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Maternal-Age Effect in Aneuploidy: Does Altered Embryonic Selection Play a Role?

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SUMMARY

The age of mothers of children with trisomy 21 (47,+21) is elevated no matter if the extra chromosome is of maternal or paternal origin, and it has been postulated that decreasing maternal selection against affected conceptuses with advancing age might explain this observation. Since the absence of sufficient data on 47,+21 abortuses precludes a direct test of this hypothesis, we have taken an indirect approach. Pooled data from spontaneous abortions and live births with autosomal trisomies, XXY and XXX, were examined to determine the natural history of these aneuploid conceptuses and its relation to maternal age. The results are consistent with decreasing embryonic selection in older women.

INTRODUCTION

The most consistent epidemiologic finding in trisomy 21 Down syndrome (47,+21) is the strong association between the birth frequency of this disorder and maternal age. Most previous efforts to explain this relationship have focused on meiosis and the various influences on this process that might be related to aging. These approaches have all made the implicit assumption that the increase in 47,+21 observed at birth reflects an increase of aneuploid embryos at conception and that the majority of these trisomies arise from an error in maternal meiosis.

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Very recently, the assumption that maternal age acts solely through an increase in nondisjunction during the first maternal meiotic division has been challenged by evidence that in about 20% of live-born 47,+21 cases the extra chromosome comes from the father [1–6] and that a maternal-age effect is present whether the extra chromosome is paternally- or maternally-derived [7]. This implies that there may be a second mechanism responsible for the association between maternal age and the frequency of 47,+21 among live births that does not directly involve nondisjunction, and previous authors have postulated that a decrease in maternal selection against affected conceptuses with advancing age could be such a mechanism [8–11].

A direct test of the influence of maternal age on selection against 47,+21 conceptuses is precluded at the present time, since there are insufficient data on abortuses with this karyotype. However, an indirect approach that considers all conceptuses with an extra autosome or X chromosome is possible. We have investigated the natural history of such conceptuses using the theoretical framework described by Stein et al. [12] and pooled data from studies of spontaneous abortions and live births. The results suggest an association between maternal age and the probability of aborting a fetus with these trisomies consistent with decreasing embryonic/fetal selection in older women.

METHODS

The prevalence of chromosome anomalies at birth is a function of the incidence of these abnormalities at conception and of the probability of fetal survival to term. Since the data on conceptuses prior to a woman's recognition of her own pregnancy are presently inadequate for analyzing maternal-age effects, research in this area is limited to studies of pregnancies of at least 4-weeks gestation. When we refer, therefore, to recognized pregnancies, we mean those known to the woman and exclude those detected only biochemically [13]. We recognize, nevertheless, that losses of these earliest pregnancies may be extensive and that until their study is feasible, any estimate of the true incidence and full history of fetuses with chromosome abnormalities is impossible.

Adopting the notation of Stein et al. [12], if p represents the probability of an autosomal or X trisomy among recognized pregnancies; r_a, the probability that a fetus with an extra autosome or X chromosome aborts spontaneously; and r_n, the probability that a nontrisomic fetus aborts spontaneously, we can define p, r_a, and r_n in terms of the frequency of autosomal and X trisomies at birth (A), the frequency of spontaneous abortion among recognized pregnancies (B), and the frequency of trisomies among these spontaneous abortions (C) as follows:

$$p = A(1 - B) + BC$$

$$r_a = \frac{BC}{A(1 - B) + BC}$$

$$r_n = \frac{B(1 - C)}{1 - [A(1 - B) + BC]} .$$

We obtained the values of A, B, and C, each specific for a quinquennial maternal-age group, from the literature. To estimate A, the frequency among live births of all the triso-

mies that might arise from similar mechanisms (i.e., all autosomal trisomies, XXY and XXX; XYY is omitted because its origin is limited to a paternal nondisjunctional event and there is no age effect on p for it), we doubled the maternal-age-specific live-birth prevalence rates of 47,+21 found in three of the largest studies reported [14–16]. This is in accord with the many chromosome surveys of newborns, which show that 47,+21 represents half of all the chosen trisomies [17–25]. (We could not employ these newborn surveys directly to obtain the required trisomy rates, since most of the samples were small and, more importantly, the results were not always presented according to maternal age.) Implicit in this procedure is the assumption that autosomal and X trisomies among live births increase in frequency with maternal age at the same rate, a point that is discussed below (see DISCUSSION).

The rates for B, the frequency of spontaneous abortion among recognized pregnancies, are based directly on pooled data [26–28], while the rates for C, the frequency of trisomies among spontaneous abortions, were estimated from the most recent studies carried out in Hawaii and New York City [29]. In this report, maternal-age-specific data on only trisomic and euploid abortions are included; abortions with other age-independent chromosomal abnormalities (e.g., triploidy, tetraploidy, and monosomy X) are omitted. To calculate a rate of trisomy among all abortions, we assumed, therefore, that the reported specimens comprised 75% of the total and adjusted the denominators to include the missing nontrisomic abnormal specimens, 25% of the total in each age group [29].

We have considered A and B as true values, not as estimates, since they are based on large populations; only C has been assumed to be an estimate, and its variance for each maternal-age group was calculated. These values were then used to solve the equations for p, r_a, and r_n. To determine the confidence limits on the point estimates of these quantities, we solved each equation first with the age-specific value of C obtained from Hassold et al. [29] (and corrected for the missing karyotypically abnormal abortions) and then with this value of C plus and minus twice its standard error.

Finally, to obtain a rough estimate of the relative contributions of p and r_a to changes in the live-born trisomy rates, we calculated what these rates would be if only one of these factors varied with age. Thus, expected rates for each quinquennia were calculated (1) using the age-appropriate point estimate of r_a with the estimates of p and r_n from the previous age group and (2) using the age-appropriate point estimate of p with the estimates of r_a and r_n from the previous age group. The predicted differences in live-birth rates between age groups were then compared to the observed differences.

RESULTS

The rates of trisomy at birth, of spontaneous abortion among recognized pregnancies, and of trisomies among abortion specimens used in our calculations are shown in table 1 for each maternal-age group. The estimated values of p, r_a, and r_n are plotted in figure 1 with their confidence limits.

As can be seen, each factor—p, r_a, r_n—has a different relationship to maternal age. There is a marked increase in p, the frequency of autosomal and X trisomies among recognized pregnancies, with maternal age. Of more interest, however, is the association of r_a with maternal age. There is an increase in maternal selection against conceptuses with an extra autosome or X chromosome to age 25–29 and then a decrease, suggesting that the probability an affected fetus will be aborted decreases with maternal age beyond 30 years. Even though the confidence limits for the youngest and oldest age groups are fairly wide, there seems little doubt that the rate of abortion of trisomic pregnancies changes with maternal age. In contrast, the curve for r_n, the probability of abortion of a nontrisomic pregnancy, does not show as much variation with maternal age.

TABLE 1

POOLED RATES OF LIVE-BORN TRISOMJES [14–16], SPONTANEOUS ABORTION [26–28], AND TRISOMIC ABORTUSES [29]

Maternal age (yrs)	Rate of trisomy among live births (A)	Rate of spontaneous abortion among recognized pregnancies (B)	Frequency of trisomy among spontaneous abortions (± 2 SE) (C)
< 20	.00146	.1019	.1134 ± .0502
20–24	.00140	.1214	.1829 ± .0398
25–29	.00176	.1383	.2452 ± .0420
30–34	.00257	.1515	.2683 ± .0476
35–39	.00732	.1730	.3161 ± .0680
≥ 40	.03006	.2594	.4286 ± .1442

In assessing the relative contributions of p and r_a to the live-born trisomy rates, we looked only at women over 29 years of age. The increasing rate for r_a up to this age indicates that increases in the live-birth trisomy rate in these women are due to increases in p; after age 30, however, both p and r_a appear to be operating. For women up to 35–39 years, r_a appears to account for about two-thirds of the increase in live-birth rates between age groups; it explains only one-third of the increase between the 35–39 and the 40 and over groups. For these oldest women, p remains the more important factor. It should be emphasized, however, that these are only rough estimates of the roles of r_a and p, since they are based on changes between quinquennial age groups.

DISCUSSION

These data illustrate a maternal-age effect on the rate of abortion of conceptuses with an extra autosome or X chromosome. They suggest that the observed maternal-age effect on the rate of trisomy among live births may be explained by the joint contribution of a decreasing r_a and an increasing p in women over age 29. As can be seen, the difference between the highest and lowest point estimates of r_a (83.3%, 95.7%) is not large; nevertheless, it is a real difference and may play a substantial role in the birth prevalence of autosomal and X trisomies. (While there appears to be poorer selection against extra-chromosome conceptions at very young maternal ages as well, the data are still too few to be certain of this effect.)

In 1977, Stein et al. [30] reported briefly the results of a study that appears to have had a design similar to ours. They did not detect an association between maternal age and r_a, but the absence of details in the report prevented us from identifying the reason for the discrepancy between their conclusion and ours. However, when we applied our approach to the data they used (47,+21 rates, abortion rates), we did find an influence of age on r_a: women 40–49 had a lower r_a than either women 20–29 or 30–39. Since the 10-year age groupings required by the very limited data on abortions available at the time of this earlier study dilute the age trend for r_a, Stein et al. [30] may have assumed that the small absolute difference between younger and older women was not important.

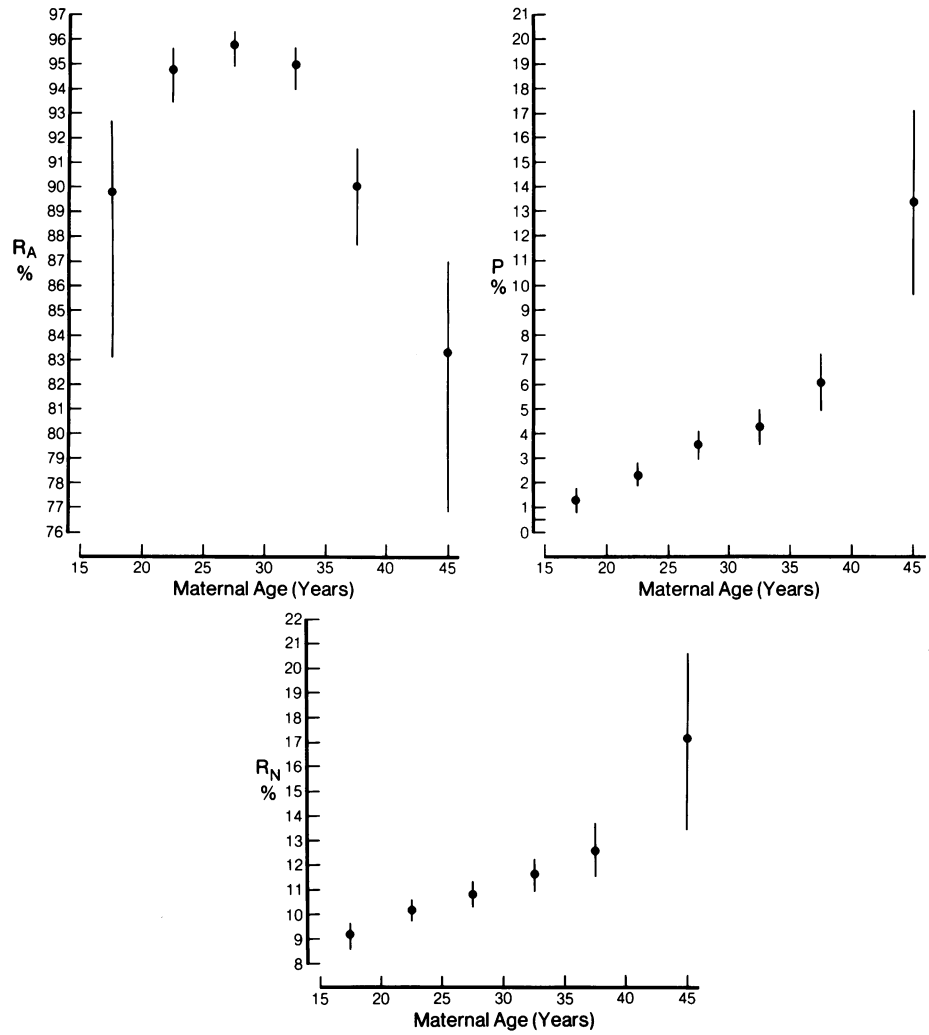

FIG. 1.—Values of p, r_a, and r_n by maternal age. *Left top:* the probability that a fetus with an extra autosome or X chromosome aborts spontaneously, r_a; *right top:* the probability of trisomy among recognized pregnancies, p; *bottom:* the probability that a nontrisomic fetus aborts spontaneously, r_n.

Our analysis of existing data, however, suggests that this difference is significant and that there is decreasing selection against pregnancies with an extra autosome or X chromosome with increasing maternal age. Because of the implications of this finding, the possibility that it is an artifact of our assumptions should be considered.

(1) To calculate the values of p, r_a, and r_n, we made use of pooled rates of Down syndrome and of spontaneous abortion. Since the individual studies in each group were sufficiently similar, pooling to increase the numbers on which rates were

based, especially in the older age groups, appears justified. Moreover, the stability of these rates permits us to treat them as nonrandom variables in later equations. The rates of trisomy in recognized abortions are far less securely known, and to account for possible sampling fluctuations, we have in all calculations used not only the reported values for C [29], adjusted for the omission of nontrisomic karyotypically abnormal abortions, but also the rates at the upper and lower extremes defined by twice the standard errors of C. Thus, while the point estimates may change as new data accumulate, the overall associations between maternal age and p, r_a, and r_n reported here should remain as described.

(2) Accurate maternal-age-specific rates for autosomal and X trisomies at birth are not available. To estimate these rates, therefore, we doubled the frequency of Down syndrome, since 47,+21 clearly comprises half of such abnormalities at birth [17–25]. The validity of this approach depends on the extent to which trisomies other than 47,+21 also increase with maternal age. Unfortunately, the rarity of other autosomal trisomies precludes an exact test of this assumption. However, it appears a reasonable estimation given data from studies of spontaneous abortions that suggest that all autosomal trisomies show some maternal-age effect [29] and from Carothers et al. [31] that show a maternal-age effect in live-born X trisomy (XXY, XXX). While these findings do not indicate if the increase in rates for the other aneuploidies completely parallels that for 47,+21 (although Hook et al. [32, 33] make this assumption for 47,+13 and 47,+18), differences in the maternal-age effect might dilute the trends in r_a reported here but should not eliminate them.

(3) In the calculations, all spontaneous abortions with an extra autosome or X chromosome have been employed, even though these comprise different aneuploidies early in gestation and at term. (XYY cases were omitted because their origin is limited to a paternal error and there is no age effect on their frequency.) This pooling was necessitated by the absence of sufficient information on rates for specific trisomies by gestational *and* maternal age. While recognizing that the trisomies common among live births (47,+21, XXX, XXY) are not in the majority among spontaneous abortions, we assume that comparing the *sum* of trisomies at either time point is valid, since current evidence favors similar rates of nondisjunction for all chromosomes. Thus, the different trisomies prevalent at different gestational ages probably reflect the innate viability of the fetus carrying the extra genetic material rather than the probability of their occurrence. Furthermore, since there is no significant difference in the proportion of all trisomic abortions that are viable at different maternal ages [29], pooling the viable and nonviable trisomies should not necessarily bias the results.

As a preliminary asssessment of these assumptions, however, we re-analyzed the existing data using only those trisomies that are potentially viable (+13, +18, +21, +X). The estimates of r_a obtained from these very limited data show the same trend as the values of r_a based on all autosomal and X trisomies. Moreover, although the confidence intervals are wide, there is a significant difference between the estimates of r_a for the oldest women (40 and over) and for those in their 30s (our unpublished data, 1981).

In summary, we suggest that most autosomal and X trisomies result from an error in maternal meiosis, the frequency of which increases with age and is reflected in an increasing p among recognized pregnancies. Most of these aneuploid conceptuses are aborted, as indicated by the large absolute values of r_a in all maternal-age groups. However, the success of this screening mechanism weakens with maternal age as shown by the decreasing values of r_a. The observed effect of maternal age on the rate of autosomal and X trisomies among live births therefore may be explained by the joint contribution of their increasing frequency among recognized pregnancies and a decreasing probability of their spontaneous elimination before term in women over age 29. This decreased selection, besides offering an additional interpretation of the maternal-age effect on the live-born trisomy rate, can help explain the existence of a maternal-age effect even when the extra chromosome, as in 47,+21 and XXY, is paternally-derived.

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