

Maternal Age and Malformations in Singleton Births

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Objective: To examine the effect of maternal age on incidence of nonchromosomal fetal malformations.

Methods: Malformations detected at birth or in the newborn nursery were catalogued prospectively for 102,728 pregnancies, including abortions, stillbirths, and live births, from January 1, 1988 to December 31, 1994. Maternal age was divided into seven epochs. Relative risks (RRs) were used to compare demographic variables and specific malformations. The Mantel-Haenszel χ^2 statistic was used to compare age-specific anomalies. Multiple logistic regression analysis was used to adjust for parity.

Results: Abnormal karyotypes were significantly more frequent in older women. After excluding infants with chromosomal abnormalities, the incidence of structurally malformed infants also was increased significantly and progressively in women 25 years of age or older. The additional age-related risk of nonchromosomal malformations was approximately 1% in women 35 years of age or older. The odds ratio for cardiac defects was 3.95 in infants of women 40 years of age or older (95% CI 1.70, 9.17) compared with women aged 20–24 years. The risks of clubfoot and diaphragmatic hernia also increased as maternal age increased.

Conclusion: Advanced maternal age beyond 25 years was associated with significantly increased risk of fetuses having congenital malformations not caused by aneuploidy. (Obstet Gynecol 2000;96:701–6. © 2000 by The American College of Obstetricians and Gynecologists.)

During the past decade, the proportion of women in the United States who gave birth after age 35 increased significantly. In 1996, there were approximately 399,510 births to women aged 35–39 years, 71,804 to women aged 40–44, and over 3000 to women aged 45–49 years.¹ Successful pregnancies are now being achieved with oocyte donations in women over age 50 and beyond natural menopause.² Recently, one such birth to a 63-year-old woman was publicized widely.³

Some of the most devastating adverse outcomes in older pregnant women are anomalies associated with chromosomal aberrations, especially aneuploidies, which occur in about one in 50 births to women at age 40.⁴ Increased aneuploidy rates are unequivocally related to advanced maternal age, but the effect of increased age on other congenital malformations is less clear. Each year the National Center for Health Statistics and the Centers for Disease Control and Prevention publish natality statistics of the entire United States, which include information on congenital malformations from birth certificates. Those agencies have cited significantly increased rates of fetal cardiac malformations and chromosomal anomalies with advanced maternal age.⁵ However, such reports have numerous shortcomings. For example, because individual congenital malformations have such low incidences, epidemiologic studies necessarily include large numbers of pregnancies. To accomplish that, information is gathered from indirect sources such as birth certificates, which often are incomplete and subject to ascertainment biases. Those reports and most similar investigations do not include information on malformations in stillborn fetuses or late abortions.

The demographic make-up of Parkland Hospital provides a unique opportunity to study congenital malformations. The large obstetric population almost entirely resides in Dallas County and its contiguous areas. Pregnancy outcomes, including stillbirths and in-hospital abortions, are carefully codified, verified, and entered in a computerized database. In a preliminary investigation,⁶ we ascertained the effects of maternal age on pregnancy complications in 20,525 women 20 years of age or older. Those pregnancies, delivered in 1987 and 1988, showed the expected increase in chromosomal abnormalities with maternal age. An unexpected finding, however, was an age-related increased incidence of nonchromosomal anomalies. With a much larger database that includes anomalies in stillbirths

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and abortuses, our purpose in the current study was to examine effects of maternal age on incidence of non-chromosomal fetal malformations.

Materials and Methods

Parkland Health and Hospital System is a public institution that serves women primarily of Dallas County. The obstetric service is staffed by residents, fellows, and faculty of the Department of Obstetrics and Gynecology of the University of Texas Southwestern Medical Center, Dallas, Texas. Our 7-year study of singleton births included calendar years 1988 through 1994. The start date coincided with the incorporation of maternal serum alpha-fetoprotein (AFP) screening with other prenatal diagnostic procedures already offered.

Antepartum and intrapartum outcomes for mothers and infants are collected at delivery by obstetric nurses. Data are verified by perinatal research nurses, then stored electronically. Information on malformations of all live infants is abstracted from the newborn nursery record from birth until discharge or death. Malformations in live infants are confirmed by neonatology fellows and faculty of the Department of Pediatrics, and all abnormal neonates are evaluated by Board-certified clinical geneticists. Uncertain discharge diagnoses are flagged and electronic records completed when diagnoses are resolved. Data are incorporated from neonatal examinations and follow-up visits.

Maternal and infant records also are kept prospectively for all stillbirths. Malformations are described by maternal-fetal medicine attending faculty, and autopsies are done by pediatric pathology faculty in more than 70% of cases. Those are reviewed monthly by a committee of maternal-fetal medicine fellows and faculty, perinatal research nurses, and perinatal pathology faculty. That information is also maintained in the electronic database.

Beginning in 1990, women with pregnancies that were terminated in-hospital after 13 weeks and before viability (defined as fetal weight of 500 g) also were included in the electronic database. Those included spontaneous and missed abortions and all pregnancy terminations done electively for malformed fetuses. Pathology reports were reviewed in all cases. For this report, fetuses or neonates with chromosomal abnormalities were analyzed separately.

Outcomes were analyzed by maternal age groups used by the National Center for Health Statistics.⁵ Each anomaly was diagnosed by using the International Classification of Diseases, 9th edition. Of over 100 categories of malformations, the most common ones were evaluated individually for this study: anencephaly, meningocele-meningomyelocele, hydrocephaly,

Table 1. Nonchromosomal and Chromosomal Abnormalities

	Total	Nonchromosomal infant anomaly	Abnormal karyotype
No. of live infants (%)	101,198 (100)	3466 (3)	155 (0.2)
No. of stillbirths (%)	829 (100)	104 (12)	16 (2)
No. of second-trimester abortions	701 (100)	97 (14)	17 (2)
Total (%)	102,728 (100)	3667 (3)	188 (0.2)

microcephaly, cardiac malformations, tracheoesophageal fistula, esophageal atresia, omphalocele, gastroschisis, rectal atresia-stenosis, malformed genitalia, renal agenesis, cleft lip, cleft palate, syndactyly, adactyly, club foot, and diaphragmatic hernia. The remainder of malformations were grouped as follows: other central nervous system (CNS) anomalies, other circulatory or respiratory anomalies, other gastrointestinal anomalies, other urogenital anomalies, other musculoskeletal anomalies, and integumental anomalies. Abnormal karyotypes were classified as Down syndrome (trisomy 21) or other chromosomal abnormalities.

Demographic characteristics of women who gave birth to anomalous infants were compared with those of normal infants by using relative risks (RRs). The Mantel-Haenszel χ^2 test for trend was used to compare age-specific anomalies. For selected malformations, maternal age categories were compared with age group 20–24 years by using RRs. To adjust for effects of parity, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multiple logistic regression. The Pearson χ^2 statistic was used to compare incidence between two classifications. $P < .05$ was considered statistically significant. Relative risks and 95% CIs were estimated by using the Mantel-Haenszel procedure.⁷ Percentages were estimated as a direct proportion and 95% CI by using the exact method.⁸

Results

From 1988 to 1994, 102,728 singleton pregnancies met inclusion criteria and were analyzed. As shown in Table 1, those included 101,198 live infants who weighed more than 500 g. Among those, 3466 (3%) had structural malformations not caused by chromosomal abnormalities and 155 had abnormal karyotypes. There were 829 stillbirths during that period, 104 (12%) with at least one malformation and 16 with confirmed abnormal karyotypes. Another 701 women had spontaneous or induced second-trimester abortions with nonmacerated, analyzable fetuses. Ninety-seven (14%) of those had malformations and 17 had abnormal karyotypes.

Table 2. Maternal Age and Malformed Infants or Abortuses Not Caused by Chromosomal Abnormalities

	Maternal age in years							Total
	≤15	16–19	20–24	25–29	30–34	35–39	≥40	
No. of births or abortuses	3020	24,501	37,864	22,711	10,443	3,515	674	102,728 (100)
No. of nonchromosomal malformed infants or abortuses	111 (3.7)	859 (3.5)	1,312 (3.5)	879 (3.9)*	409 (3.9)*	153 (4.4)*	34 (5.0)*	3,757 (3.7)

* Significantly increased incidence ($P = .01, .03, .01,$ and $.03$) for maternal age categories 25–29, 30–34, 35–39, and ≥ 40 years, respectively, compared with women 20–24 years old (referent group).

Table 2 shows incidences of malformations not caused by chromosomal aberrations according to maternal age group. Using 20–24 years as the referent group, the incidence of malformations increased significantly and progressively in women 25 years of age or older.

The RR of karyotype abnormalities in relation to maternal age is shown in Figure 1. The rate of infants with abnormal chromosome complements increased from 1 per 1000 in women aged 15 or younger to 6.3 per 1000 for those 35–39 years of age and 23.7 per 1000 for those older than 40 years of age (P for trend $< .001$). Rates of Down syndrome increased from 0.5 per 1000 at age 15 or younger to 17.3 per 1000 in women aged 40 years or older ($P = .001$ for trend).

Selected maternal demographic characteristics were compared between women who delivered anomalous infants not caused by chromosomal abnormalities and those whose infants had no recorded birth defects. Nulliparas accounted for 39% of the population and were not over-represented in the group with anomalous infants. Thirty percent of our population was black, 17% was white, 50% was Hispanic, and 3% were of other

ethnicity. A table detailing the racial demographics and distribution parity for the entire population is available on request from the authors. As shown in Table 3, black women had significantly increased RR of anomalous infants not caused by chromosomal abnormalities compared with nonblack women in all but the two older age groups. Hispanic women in those same age groups had significantly reduced risk compared with other women.

Age-related trends were calculated for all malformations and groupings listed in the Methods section, and there were significant trends with increasing maternal age. Odds ratios for individual malformations significantly associated with maternal age are summarized in Table 4. The chance of cardiac defects was higher in infants of women older than 40 years of age (OR 3.95, 95% CI 1.70, 9.17) compared with women aged 20–24 years. The odds of club foot and diaphragmatic hernia also increased with maternal age. Increased rates of gastroschisis were significantly associated with decreasing maternal age (P for trend = $.001$). Rates of polydactyly also increased significantly with decreasing maternal age (P for trend = $.02$). After we adjusted for parity, the increased risk of gastroschisis and polydactyly in young mothers did not persist. Odds of cardiac defects, club foot, and diaphragmatic hernia in older mothers remained significantly increased.

Discussion

Our analysis offers at least three important findings about congenital malformations. We confirmed the well-known association of increased maternal age with chromosomal aberrations, especially aneuploidies. Also, women who were 25 years of age or older at delivery had significantly and progressively greater risk of having fetuses with nonchromosomal malformations compared with women 20–24 years old. By age 35 years, the additional age-related risk of having infants with nonchromosomal malformations was approximately 1%. For women aged 40 years or older the increase in risk was about 2.5% over that of women younger than age 25 years. Finally, we found a maternal

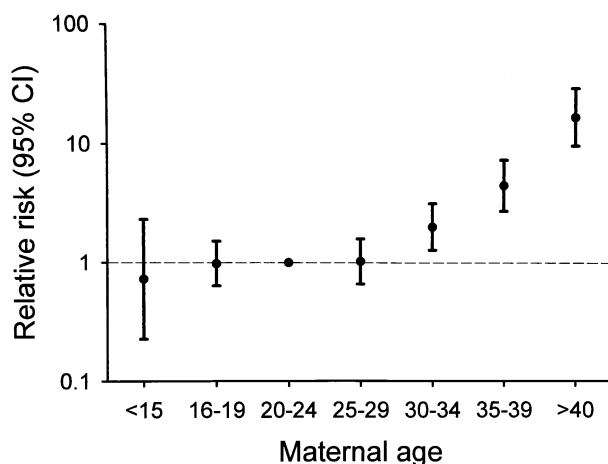


Figure 1. Relative risk and 95% confidence intervals (presented semi-logarithmically) for abnormal karyotypes compared with baseline risks at age 20–24 (P for trend $< .001$).

Table 3. Relative Risks (95% Confidence Intervals) of Nonchromosomal Anomalies by Maternal Race*

Race	Relative risk by maternal age in years (95% CI)						
	≤15	16–19	20–24	25–59	30–34	35–39	≥40
Black	1.46 [†] (1.01, 2.12)	1.22 [†] (1.07, 1.40)	1.33 [†] (1.19, 1.48)	1.48 [†] (1.29, 1.70)	1.47 [†] (1.20, 1.80)	1.28 (0.90, 1.80)	0.66 (0.26, 1.68)
White	1.02 (0.58, 1.80)	1.00 (0.84, 1.18)	0.93 (0.81, 1.07)	0.96 (0.80, 1.15)	1.18 (0.92, 1.51)	0.95 (0.61, 1.48)	0.71 (0.26, 1.99)
Hispanic	0.61 [†] (0.41, 0.92)	0.81 [†] (0.71, 0.92)	9.81 [†] (0.73, 0.90)	0.76 [†] (0.67, 0.86)	0.72 [†] (0.60, 0.87)	0.89 (0.65, 1.21)	1.38 (0.70, 2.72)
Other	2.62 (0.69, 9.92)	1.34 (0.77, 2.33)	1.01 (0.71, 1.44)	0.90 (0.64, 1.27)	0.65 (0.39, 1.09)	0.82 (0.41, 1.65)	1.23 (0.45, 3.38)

* Within each age group, a single race was compared with all others.

[†] Statistically significant risks.

age-related increased risk for specific nonchromosomal malformations. Cardiac defects, club foot, and diaphragmatic hernia all were increased with advanced maternal age.

Our results are at variance with those of other studies, so important methodologic considerations should be emphasized. Data collection of anomalous stillbirths, abortions, and live births was prospective and ongoing throughout the 7-year study. With few exceptions, those births were from a definable catchment area. Data were collected by direct examination of malformed fetuses and infants and included careful examination of stillborns with a necropsy rate of 70%. We included fetal malformations from elective and spontaneous terminations after 13 weeks and before attainment of fetal weight of 500 g.

Baird and colleagues⁹ did a similar analysis of data by using certificates from nearly 577,000 births in British Columbia from 1966–1981. Data from stillborns were not available, but attempts were made to include pregnancy terminations for anomalies before viability. However, only seven cases were added to almost 27,000 anomalous live infants. Those investigators found no

age-specific increase in nonchromosomal birth defects, although they reported a linear decrease with maternal age for patent ductus arteriosus and pyloric stenosis and a bell-shaped curve distribution for congenital hip dislocation with a peak at age 30 years.

Pradat¹⁰ examined data from two Swedish registries to analyze the effect of maternal age on congenital heart defects. From 1981–1986, nearly 574,000 live infants and stillbirths were delivered after 28 weeks, and serious malformations were catalogued. When 202 infants with known chromosomal anomalies were excluded (83% were Down syndrome), the incidence of congenital heart defects did not increase with maternal age. Those data were not collected until 28 weeks' gestation, so it is reasonable to conclude that many anomalies were not catalogued because the propensity of increased anomalies in preterm liveborns and stillborns is well documented. Those investigators also excluded fetuses that were terminated because of anomalies.

The National Center for Health Statistics⁵ analyzed the effects of advanced maternal age on risks of congenital malformations. Those data showed a significant trend of increasing congenital heart disease with ad-

Table 4. Odds Ratios (95% Confidence Intervals) for Specific Nonchromosomal Malformations by Maternal Age Group

Malformation	Odds ratio by maternal age in years (95% CI)						
	≤15	16–19	20–24	25–29	30–34	35–39	≥40
Gastroschisis	1.21 (0.27, 5.46)	1.68 (0.81, 3.44)	1.00	0.36 (0.08, 1.60)		0.40* (0.05, 3.07)	
Polydactyly	1.49 (0.94, 2.38)	1.16 (0.92, 1.46)	1.00	0.92 (0.72, 1.17)	0.83 (0.59, 1.16)	0.75 (0.43, 1.31)	0.55 (0.13, 2.24)
Cardiac abnormality	0.59 (0.27, 1.28)	0.87 (0.64, 1.17)	1.00	1.30 (0.98, 1.74)	1.38 (0.94, 2.03)	1.43 (0.77, 2.64)	3.95 [†] (1.70, 9.17)
Clubfoot	0.54 (0.13, 2.27)	0.84 (0.50, 1.44)	1.00	1.11 (0.65, 1.89)	1.66 (0.87, 3.13)	2.96 [†] (1.33, 6.56)	2.03 (0.27, 15.11)
Diaphragmatic hernia		1.24* (0.27, 5.62)	1.00	1.42 (0.23, 8.67)	3.44 (0.54, 21.8)	10.58 [†] (1.60, 69.8)	28.62 [†] (2.63, 311.1)

* Women 20–24 years are the reference group. Malformations associated with abnormal karyotypes have been excluded. Rates for these age groups have been combined due to small numbers.

[†] Statistically significant values.

vancing maternal age, but infants with chromosomal abnormalities were not considered separately in that large epidemiologic study. Advanced maternal age was indisputably associated with fetal karyotypic abnormalities; however, abnormal karyotype was also associated with cardiac malformations. To evaluate the influence of those important variables, we excluded women with known abnormal karyotypes from our analyses of other malformations. Despite that exclusion, cardiac defects remained significantly increased in women 40 years or older (OR 3.95, 95% CI 1.70, 9.17) compared with women 20–24 years old.

Another major shortcoming of using National Center for Health Statistics data to counsel women is that birth certificates are the sole source of information. The Center's reported rate of congenital heart disease for the entire U.S. population is only 1.13 per 1000 compared with our rate of 3.20 per 1000. Others have observed prevalences similar to ours.^{9–11} Using the incidence of Down syndrome as an "internal standard," the National Center for Health Statistics reported incidence of trisomy 21 was one per 1000 for women 35–39 years old and 3.7 per 1000 for those 40–49 years old. In our database, incidences for those two age groups were 5.1 per 1000 and 17 per 1000, respectively. Thus, underascertainment can be a problem when birth certificates only are used to obtain data.

That young maternal age is a risk factor for gastroschisis has been reported by several investigators over the past 2 decades.^{12–14} Our initial increased rates of polydactyly in younger mothers were similar to rates reported by Gittelsohn and Milham.¹⁵ The rate of polydactyly declined steadily across maternal ages, from 95 per 100,000 at age 20 years or younger to 40 per 100,000 over age 40 years. Those studies, however, did not account for parity. Our analysis suggests that parity might be a more important risk factor of those anomalies than maternal age.

One potential explanation for increased malformations in older women is ascertainment bias. Among approximately 600 women aged 35 years or older who deliver at our institution every year, about half receive genetic counseling and sonography, and only a third of that latter group choose amniocentesis. We do not perform sonography routinely in our general obstetric population, but nearly 60% of prenatal patients have at least one ultrasonographic examination. Thus, although ascertainment bias is a possibility, it is unlikely to account for significant increases in total birth defects.

Other explanations for increased risk as women age include the possibility that structural abnormalities are related to genetic defects that are currently unknown or undetectable. Accumulation of environmental expo-

sures over time also might have an effect. The unclear etiology of the increase calls for further research.

These observations are important for the many women who have delayed childbearing until the later years. The slight increase in selected malformations in fetuses of women at the extremes of reproductive age is a concern. When considered with other studies of childbearing in women of advanced maternal age,^{16–18} our data show that the maternal age-related risk of infants with nonchromosomal malformations is increased compared with that of younger women.

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