a relevant family history. With the expanding use of screening methods, the indications for invasive fetal testing have been extended to previously "low-risk" women who have become "high risk" by virtue of abnormal biochemical screening or suspicious anatomic markers detected at a screening ultrasound examination. Women choosing to undergo prenatal diagnostic procedures are known to exhibit high rates of abortion when an affected fetus has been cytogenetically identified.[8]

Previous studies have evaluated ethnic differences in the incidence or birth prevalence of Down syndrome in the state of California[9] and in 17 states that have population-based birth defects surveillance programs.[10] However, these studies have not compared the population-level impact of advanced maternal age on birth prevalence of Down syndrome among different ethnic groups by means of national birth cohort data. Furthermore, previous studies have not analyzed the differential rates of usage of prenatal diagnostic services such as amniocentesis among different ethnic groups at the national level or how such differences might be related to prevalence rates of congenital anomalies.

The objectives of our study were to (1) compare the population-level impact of advanced maternal age on the birth prevalence of Down syndrome in African Americans, Mexican Americans, and non-Hispanic Whites with national birth cohort data for the years 1989 to 1991 and (2) explore whether ethnic differences in the impact of advanced maternal age on the risk of Down syndrome in the United States might reflect differences in use of prenatal diagnostic technologies. Because optimum opportunities for benefiting from prenatal diagnostic technologies require early initiation of prenatal care, we also compared time of initiation of prenatal care among the 3 ethnic groups.

Methods

Data Source

We used birth data for the years 1989 to 1991 obtained from the National Center for Health Statistics.[11] The base population for the study consisted of live births to African American, Mexican American, and non-Hispanic White women in the United States during the study years. Live births with missing data on

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presence or absence of Down syndrome at birth were excluded from the study population. As a result, 13.8% of live births to African American women, 8.1% of live births to Mexican American women, and 11.2% of live births to non-Hispanic White women were excluded. After exclusion of these live births, the study population of 9 603 060 consisted of 1 672 808 live births to African American women, 1 043 873 live births to Mexican American women, and 6 886 379 live births to non-Hispanic White women.

Statistical Analysis

We used logistic regression to estimate the effect of maternal age on the birth prevalence of Down syndrome in the 3 ethnic groups. To assess the statistical significance of interactions between maternal ethnicity and age effects, we fitted nested models with and without interaction terms for maternal age and ethnicity and used likelihood ratio tests to examine the significance of interactions.[12] To compare the likelihood of amniocentesis use among the groups, we used a Mantel–Haenszel analysis of age-specific odds of amniocentesis use and tested for significant interactions between maternal age and ethnicity.[13,14] To assess the population-level impact of advanced maternal age, we used the proportion of mothers 35 years or older and the odds ratio for Down syndrome associated with advanced maternal age to calculate the attributable fractions for the population.[14,15] The Stata statistical package[16] was used in conducting all analyses.

Results

Figure 1 presents the results of the analysis comparing the effects of advanced maternal age on the birth prevalence of Down syndrome among African Americans, Mexican Americans, and non-Hispanic Whites. The results show the well-known exponential rise of the risk for Down syndrome with advancing maternal age for all 3 groups (Figure 1). However, there were significant interactions between maternal age and ethnicity effects (likelihood ratio χ^2, $P<.0001$), indicating that the effect of maternal age on the birth prevalence of Down syndrome was significantly different among the 3 groups. The odds ratio and the population attributable risk of Down syndrome due to maternal age of 35 years or older were highest for Mexican Americans (odds ratio [OR]=6.5, 95% confidence interval [CI]=5.4, 7.7, population attributable risk [PAR]=28%), intermediate for African Americans (OR=5.2, 95% CI=4.3, 6.3, PAR=19%), and lowest for non-Hispanic Whites (OR=3.2, 95% CI=3.0, 3.5, PAR=17%).

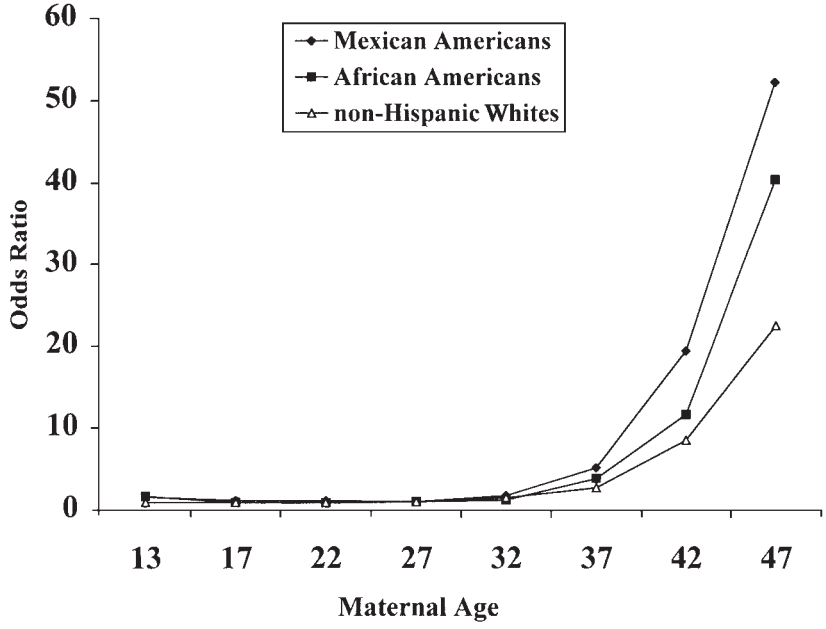

FIGURE 1—Risk for Down syndrome at birth, by maternal age and ethnicity: United States, 1989–1991 (likelihood ratio test for significance of interactions between maternal age and race/ethnicity effects, *P*<.0001).

Advanced maternal age had a greater impact (higher population attributable risk) on birth prevalence of Down syndrome for Mexican American and African American women, even though a significantly lower proportion of Mexican American and African American women were 35 years or older. The percentages of live births to women 35 years or older were approximately 9.4% among non-Hispanic Whites, 7.0% among Mexican Americans, and 5.7% among African Americans ($P<.001$).

Mantel–Haenszel analysis of age-specific odds of amniocentesis use for the 3 groups showed that non-Hispanic White women had the highest rates, while African American women were less likely and Mexican American women least likely to use amniocentesis (Table 1). Among all age groups, but particularly women aged 35 to 39 years and women 40 years or older, African American and Mexican American women had odds of amniocentesis use that were about two thirds and one third the odds, respectively, of their non-Hispanic White counterparts ($P<.001$). The greatest ethnic disparities in odds of amniocentesis use were found for Mexican American women aged 35 to 39 years (OR=0.30, 95% CI=0.29, 0.31) and 40 years or older (OR=0.26, 95% CI=0.24, 0.28) in comparison with their non-Hispanic White counterparts.

In addition, the Mantel–Haenszel analysis of age-specific odds of first-trimester (1–3 months) initiation of prenatal care showed that non-Hispanic White women were about 3 times more likely than Mexican American and African American women to initiate prenatal care during the first trimester of their pregnancy. The greatest disparities in the odds of first-trimester initiation of prenatal care were found for Mexican American women aged 30 to 34 years (OR=0.21, 95% CI=0.20, 0.21) and 35 to 39 years (OR=0.22, 95% CI=0.21, 0.22) in comparison with their non-Hispanic White counterparts.

Discussion

Our results suggest that advanced maternal age has a greater impact on the risk of Down syndrome for African American and, particularly, Mexican American women than for non-Hispanic White women in the United States. These findings are consistent with data from previous studies showing ethnic differences in the incidence or birth prevalence of Down syndrome from analysis of state-level population data.[9,10,17] Analysis of age-specific odds showed that African American women and, to a greater extent, Mexican American women were substantially less likely to use amniocentesis. This observation was particularly true for African American and Mexican American women 35 years or older. This set of findings is consistent with the hypothesis that ethnic differences in the impact of advanced maternal age on the risk of Down syndrome in the United States

TABLE 1—Odds of Amniocentesis Use, by Age and Ethnicity of Mother: United States, 1989–1991

	African Americans		Mexican Americans	
Maternal Age, y	Odds Ratio[a]	95% Confidence Interval	Odds Ratio[a]	95% Confidence Interval
<20	0.72	0.70, 0.75	0.74	0.71, 0.78
20–29	0.78	0.76, 0.79	0.69	0.68, 0.71
30–34	0.60	0.59, 0.62	0.54	0.52, 0.56
35–39	0.42	0.41, 0.43	0.30	0.29, 0.31
>40	0.43	0.40, 0.45	0.26	0.24, 0.28
All[b]	0.60	0.60, 0.61	0.50	0.50, 0.51

[a]Reference group: non-Hispanic White mothers.
[b]Mantel–Haenszel estimate of age-adjusted combined odds ratio of amniocentesis use for African Americans/Mexican Americans as compared with non-Hispanic Whites; test for heterogeneity of odds ratios (significance of maternal age/ethnicity interaction), $P < .0001$.

might reflect differences in women's use of prenatal diagnostic technologies.

We are not aware of any evidence to suggest that there might be biological reasons for the observed age-related differences in birth prevalence of Down syndrome among the 3 ethnic groups. Previous studies have reported ethnic variations in gestational age–specific levels of biochemical screening markers, including alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol.[18,19] In one study,[18] the same general pattern of differences was observed for all 3 markers, and the authors concluded that averaging the values for all ethnic groups tends to inappropriately lower the calculated Down syndrome risks for African American and Asian women. Another study[19] of ethnic differences in levels of biochemical screening markers also showed significant differences, but the authors concluded that such differences would be expected to have only a minimal effect on the odds of detecting Down syndrome. The results of neither study suggest that ethnic differences in levels of biochemical markers might be responsible for the substantial magnitude of the age-related differences in risk of Down syndrome or use of amniocentesis observed among the 3 ethnic groups in our study.

However, the possibility that the age-related differences observed in this study might be, to some extent, biological in origin or have some other explanation unrelated to use of prenatal diagnostic technologies cannot be excluded. On the other hand, given our findings of marked ethnic variations in amniocentesis use, differences in access to or use of prenatal diagnostic services among women in the 3 ethnic groups seem a more plausible explanation.

Our analyses were based on birth certificate data, which are likely to represent underestimates of the true birth prevalence of Down syndrome,[10] owing to incomplete case ascertainment or reporting. There may also be differential underdiagnosis or reporting by maternal ethnicity. However, a pattern of ethnicity and age-specific biases in case ascertainment or reporting that would produce the results observed in our study seems unlikely. Specifically, differential misclassifications are unlikely to result in higher estimates of age-related increases for Mexican Americans and African Americans. Such diagnostic or reporting biases would require substantial overestimation of age-related increases in Down syndrome for Mexican Americans and African Americans or substantial underestimation of age-related increases for non-Hispanic Whites. There is no evidence from previous studies that would predict such a pattern of differential misclassification. Therefore, even though birth certificate data are likely to underestimate the true birth prevalence of Down syndrome, there is no reason to believe that there is much greater underreporting or less complete case ascertainment for non-Hispanic White women 35 years or older than for their African American and (more so) Mexican American counterparts.

Birth certificate data may also represent underestimates of amniocentesis use and, furthermore, do not specify the indication for or the timing of the procedure. Although it is possible that underreporting of prenatal diagnostic procedures is correlated with ethnicity or age of the mother, we have no evidence to suggest that such a phenomenon explains the ethnic differences observed in our study. Previous studies have identified similar racial patterns of amniocentesis use.[9,17,20] Given the nature of the data used for this study, our findings need to be confirmed and elaborated by other studies that can measure amniocentesis use more precisely.

Possible explanations for lower use of amniocentesis among Mexican American and African American women also need further study. If women are to have optimum opportunities for benefiting from prenatal diagnostic technologies, they need to initiate prenatal care early in their pregnancies. Our results regarding timing of initiation of prenatal care suggest that late initiation or lack of such care might be one impediment to African American and Mexican American women's access to prenatal diagnostic technologies. Because African American women and, to a greater extent, Mexican American women are less likely to initiate prenatal care during the first trimester of their pregnancies, lower rates of amniocentesis use among these women might be related in part to their late initiation or lack of prenatal care.

Whatever might be the role of timing of initiation of prenatal care, however, issues relevant to access and use of prenatal diagnostic technologies are clearly much more complex than timing or adequacy of prenatal care alone. Important issues to consider include a host of individual, family, and system-related factors, such as parental preferences, health insurance coverage, differences in the content and quality of prenatal care, and specific public and private policies regarding prenatal diagnostic and intervention services.

There are relatively few data on ethnic (or, in general, socioeconomic) differences in access to prenatal diagnostic services. Nor are there sufficient data regarding how women in different ethnic groups reach their decisions about undergoing prenatal diagnosis, how they perceive their reproductive risks, and how they make their choices about continuation or termination of pregnancy in the event of discovering a fetal anomaly.[21] The role of socioeconomic and cultural factors as determinants of access to and choices regarding prenatal diagnostic services needs further study.

In conclusion, the results of our study of US birth data suggest that advanced maternal age (35 years or older) has a greater impact on the risk of Down syndrome for infants born to African American and Mexican American women than for infants born to non-Hispanic Whites, even though a significantly lower proportion of Mexican American and African American mothers are in this age group. This finding might reflect the lower availability and use of prenatal diagnostic technologies among African American and, particularly, Mexican American women. □

Contributors

B. Khoshnood conceived the study and conducted the data analyses. B. Khoshnood and P. Pryde wrote the original draft of the paper, and S. Wall and K. Lee made substantial contributions to interpretation of the data and subsequent revisions of the manuscript. All the authors participated in interpreting the data and in editing or writing manuscript drafts.

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References

1. Bell J. The epidemiology of Down syndrome. *Med J Aust.* 1991;155:115–117.
2. Leck I. Structural birth defects. In: Pless IB, ed. *The Epidemiology of Childhood Disorders*. New York, NY: Oxford University Press Inc; 1994: 66–117.
3. Ventura SJ. Trends and variations in first births to older women, United States, 1970–86. *Vital Health Stat 21*. 1989;No. 47:1–27.
4. Baird PA, Sadovnick AD. Maternal age-specific rates for Down syndrome: changes over time. *Am J Med Genet*. 1988;29:917–927.
5. Haddow JE, Palomaki GE, Knight GJ, et al. Prenatal screening for Down syndrome with use of maternal serum markers. *N Engl J Med*. 1992; 327:588–593.
6. Benacerraf BR. The second-trimester fetus with Down syndrome: detection using sonographic features. *Ultrasound Obstet Gynecol*. 1996;7: 147–155.
7. Taipale P, Hiilesmaa V, Salonen R, Ylostalo P. Increased nuchal translucency as a marker for fetal chromosomal defects. *N Engl J Med*. 1997;337: 1654–1658.
8. Verp MS, Bombard AT, Simpson JL, Elias S. Parental decision following prenatal diagnosis of fetal chromosome abnormality. *Am J Med Genet*. 1988;29:613–622.
9. Bishop J, Huether C, Torfs C, Lorey F, Deddens J. Epidemiologic study of Down syndrome in a racially diverse California population, 1989–1991. *Am J Epidemiol*. 1997;145: 134–147.
10. Centers for Disease Control and Prevention. Down syndrome prevalence at birth—United States, 1983–1990. *MMWR Morb Mortal Wkly Rep.* 1994;43:617–622.
11. *1989, 1990, and 1991 Birth Cohort Linked Birth and Infant Death Data Set* [CD-ROM]. Hyattsville, Md: National Center for Health Statistics; 1996.
12. Hosmer D, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons Inc; 1989.
13. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22: 719–748.
14. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research.* New York, NY: Van Nostrand Reinhold; 1982:161.
15. Greenland S, Robins JM. Conceptual problems in the definition and interpretation of attributable fractions. *Am J Epidemiol*. 1988;128: 1185–1197.
16. *Stata, Version 5.0* [computer program]. College Station, Tex: Stata Corp; 1997.
17. Krivchenia E, Huether CA, Edmonds LD, May DS, Guckenberger S. Comparative epidemiology of Down syndrome in two United States populations, 1970–1989. *Am J Epidemiol*. 1993;137: 815–828.
18. O'Brien J, Dvorin E, Drugan A, Johnson M, Yaron Y, Evans M. Race-ethnicity-specific variation in multiple-marker biochemical screening: alpha-fetoprotein, hCG, and estriol. *Obstet Gynecol.* 1997;89:355–358.
19. Benn P, Clive J, Collins R. Medians for second-trimester maternal serum alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol: differences between races or ethnic groups. *Clin Chem.* 1997;43:333–337.
20. Sokal DC, Byrd JR, Chen AT, Goldberg MF, Oakley GPJ. Prenatal chromosomal diagnosis. Racial and geographic variation for older women in Georgia. *JAMA*. 1980;244:1355–1357.
21. Pryde PG, Drugan A, Johnson MP, Isada NB, Evans MI. Prenatal diagnosis: choices women make about pursuing testing and acting on abnormal results. *Clin Obstet Gynecol*. 1993;36: 496–509.