Am. J. Hum. Genet. 67:395–404, 2000

Trisomic Pregnancy and Earlier Age at Menopause

Jennie Kline,[1,3,4] Ann Kinney,[2,6] Bruce Levin,[5] and Dorothy Warburton[7]

[1]Epidemiology of Developmental Brain Disorders Department and [2]Research Foundation for Mental Hygiene, New York State Psychiatric Institute; and [3]Gertrude H. Sergievsky Center, Divisions of [4]Epidemiology and [5]Biostatistics in the Joseph L. Mailman School of Public Health, [6]Graduate School of Arts and Sciences, and [7]Departments of Genetics and Development and of Pediatrics, Columbia University, New York

We tested the hypothesis that the connection between advanced maternal age and autosomal trisomy reflects the diminution of the oocyte pool with age. Because menopause occurs when the number of oocytes falls below some threshold, our hypothesis is that menopause occurs at an earlier age among women with trisomic pregnancies than it does among women with chromosomally normal pregnancies. To determine their menstrual status, we interviewed women from our previous study of karyotyped spontaneous abortions who, in 1993, were age ⩾44 years. Premenopausal women completed interviews every 4–5 mo, until menopause or until the study ended in 1997. The primary analyses compare 111 women whose index pregnancy was a trisomic spontaneous abortion with two groups: women whose index pregnancy was a chromosomally normal loss ($n = 157$) and women whose index pregnancy was a chromosomally normal birth ($n = 226$). We used a parametric logistic survival analysis to compare median ages at menopause. The estimated median age at menopause was 0.96 years earlier (95% confidence interval −0.18 to 2.10) among women with trisomic losses than it was among women with chromosomally normal losses and chromosomally normal births combined. Results were unaltered by adjustment for education, ethnicity, and cigarette smoking. Our results support the hypothesis that trisomy risk is increased with decreased numbers of oocytes. Decreased numbers may indicate accelerated oocyte atresia or fewer oocytes formed during fetal development.

Introduction

This study seeks to elucidate the well-established association of advancing maternal age with autosomal trisomy (Kline et al. 1989). At least 3% of clinically recognized pregnancies are trisomies; >90% end in spontaneous abortion (Kline et al. 1989). Both the few trisomies that are compatible with survival to birth (primarily trisomies 13, 18, and 21 [Down syndrome]) and the majority of autosomal trisomies that end in spontaneous abortion increase in frequency with maternal age (Hassold and Chiu 1985; Risch et al. 1986). In most autosomal trisomies, the extra chromosome is of maternal origin; almost all are due to errors during maternal meiosis I (Koehler et al. 1996; Lamb et al. 1996, 1997).

It seems reasonable to infer that trisomy results from physiological processes that are intimately tied to chronological age. One candidate process is the decline in the size of the ovarian oocyte pool with age. The germ-cell population is largest (~7 million) during fetal development and decreases approximately exponentially with chronological age (Block 1952; Baker 1963; Thomford et al. 1987; Faddy et al. 1992). Within this overall pattern, at any given chronological age, follicle counts vary among women (Block 1952; Faddy et al. 1992; Reuss et al. 1996). Variability may reflect differences either in the number of oocytes laid down or in rates of atresia, each potentially influenced by endogenous or exogenous factors.

We hypothesized that the association of chronological age with trisomy reflects an association between the number of oocytes and trisomy, with trisomy risk higher in women with fewer oocytes (Warburton 1989; Kline and Levin 1992). Since menopause occurs when the number of follicles falls below some threshold (Kline and Levin 1992), our hypothesis is that menopause occurs earlier in women who have had trisomic pregnancies than in women who have had chromosomally normal pregnancies (whether losses or births).

Subjects and Methods

Participants

Subjects were from a follow-up investigation of women who had participated, during 1974–86, in a New York City hospital–based case-control study of spontaneous abortions (Kline et al. 1995). Beginning in

Received March 31, 2000; accepted for publication June 1, 2000; electronically published June 28, 2000.

Address for correspondence and reprints: Dr. Jennie Kline, Psychiatric Institute, Unit 53, 1051 Riverside Drive, New York, NY 10032. E-mail: jkk3@columbia.edu

0002-9297/2000/6702-0017$02.00

January 1993, we attempted to enroll private patients (i.e., patients of private physicians), age ⩾44 years, whose index spontaneous abortion was trisomic (n = 150) or chromosomally normal (n = 209) and a sample of the original control group who had chromosomally normal live births (n = 264). To achieve comparability in age at follow-up, we selected, from the original live-birth control group, all women born during 1933–42 (i.e., women 51–60 years of age) and 50% of women born in each 2-year birth interval from January 1943 to July 1949 (i.e., women 44-50 years of age). Both chromosomally normal comparison groups excluded women with prior known trisomic pregnancies. The study was approved by our institutional review board.

The intake interview was completed by 524 (84%) women; analyses excluded 2 women in the live-birth cohort who had subsequent trisomic pregnancies (table 1). Interview rates for the trisomy, chromosomally normal loss, and live-birth cohorts were 80%, 80%, and 89%, respectively. Interview rates were higher for women born in the United States, although this factor did not explain the lower interview rates among women with losses. Interview rates did not vary independently with age at follow-up, year of entrance into the original study, obstetric history, ethnicity, or marital status.

At intake, women completed a telephone interview that included questions about menses, obstetric and gynecologic histories, hormonal medications, and common exposures. We attempted to follow, at 4-mo intervals, the 407 women who either were still menstruating (i.e., who had had at least one menstrual period during the previous year) or were bleeding while taking hormones. (We distinguish "menstruation" from "bleeding on hormones," because hormones can induce bleeding after the age when menopause would have occurred.) Follow-up ended either when a woman reached menopause (natural

Table 1

Selected Characteristics of the Sample

		Chromosomally Normal	
	Trisomic Loss	Loss	Live Birth
No. of women in sample	150	209	264
No. (%) interviewed [a]	120 (80.0)	168 (80.4)	236 (89.4)
No. excluded because of subsequent trisomy	0	0	2
Eligible women, from intake interview:			
No.	120	168	234
Mean age (SD [years]):[b]			
At index pregnancy	36.1 (4.0)	34.3 (3.9)	34.5 (3.8)
At intake	49.3 (3.8)	49.2 (3.4)	48.4 (3.1)
Ethnicity (%): [b]			
White, non-Hispanic	80.0	69.0	77.8
Black, non-Hispanic	5.8	16.1	6.0
Other	14.2	14.9	16.2
Born in the United States (%)	75.8	73.2	70.9
Education (%): [b,c]			
Some high school or high school graduate	8.3	16.7	15.0
Some college	15.0	20.2	22.6
College graduate	19.2	29.8	23.9
Postgraduate	57.5	33.3	38.5
Mean no. (SD) of births	1.8 (1.2)	2.0 (2.7)	2.5 (1.3)
Mean no. (SD) of spontaneous abortions	1.8 (1.1)	2.4 (1.7)	.6 (.9)
Mean no. (SD) of induced abortions	.4 (.8)	.5 (.9)	.4 (.9)
Cigarette smoking (%):			
Never smoked	53.3	52.4	52.6
Ex-smoker	39.2	35.7	36.2
Current smoker	7.5	11.9	11.1
No. with menopause at intake[d]	31	38	46
No. eligible for follow-up:	89	130	188
Completed at least one follow-up interview	82 (92.1)	125 (96.2)	184 (97.9)
Menopause at end of follow-up	21	38	46

[a] Of the 99 women not interviewed, 83 refused participation, 10 could not be located, and 6 were either deceased or too ill for interview.

[b] Age at index pregnancy, age at intake interview, ethnicity, and education are each independently associated ($P < .05$) with outcome of the index pregnancy.

[c] For 478 women, education at the time of the intake interview; for 44 women who completed a short version of the intake interview, education at the time of the earlier case-control study.

[d] Includes women with natural menopause, surgical menopause, and menopause while taking hormones.

or surgical) or with termination of the study in November 1997.

To minimize opportunities for differential ascertainment of menstrual or other data, interviewers obtained the obstetric history at the end of the intake interview. Follow-up interviews were conducted by an interviewer other than the intake interviewer. Interviewers did not know the study hypothesis.

Comparability of the Three Groups

Mean age at the index pregnancy for the trisomy cohort was ~1.7 years later than that for either comparison group; mean age at follow-up for the trisomy cohort was similar to that for the chromosomally normal–loss cohort and 0.9 years later than that for the live-birth cohort (table 1). The cohorts differed in ethnicity and education but not in place of birth. Rates of cigarette smoking—the only exposure consistently associated with age at menopause—did not differ. As expected, since the sample consisted of women identified at the time of a previous pregnancy, prior spontaneous abortions were higher among women whose index pregnancy was a loss; parity was higher among women whose index pregnancy was a live birth.

Menstrual Status

At intake, we asked each woman whether she had had a menstrual period in the past 12 mo and, if so, the date. We also asked whether, in the month before her last period, she had taken estrogen, oral contraceptives, or other medications that affect periods and, if so, the date of the period before she began the medication. Women were asked about their use of estrogen for menopausal symptoms or prevention of diseases such as bone loss and about surgery involving removal of the uterus, ovaries, or fallopian tubes. At each follow-up interview, we obtained similar information.

In keeping with convention, we classified as naturally menopausal women who went through 12 mo without menstruating (or bleeding on hormones) in the absence of known causes of amenorrhea—surgical removal of the uterus or ovaries ($n = 43$) and chemotherapy or radiotherapy ($n = 8$). These events, as well as the use of hormones that induce bleeding, prevent observing age at natural menopause. The primary analyses drew on interview data until the occurrence of such a censoring event.

Before reaching menopause, 121 (23%) women used either estrogen with or without progesterone ($n = 107$), oral contraceptives ($n = 10$), or both ($n = 4$). The majority of women began hormone use before experiencing a lengthy episode of amenorrhea; 48 women discontinued use at least once, and, among them, 32 resumed menstruating. Our analyses censored observations at the interview in which the woman's last menstrual period (LMP) occurred. (We use "LMP" to refer to bleeding in the absence of estrogen or oral contraceptive use.) For example, for women who began hormone use in the year before the intake interview and who continued use, observations were censored at the intake interview; for women who began hormone use after intake and who continued use, observations were censored at the interview in which hormone use began; and, for women who stopped taking hormones and who resumed menstruating, we drew on observations until the last informative interview. The primary analyses excluded 28 "uninformative" women who began taking hormones before reaching menopause and whose LMP occurred >1 year before the intake interview.

An additional 24 women used other hormonal medications. Most took progesterone only ($n = 16$) or "unknown" medications for indications for which progesterone is commonly prescribed ($n = 4$). Since it is unlikely that progesterone alters the timing of natural menopause, we treated bleeding episodes on progesterone as menstrual periods. Of the remaining four "other-medication" users, three resumed menstruating after use and one had a hysterectomy. In summary, the end of observation was defined by either natural menopause or one of four possible censoring events: surgical menopause, estrogen or oral contraceptive use, amenorrhea induced by chemotherapy or radiotherapy, or the last study interview.

Analysis

We used a parametric logistic survival analysis to test differences in the distributions of age at menopause; in particular, we compared median age at menopause of the trisomy cohort with that of the chromosomally normal cohorts, both separately and combined.

Our analysis combined information from both the cross-sectional data obtained at the intake interview and the prospective data obtained at follow-up interviews. The two types of data provide different degrees of precision as to the date of the LMP for women who reached natural menopause. Retrospective reports of age at natural menopause, like those obtained at intake, are subject to error (MacMahon and Worcester 1966). To avoid imprecision, we used, for intake data, only information on the exact age at interview and on menstrual status (reached natural menopause vs. menstruating). For women who had not reached menopause at intake, we used the more precise information provided by the date of LMP.

To model age at ascertained menopause (LMP + 12 mo), we used a logistic cumulative incidence function (MacMahon and Worcester 1966; Brambilla and Mc-

Kinlay 1989). In this analysis, the term "left-censoring" means that the only information known (or used) is that natural menopause occurred before ("to the left of") the beginning of observation. The term "right-censoring" means that the only information known is that natural menopause would occur after ("to the right of") the end of observation. In our logistic survival analysis, women who were already menopausal at intake enter the likelihood function as left-censored observations as of their age at intake. Women who reached natural menopause during follow-up entered the likelihood function as observed events at their exact age at ascertained menopause. Women with surgical menopause were right-censored either as of their age at surgery (if before intake) or at LMP + 12 mo (if during follow-up). Women who did not reach natural menopause by the end of observation were right-censored; we defined age at the end of observation as age at LMP + 12 mo since, by definition, *ascertained* menopause could not have occurred before this time.

Let T denote age at ascertained natural menopause. For women entering the study who already were menopausal at age t, a factor is entered into the likelihood of $P[T < t] = \exp\{\theta_1 + \theta_2(t - 50)\}/[1 + \exp\{\theta_1 + \theta_2(t - 50)\}]$, where θ_1 and θ_2 are intercept and slope parameters, respectively, of the logistic model; θ_1 is the log odds on ascertained menopause at age <50 years versus age >50 years. For observations that are right-censored at age t, the likelihood factor is $P[T > t] = 1 - P[T < t] = 1/[1 + \exp\{\theta_1 + \theta_2(t - 50)\}]$. For observed menopause events at age $T = t$, the likelihood factor is the logistic density function, $f(t) = \theta_2 \exp\{\theta_1 + \theta_2(t - 50)\}/[1 + \exp\{\theta_1 + \theta_2(t - 50)\}]^2$. The logistic hazard function is $f(t)/P[T > t] = \theta_2 P[T < t]$. θ_2 can be interpreted as the maximum hazard for menopause over a woman's lifetime. The likelihood function is the product of one of the above three expressions for each woman. To check the validity of the model, we compared the model-based survival function with a nonparametric maximum likelihood estimate (Turnbull 1976) accounting for the presence of left and right censoring. The fit was excellent.

The median age at ascertained menopause in this model is $50 - \theta_1/\theta_2$. We estimated median-age differences between the trisomy cohort and the two comparison groups by specifying linear models for θ_1 and log θ_2. Where these shifts are similar, we calculated a weighted average of the maximum likelihood estimates of the two shifts, with weights chosen to minimize the variance of the combined estimate.

Education and ethnicity differed between the cohorts, and each was associated with age at menopause (see table 3, footnote b); cigarette smoking was associated, albeit not significantly, with earlier age at menopause. We present both unadjusted and adjusted estimates of the shifts in median age at natural menopause.

To examine the effect of treating hormone use as a censoring event, we undertook four sensitivity analyses. Results were similar when we classified (1) the uninformative women as naturally menopausal; (2) the uninformative women as still menstruating; (3) the uninformative women plus current hormone users (women whose observations were censored by hormone use; $n = 51$) as naturally menopausal; and (4) the uninformative women plus long-term hormone users (≥1 years; $n = 40$) as naturally menopausal.

We also tested two subsidiary predictions. First, on the basis of our mathematical model relating age to the number of ovarian oocytes, trisomy risk, and menopause, we predicted that the magnitude of the shift toward earlier menopause would be larger for women with trisomic pregnancies at age ≥34 years than for younger women (Kline and Levin 1992). Second, we predicted that shifts toward earlier menopause would be largest for women with trisomic pregnancies whose mean maternal age is highest—that is, the double trisomies and trisomies of the smaller chromosomes (Hassold and Chiu 1985; Warburton et al. 1986).

Results

Natural menopause had been reached, by the end of the study, by 35% of women with trisomic losses, 29% of women with chromosomally normal losses, and 29% of women with live births (table 2). The primary analyses draw on women who were informative at intake: 111 with trisomic losses, 157 with chromosomally normal losses, and 226 with live births.

Age at natural menopause occurred earlier in the trisomy cohort (table 3). Without adjustment for covariates, the estimated median age at ascertained menopause was 53.4 years for the trisomy cohort, 54.2 years for the chromosomally normal–loss cohort, and 54.4 years for the live-birth cohort. When evidence from the two comparison groups were combined, the estimated median age at menopause occurred 0.96 years earlier in the trisomy cohort than in the chromosomally normal cohorts (95% confidence interval [CI] −0.18 to 2.10). Estimated shifts were essentially unaltered by adjustment for education, ethnicity, and cigarette smoking (shift = 1.02 years). The cumulative-incidence curve for age at ascertained menopause, obtained from the parametric logistic model, fit the data well (fig. 1). There were no statistically significant differences, in the slopes (θ_2) of the cumulative-incidence function, between the trisomy cohort and the two comparison groups, nor were there differences related to the covariates.

We repeated the analyses to examine the sensitivity of the results to treatment of hormone use as a censoring event and to the exclusion of uninformative women.

Table 2

Menopause Status and Estrogen/Oral Contraceptive Use Prior to Menopause in Women with Trisomic Losses, Chromosomally Normal Losses, and Live Births: Last Informative Interview

	No. (%) of Women with		
		Chromosomally Normal	
	Trisomic Loss	Loss	Live Birth
Natural menopause at intake[a]	27 (22.5)	25 (14.9)	32 (13.7)
Natural menopause during follow-up[a]	15 (12.5)	24 (14.3)	36 (15.4)
Surgical menopause at intake	4 (3.3)	13 (7.7)	13 (5.6)
Surgical menopause during follow-up	0 (.0)	8 (4.8)	5 (2.1)
Menstrual period in the past year:			
No current hormone use[b]	54 (45.0)	75 (44.6)	111 (47.4)
Current hormone use[b]	11 (9.2)	12 (7.1)	29 (12.4)
Uninformative at intake[c]	9 (7.5)	11 (6.5)	8 (3.4)
Total	120	168	234

Note.—The last informative interview is defined by either natural menopause or one of four possible censoring events: surgical menopause, estrogen or oral contraceptive use, amenorrhea induced by chemotherapy or radiotherapy, or the last study interview. Because of censoring, fewer women are classified as naturally or surgically menopausal on the basis of data from the last informative interview ($n = 202$) rather than on the basis of data drawing on all observations ($n = 220$; table 1).

[a] Includes 8 women (5 at intake, 3 during follow-up) who used premenopausal hormones and reached menopause.

[b] Premenopausal hormone use includes estrogen and oral contraceptives. We define as "current" hormone users those women whose observations are censored because of premenopausal hormone use.

[c] The women's LMP was >1 year before the interview, and they had begun hormone use before menopause occurred. We were thus unable to observe natural menopause.

Three of the four sensitivity analyses yielded estimates of >0.96 years. The estimated shift between the trisomy cohort and the two comparison groups combined was smallest when uninformative women were classified as menstruating at intake (unadjusted shift = 0.78; 95% CI −0.38 to 1.93) and largest when uninformative women were classified as having reached menopause at intake (unadjusted shift = 1.19; 95% CI 0.04–2.34).

The magnitude of the shifts toward earlier menopause did not vary significantly with age at index pregnancy. Estimated shifts for women with index pregnancies at age <34 years and at age ⩾34 years were 1.34 and 0.69, respectively (table 4).

Median age at menopause tended to be earlier for all trisomy groups except those with trisomies 6–12. Menopause occurred earlier, by an estimated 2.39 years, for double trisomies; 1.63 years for trisomies 13–15, 17, and 18; and 1.47 years for trisomies 20–22 (table 4). Data were too sparse either to test associations with trisomies of each chromosome separately or to test whether associations with trisomy group varied with age at index pregnancy.

Discussion

The hypothesis that the connection between advancing maternal age and autosomal trisomy reflects the diminution of the oocyte pool predicts that menopause will occur earlier in women with trisomic pregnancies. Our data support the hypothesis: median age at menopause is ~1 year earlier among women with trisomic spontaneous abortions than that among women with chromosomally normal pregnancies. Estimated shifts in age at menopause were essentially the same with and without adjustment for education, ethnicity, or cigarette smoking.

Strictly speaking, we cannot exclude, at the 5% level of significance, using a two-tailed test, the null hypothesis of no difference (95% CI −0.18 to 2.10; $P = .097$). Nevertheless, we do not "accept" the null hypothesis, for several reasons. (1) The scientific hypothesis was a priori and predicted the direction and effect size observed. (2) Associations were consistent: comparisons with both the chromosomally normal–loss cohort, who derived from the same sample as the trisomy cohort, and the live-birth cohort yielded similar estimates of the shift in age at menopause (0.87 and 1.03 years, respectively). (3) Associations were robust, altered only slightly by different analytic approaches for women who began using estrogen or oral contraceptives prior to reaching menopause; estimated shifts had a range of 0.78–1.19 years, depending on assumptions about the relation between premenopausal hormone use and true "unobserved" menopause status. Our primary analysis yields an estimate in the middle of this range.

Overall, among women with chromosomally normal pregnancies, estimated median age at LMP was ~53.3 years, which is ~2 years later than estimates from a similar study done in the early 1980s (McKinlay et al.

Table 3

Age at Ascertained Natural Menopause in Women with Trisomic Losses Compared with Women with Chromosomally Normal Losses and Those with Live Births: Median Ages and Shifts in Median Ages

	No. of Women[a]	Median Age (SE) (years)	Shift in Median Age (95%CI), Comparing Women with Chromosomally Normal Pregnancies and Those with Trisomic Pregnancies (years)	
			Unadjusted	Adjusted [b]
Trisomic loss	111	53.36 (.52)		
Chromosomally normal loss	157	54.22 (.46)	.87 (−.43 to 2.17)	.92 (−.40 to 2.24)
Chromosomally normal live birth	228	54.38 (.40)	1.03 (−.20 to 2.26)	1.07 (−.13 to 2.28)
Chromosomally normal combined[c]			.96 (−.18 to 2.10)	1.02 (−.11 to 2.14)

[a] Excludes 28 women whose data were uninformative because they began premenopausal hormone use >1 year before the intake interview.

[b] Adjusted for influence of education (some high school or high school graduate, some college, college graduate, postgraduate), ethnicity (white non-Hispanic, black non-Hispanic, other) and cigarette smoking (current smoker, ex-smoker, never smoked) on θ_1 (the log odds on ascertained menopause at age <50 years vs. age >50 years). These covariates were not significantly associated with log θ_2, the slope coefficient. Education was associated with θ_1 ($P = .02$), although the pattern was not monotonic; median age at menopause was later for college graduates than for postgraduates. Ethnicity was associated with θ_1 ($P = .02$); median age at menopause was ealier for "other" ethnicity and black non-Hispanic than for white non-Hispanic. Cigarette smoking was not significantly associated with θ_1 ($P = .29$); median age at menopause tended to be earlier in ex-smokers and current smokers than in those who had never smoked.

[c] Median age at ascertained menopause was not estimated for the two comparison groups combined. The estimate for the difference between the trisomy cohort and the two chromosomally normal cohorts combined was obtained by taking a weighted average of the individual shifts.

1985; Brambilla and McKinlay 1989). The difference in age is not unreasonable, however, because the prevalence of current cigarette smoking in our sample was much lower (11%, vs. 39% in McKinlay et al. 1985).

Four studies report age at menopause of women with children who have Down syndrome (Oster 1953; Smith and Record 1955; Sigler et al. 1967; Phillips et al. 1995). Interpretation of these studies is undermined by imprecise definitions of menopause; indeed, two reports (Oster 1953; Smith and Record 1955) classified some women as menopausal before the trisomic pregnancy. One study (Sigler et al. 1967) had the advantage of an age-matched comparison group and follow-up some years after the birth of the child; the direction of results is consistent with our hypothesis. The most recent study (Phillips et al. 1995) was deemed not to support the hypothesized shift in age at menopause; unfortunately, interpretation is hindered by methodological limitations (e.g., controls were selected only for cases that had reached menopause).

Our ovarian-aging hypothesis stems, in part, from the work of Brook et al. (1984). Chronological age was separated from physiological reproductive age by comparison of mice with unilateral oophorectomy to age-matched sham-operated mice. Oophorectomized mice had a higher rate of chromosomal anomalies and earlier onset of estrous acyclicity (Brook et al. 1984), thus implicating the size of the oocyte pool in the occurrence of nondisjunction. Results from a case-control study of women with trisomy 21 pregnancies, although imprecise because of the rarity of oophorectomy, are compatible with those in mice: surgical removal of part or all of an ovary was reported more often for cases than for controls (Freeman et al. 2000).

As women age, the decline in the size of the total oocyte pool is accompanied by a decline in the number of antral follicles that mature during each menstrual cycle (Peters and McNatty 1980). Mechanisms related to nondisjunction could, in theory, operate at any time between the formation of the oocyte pool (when the woman herself is in utero and meiosis I begins) and the completion of meiosis I at ovulation. Two studies implicate factors occurring around the time of oocyte maturation rather than around the time of ovulation (Volarcik et al. 1998). Rates of nondisjunction were observed in preovulatory oocytes—retrieved from either natural (Volarcik et al. 1998) or hormone-stimulated cycles (Battaglia et al. 1996)—and were induced to complete meiosis I in vitro. Nondisjunction occurred more often in oocytes retrieved from older women than in those from younger women. Among the mechanisms hypothesized to operate in the aging ovary are defects in oocyte maturation (Volarcik et al. 1998), a change in the hormonal milieu (Brook et al. 1984; Eichenlaub-Ritter 1996), and a change in the levels of proteins that influence proper chromosome segregation (Koehler et al. 1996). These mechanisms, in turn, might be influenced either by the size of the underlying oocyte pool or by the number of maturing follicles. For example, levels of circulating follicle-stimulating hormone (Reyes et al. 1977; Metcalf and Livesay 1985; Lee et al. 1988; Lenton et al. 1988; MacNaughton et al. 1992) and inhibin B (Klein et al. 1996) change during the reproductive years. It is not yet clear, however, whether

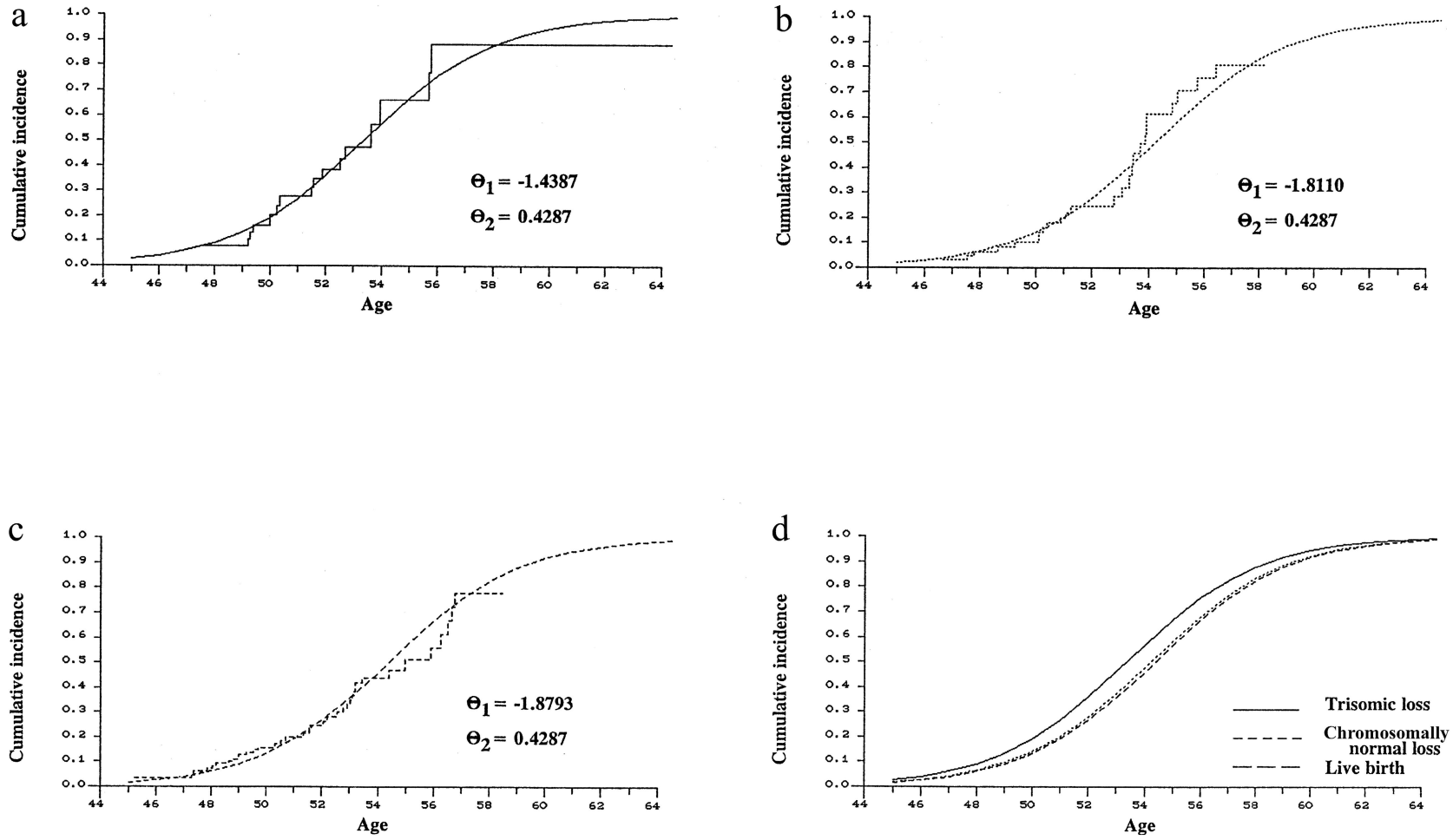

Figure 1 Comparison of cumulative incidence of ascertained menopause, from nonparametric maximum likelihood estimate (Turnbull 1976) and logistic survival model, in women with trisomic losses (*a*), chromosomally normal losses (*b*), and chromosomally normal live births (*c*). Comparison of cumulative incidence estimates for the three groups (*d*) also is shown.

Table 4

Estimated Shifts in Median Age at Ascertained Natural Menopause in Women with Trisomic Losses, Classified by Age at Index Pregnancy and Type of Trisomy, Compared with Women with Chromosomally Normal Losses and Those with Live Births

	No. of Women[b]	No. Reaching Menopause	Shift in Median Age (95% CI), Comparing Women with Chromosomally Normal Pregnancies (Losses and Live Births) and Those with Trisomic Pregnancies[a]	
			Unadjusted	Adjusted[c]
Age at index pregnancy = 27–33 years:				
Trisomic loss	28	4	1.34 (−2.60 to 5.28)	1.17 (−2.90 to 5.24)
Chromosomally normal loss	73	9		
Chromosomally normal live birth	83	12		
Age at index pregnancy = 34–46 years:				
Trisomic Loss	83	38	.69 (−.53 to 1.92)	.82 (−.37 to 2.01)
Chromosomally normal loss	84	40		
Chromosomally normal live birth	143	56		
Trisomy type:				
1–5	9	3	.48 (−3.65 to 4.60)	.97 (−2.96 to 4.90)
6–12	14	2	−3.45 (−7.33 to .43)	−3.67 (−7.56 to .22)
13–15, 17, 18	28	15	1.63 (−.19 to 3.45)	1.91 (.14 to 3.68)
16	25	6	.87 (−1.50 to 3.24)	.84 (−1.55 to 3.24)
20–22	24	9	1.47 (−.93 to 3.86)	1.21 (−1.15 to 3.56)
Double trisomies	10	7	2.39 (−.44 to 5.22)	2.26 (−.56 to 5.08)
Chromosomally normal loss	157	49		
Chromosomally normal live birth	226	68		

[a] Estimates of shifts in median age at menopause, obtained from six separate analyses, each of which compared specific trisomy types with chromosomally normal losses and births. Analyses exclude one woman with trisomy of a group E chromosome, which was not classified more specifically.

[b] Excludes 28 women whose data were uninformative because they began premenopausal hormone use >1 year before the intake interview.

[c] Adjusted for influence of education, ethnicity, and cigarette smoking on θ_1. For categories of covariates, see table 3, footnote b.

changes in circulating hormones correspond, as predicted, with changes in intraovarian hormones.

Alternatively, Warburton (1989) hypothesized that the decrease in the number of oocytes that mature during each cycle relates directly to nondisjunction by lowering the chance that an oocyte at an optimal stage of maturation is available at ovulation. Support for this hypothesis is found in studies of rodents whose immature or postmature follicles show higher rates of nondisjunction (Eichenlaub-Ritter 1996).

On the basis of a mathematical model linking age to oocyte counts, trisomy, and timing of menopause, we previously had predicted that age at menopause would be 0.9 years earlier in women with trisomic pregnancies (Kline and Levin 1992). Our observations meet this prediction. Although we posited accelerated oocyte atresia as the underlying common pathway to trisomy and menopause, we cannot distinguish between this pathway and the equally plausible hypothesis that fewer oocytes were formed during fetal development in women who later conceived trisomic pregnancies.

Our model also predicted that shifts toward earlier age at menopause would be more marked among women with trisomic pregnancies at older ages. Our data do not meet this prediction: estimated shifts were larger, although not significantly so, among women age <34 years at trisomic pregnancy than among women age ⩾34 years at trisomic pregnancy (1.34 and 0.69 years, respectively). If the observed shifts are taken at face value, one or more of the assumptions in our mathematical model may be incorrect, which would not be surprising, since our model is only one of several that might link age to oocyte counts, trisomy risk, and menopause onset. Inferences from these comparisons are limited, however, because only 14% of women with index pregnancies at younger ages had reached menopause by the study's conclusion, rendering our estimate of the shift in median age at menopause imprecise in this subgroup.

We also predicted larger shifts toward earlier menopause in women with trisomic pregnancies whose mean maternal age was highest. Here, too, small numbers limit our ability either to estimate associations with precision or to test differences between trisomy types, but in this case our data are consistent with this prediction, with the largest shifts in age at menopause observed for double trisomies and trisomies of the smallest chromosomes.

In summary, our data connect trisomic pregnancy to earlier age at menopause. They support the hypothesis

of a link between either depletion of the oocyte pool or the coincident decline in the numbers of oocytes that mature each cycle and increased risk of a trisomic pregnancy.

Acknowledgments

The research was supported, in part, by National Institute on Aging grants R01 AG 10251 and R01 AG 15386. We thank Drs. Zena Stein and Mervyn Susser, for their insight and advice throughout the study, from design through analysis through reading of the paper; Dr. Amalia Kelly, for advice during the analytic stage and for her careful reading of the manuscript; and Dr. Richard Neugebauer, for his critical reading and suggestions. We thank the interviewers: Ana Álvarez, Renée Davenport, Pamela Brown-Peterside, Victoria Frye, Mary Latka, Gladys Rodriguez, and Amy Yang. We thank the women who joined us again in the present study, furthering their contribution to research in this area.

References

Baker TG (1963) A quantitative and cytological study of germ cells in human ovaries. Proc R Soc Lond B Biol Sci 158: 417–433

Battaglia DE, Goodwin P, Klein NA, Soules MR (1996) Influence of maternal age on meiotic spindle assembly in oocytes from naturally cycling women. Hum Reprod 11:2217–2222

Block E (1952) Quantitative morphological investigations of the follicular system in women: variations at different ages. Acta Anat (Basel) 14:108–123

Brambilla DJ, McKinlay SM (1989) A prospective study of factors affecting age at menopause. J Clin Epidemiol 11: 1031–1039

Brook JD, Gosden RG, Chandley AC (1984) Maternal aging and aneuploid embryos: evidence from the mouse that biological and not chronological age is the important influence. Hum Genet 66:41–45

Eichenlaub-Ritter U (1996) Parental age-related aneuploidy in human germ cells and offspring: a story of past and present. Environ Mol Mutagen 28:211–236

Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF (1992) Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod 7:1342–1346

Freeman SB, Yang Q, Allran K, Taft LF, Sherman SL (2000) Women with a reduced ovarian complement may have an increased risk for a child with Down syndrome. Am J Hum Genet 66:1680–1683

Hassold T, Chiu D (1985) Maternal age-specific rates of numerical chromosome abnormalities with specific reference to trisomy. Hum Genet 70:11–17

Klein NA, Illingworth PJ, Groome NP, McNeilly AS, Battaglia DE, Soules MR (1996) Decreased inhibin B secretion is associated with the monotropic FSH rise in older, ovulatory women: a study of serum and follicular fluid levels of dimeric inhibin A and B in spontaneous menstrual cycles. J Clin Endocrinol Metab 81:2742–2745

Kline J, Levin B (1992) Trisomy and age at menopause: predicted associations given a link with rate of oocyte atresia. Paediatr Perinat Epidemiol 6:225–239

Kline J, Levin B, Kinney A, Stein Z, Susser M, Warburton D (1995) Cigarette smoking and spontaneous abortion of known karyotype: precise data but uncertain inferences. Am J Epidemiol 141:417–427

Kline J, Stein Z, Susser M (1989) Conception to birth: epidemiology of prenatal development. Oxford University Press, New York

Koehler KE, Hawley RS, Sherman S, Hassold T (1996) Recombination and nondisjunction in humans and flies. Hum Mol Genet 5:1495–1504

Lamb NE, Feingold E, Savage A, Avramopoulos D, Freeman S, Gu Y, Hallberg A, et al (1997) Characterization of susceptible chiasma configurations that increase the risk for maternal nondisjunction of chromosome 21. Hum Mol Genet 6:1391–1399

Lamb NE, Freeman SB, Savage-Austin A, Pettay D, Taft L, Hersey J, Gu Y, et al (1996) Susceptible chiasmate configurations of chromosome 21 predispose to non-disjunction in both maternal meiosis I and meiosis II. Nat Genet 14: 400–405

Lee SJ, Lenton EA, Sexton L, Cooke ID (1988) The effect of age on the cyclical patterns of plasma LH, FSH, oestradiol and progesterone in women with regular menstrual cycles. Hum Reprod 3:851–855

Lenton EA, Sexton L, Lee S, Cooke ID (1988) Progressive changes in LH and FSH and LH: FSH ratio in women throughout reproductive life. Maturitas 10:35–43

MacMahon B, Worcester J (1966) Age at menopause. US Vital Health Stat II, 19:161–173

MacNaughton J, Banah M, McCloud P, Hee J, Burger H (1992) Age related changes in follicle stimulating hormone, luteinizing hormone, oestradiol and immunoreactive inhibin in women of reproductive age. Clin Endocrinol (Oxf) 36: 339–345

McKinlay SM, Bifano NL, McKinlay JB (1985) Smoking and age at menopause in women. Ann Intern Med 103:350–356

Metcalf MG, Livesay JH (1985) Gonadotrophin excretion in fertile women: effect of age and the onset of the menopausal transition. J Endocrinol 105:357–362

Oster J (1953) Mongolism: a clinicogenealogical investigation comprising 526 mongols living on Seeland and neighboring islands in Denmark. Danish Science Press, Copenhagen, pp 96–100

Peters H, McNatty KP (1980) The ovary. University of California Press, Berkeley

Phillips OP, Cromwell S, Rivas M, Simpson JL, Elias S (1995) Trisomy 21 and maternal age of menopause: does reproductive age rather than chronologic age influence risk of nondisjunction? Hum Genet 95:117–118

Reuss ML, Kline J, Santos R, Levin B, Timor-Tritsch I (1996) Age and the ovarian follicle pool assessed with transvaginal sonography. Am J Obstet Gynecol 174:624–627

Reyes FI, Winter JSD, Faiman C (1977) Pituitary-ovarian relationships preceding the menopause. Am J Obstet Gynecol 129:557–564

Risch N, Stein Z, Kline J, Warburton D (1986) The relationship between maternal age and chromosome size in autosomal trisomy. Am J Hum Genet 39:68–78

Sigler AT, Cohen BH, Lilienfeld AM, Westlake JE, Hetznecker WH (1967) Reproductive and marital experience of parents of children with Down's syndrome (mongolism). J Pediatr 70:608–614

Smith A, Record RG (1955) Fertility and reproductive history in mothers of mongoloid defectives. Brit J Prev Soc Med 9: 89–96

Thomford PJ, Jelovsek FR, Mattison PR (1987) Effect of oocyte number and rate of atresia on the age of menopause. Reprod Toxicol 1:41–51

Turnbull BW (1976) The empirical distribution function with arbitrarily grouped, censored, and truncated data. J R Stat Soc Series B 38:290–295

Volarcik K, Sheean L, Goldfarb J, Woods L, Abdul-Karim FW, Hunt P (1998) The meiotic competence of in-vitro matured human oocytes is influenced by donor age: evidence that folliculogenesis is compromised in the reproductively aged ovary. Hum Reprod 13:154–160

Warburton D (1989) The effect of maternal age on the frequency of trisomy: change in meiosis or *in utero* selection? In: Hassold TJ, Epstein CJ (eds) Molecular and cytogenetic studies of non-disjunction. Alan R Liss, New York, pp 165–181

Warburton D, Kline J, Stein Z, Strobino B (1986) Cytogenetic abnormalities in spontaneous abortions of recognized conceptions. In: Porter IH, Hatcher NH, Willey AM (eds) Perinatal genetics: diagnosis and treatment. Academic Press, New York, pp 23–40