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Association of Stressful Life Events with Chromosomally Normal Spontaneous Abortion

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Spontaneous abortion is the most common adverse reproductive outcome. Despite evidence that negative life events increase risk for a number of medical disorders, their role in pregnancy disruption has not been investigated. The present study tested an a priori hypothesis that recent negative life events increase the odds of spontaneous abortion of a chromosomally normal conceptus. Between 1984 and 1986, 192 women aged 18–42 years who visited a medical center after spontaneous abortion were interviewed about positive and negative events that had occurred in the 4–5 months preceding the loss. Subsequently, women with chromosomally normal (n = 111) and chromosomally abnormal (n = 81) losses were identified on the basis of tissue culture after interview. The women with chromosomally abnormal loss provided an estimate of the expected frequency of life events against which to compare the event frequencies of women with chromosomally normal loss. Analyses were adjusted for duration of the recall period, payment status, maternal age, education, and ethnicity. Seventy percent of the women with chromosomally normal losses reported having had one or more negative life events in the months preceding loss, compared with 52% of the women with chromosomally abnormal losses (adjusted odds ratio = 2.6, 95% confidence interval (CI) 1.3–5.2). For private patients (n = 69), the adjusted odds ratio was 4.2 (95% CI 1.3–13.4); for public patients (n = 123), it was 1.9 (95% CI 0.8–4.8). The associations held for postconception events alone and were absent for positive events. Results were unaltered by adjustment for smoking, caffeine intake, and alcohol consumption. With recall bias precluded by the study design, the strength, timing, and specificity of these associations suggest that recent negative life events play a role in chromosomally normal spontaneous abortion. Efforts to replicate these results and to elucidate underlying biologic mechanisms are required. *Am J Epidemiol* 1996;143:588–96.

abortion; chromosome abnormalities; stress, psychological

Spontaneous abortion is the most common adverse reproductive outcome, occurring in 10–15 percent of clinically recognized pregnancies (1). Environmental risk factors have been extensively studied, with common exposures such as caffeine, alcohol, and cigarettes receiving much attention (1). Chemical exposures in occupational and domestic settings, as well as arduous working conditions, have also been of concern (2, 3). In general, these investigations have reported inconsistent or at best modest associations between these exposures and reproductive loss.

Stressful life events are established instigators of endocrinologic (4) and immunologic (5) change and have been implicated in a wide range of acute and chronic medical disorders (5–7). These findings suggest that stress can compromise embryonic or fetal growth. Accordingly, over the past few decades, numerous investigators have examined the role of recent negative events in complications of late pregnancy and delivery and in disorders of the neonate (8). However, despite much speculation, the contribution of stressful life events to the risk of spontaneous abortion specifically remains untested.

Spontaneous abortions comprise two distinct categories—chromosomally normal and chromosomally abnormal. The latter, representing approximately 40–50 percent of such pregnancies, are diverse entities characterized by aberrant quantities of genetic materi-

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Abbreviations: CI, confidence interval; LMP, last menstrual period; OR, odds ratio.

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al—e.g., trisomy, monosomy X, triploidy. External events can play little if any role in spontaneous abortion for all chromosomal abnormalities combined. On the one hand, each chromosomal abnormality arises from a specific type of error, usually in cell division, occurring before or at conception. Maternal pre- or periconception events are unlikely to cause any single type of error, and it is biologically implausible that such events would cause multiple types of errors. Furthermore, since chromosomal abnormalities are present at conception, postconception events cannot contribute to their genesis. On the other hand, over 90 percent of chromosomal abnormalities prove lethal in utero, with the defective karyotype rather than maternal insufficiencies or extrinsic environmental factors accounting for the demise and subsequent expulsion of the conceptus (1). This extreme lethality in utero effectively eliminates any substantial contribution of postconception life events to the survival of fetuses with chromosomal abnormalities. Consequently, a detectable influence of life events on reproductive loss, if present, will necessarily be limited to chromosomally normal spontaneous abortions.

The present study asked women who visited a medical center after a recent spontaneous abortion about life events that had occurred during the 6 months preceding the date of interview. Subsequently, we identified women with chromosomally normal and chromosomally abnormal losses on the basis of karyotype results reported later. As explained above, women with chromosomally abnormal losses provide a reasonably unbiased estimate of the expected frequency of life events occurring before conception and during the early weeks of pregnancy. In the analysis, the frequencies of life events reported by women with chromosomally normal losses are then compared with these expected levels. This design, essentially a case-control study using alternative-condition controls, ensures identical conditions of recall for the two study groups, both interviews taking place following a spontaneous abortion. Since stress can produce rapid (4) as well as enduring (9, 10) hormonal disturbances, this design also has the advantage of making both proximate and more distant life events available for analysis.

MATERIALS AND METHODS

Antecedent case-control study

Subjects in this investigation were drawn from women aged 18–44 years who were participating in an antecedent case-control study of biologic and environmental risk factors for spontaneous abortion (11). Spontaneous abortion was defined as the involuntary termination of an intrauterine pregnancy before 28 weeks of completed gestation, calculated from the last menstrual period (LMP), with the conceptus being dead upon expulsion.

From October 1984 through May 1986, the antecedent case-control study identified and conducted in-person interviews with 77 percent of women attending the private and public facilities at one New York City hospital for a spontaneous abortion. Among these women, the abortus was retrieved and the karyotype obtained for 58 percent.

Pregnant women registered at the hospital before 22 weeks' gestation served as controls. These pregnant women were selected to be similar to the women with spontaneous abortion regarding age and payment status (private or public).

Current study

At the conclusion of the interview, all women over age 17 years were invited to enter a second study if they spoke English or Spanish and were available for a telephone interview. The protocol of the second study was explained to each woman in her primary language, and assurances were given that refusal to participate in the study would not influence the care she received at the medical center. These women were to be interviewed approximately 2 weeks (time 1), 6 weeks (time 2), and 26 weeks (time 3) after spontaneous abortion for evaluation of their psychiatric status. Women recruited too late for the time 1 assessment were first interviewed at time 2 or time 3. Among eligible women, those interviewed (n = 382, 73 percent) and those not interviewed were similar with regard to all major sociodemographic and reproductive characteristics (12, 13).

The interview at time 1 (or, for late entrants, time 2) included a checklist regarding life events that took place during the 6 months preceding the day of interview. Among women participating in the study of psychiatric effects of spontaneous abortion (n = 382), 58 percent had karyotyped specimens (n = 223). These women and those without karyotyped specimens were similar in terms of major sociodemographic and reproductive history variables. However, consistent with findings in the antecedent case-control study, length of gestation was 2 weeks longer, on average, for women with karyotyped losses than for women without karyotyped losses, since both retrieval of the abortus and success in karyotyping improve with length of gestation (11). Among the women with karyotyped specimens, 192 completed a life event checklist at time 1 or time 2. These women with both karyotyped specimens and life event data (n = 192) and the women with karyotyped specimens but no life

event data ($n = 31$) were similar in terms of sociodemographic and reproductive variables. Finally, the women with karyotyped losses who received a life event interview ($n = 192$) and women who did not have karyotyped losses but completed the life event interview were similar with regard to major sociodemographic variables, reproductive characteristics, and frequency of life events prior to spontaneous abortion. The 192 women with both karyotyped specimens and life event data were the subjects of this report.

Study measures

Data on sociodemographic and pregnancy characteristics, cigarette smoking, caffeine intake, alcohol consumption, and reproductive history were derived largely from the antecedent case-control interview (11).

Life events were measured using an inventory developed by Dohrenwend et al. (14). Methods for item construction and for rating event magnitude and valence—positive (pleasant), negative (adverse), or ambiguous—have been described elsewhere (14). Events of low magnitude, as well as events of moderate magnitude that are rare among women of reproductive age (as determined from a prior community survey), were excluded; 31 major negative events and 22 major positive events were retained. Based on results from earlier research (6), only negative events were classified as stressful a priori.

The checklist's negative items can be grouped into seven broad categories defined by the social realm affected (e.g., work, health) and by the person central to the occurrence (e.g., the woman, her partner, a friend, etc.). These seven categories are as follows: 1) financial (e.g., loss of property) or employment (e.g., being fired) problems affecting the woman or her partner; 2) deterioration in the woman's relationship with her partner (e.g., infidelity); 3) criminal/legal matters pertaining to the woman, her partner, or her child; 4) criminal/legal matters pertaining to the woman's other relatives, friends, or other persons important to her; 5) reproductive losses among relatives, friends, or important others; 6) serious illnesses or injuries to relatives, friends, or important others; and 7) deaths among relatives, friends, or important others. Positive events regarding the same social areas and central figures were also surveyed. Thus, a salary increase for the woman, an improvement in her relationship with her partner, a criminal acquittal, and a parent's recovery from an illness were all reportable as positive events.

Each woman was asked to report all events that occurred during the 6 months prior to the interview, dating each event from the time she learned of its occurrence. Events that might have a direct physiologic impact on the woman (e.g., physical injury to the woman) and events occurring after the spontaneous abortion were excluded. Since most spontaneous abortions occur during the first trimester and women were interviewed within approximately 6 weeks of their loss, the pre-abortion recall period covered by the interview typically included events that happened in the weeks before conception as well as after conception. When administering the checklist, interviewers were unaware of the date of the woman's last menstrual period and made no reference to the date of the spontaneous abortion.

Analytic plan. The analysis had two main components. First, we examined whether chromosomally normal loss was associated with negative life events occurring at any time during the 4–5 months preceding the spontaneous abortion, irrespective of the date of conception. Second, we considered the association of chromosomally normal loss with preconception and periconception events (hereafter called "pre-/periconception events") and with postconception events separately. For each woman, we calculated the overall number of negative events occurring prior to the spontaneous abortion, the number occurring in the pre-/periconception period (defined as the interval between the start of the recall period and the 28th day following LMP, inclusive), and the number occurring in the postconception period (from the 29th day after LMP to the date of expulsion). The postconception period was dated from the first missed menstrual period rather than from day 14 after LMP, to reduce possible erroneous assignment by subjects of periconception events to the postconception period. (The results did not differ if postconception events were dated from the presumed date of conception at LMP plus 14 days or the date of implantation at LMP plus 21 days.) For each time period, women were classified as exposed to life events if they reported experiencing one or more events during that period.

Analytic method and selection of control variables. The association of chromosomally normal loss with life events was estimated by comparing the odds of having one or more life events among women with chromosomally normal losses with those among women with chromosomally abnormal losses. Adjusted odds ratios were obtained using unconditional maximum likelihood logistic regression with the binary event variable as the outcome.

Analyses of events occurring in the pre-/periconception period, in the postconception period, and at any time during the entire recall period prior to the spontaneous abortion were adjusted for variation across subjects in the number of days of recall. Since chro-

mosomally abnormal loss occurs earlier in gestation than chromosomally normal loss, on average, and the overall length of the recall period did not differ between women with chromosomally normal and abnormal losses, the mean length of the pre-/periconception recall period was necessarily greater for women with abnormal losses. This variation between study groups in length of the pre-/periconception time interval, which thereby created differential opportunity for event occurrence between groups, required adjustment in the analyses restricted to the pre-/periconception period. Conversely, the postconception recall period was longer for women with chromosomally normal losses than for women with abnormal losses. Consequently, analyses of events restricted to the postconception period also required adjustment for days of recall. For consistency, analyses of events for the entire recall period combined were also adjusted for total number of days of recall prior to spontaneous abortion, although the two study groups did not differ in this regard. Payment status (private vs. public) and maternal age were also entered as covariates from the outset.

Major sociodemographic factors and subject's point of study entry (time 1 or time 2) were each evaluated in turn as potential covariates. Each factor was entered initially into the logistic equation if it was associated with either chromosomally normal loss or negative life events (0 vs. ≥ 1) in univariate analyses at $p < 0.10$. For parsimony, we deleted any term thereafter from the multivariate equation if its removal did not change the log likelihood value significantly at $p < 0.10$.

Life events may influence alcohol consumption, caffeine intake, or cigarette smoking. However, the introduction of indicators of smoking behavior (15) and of pre-/periconception and postconception alcohol use (1) and caffeine intake (11) into the logistic regression model did not change the log likelihood value sufficiently to warrant inclusion. The final logistic regression model was limited to the following terms: length of the recall period in days (the number of days comprising the entire recall period prior to spontaneous abortion, the pre-/periconception period or the postconception period, depending upon the analysis); payment status (private/public), maternal age (continuous); ethnicity (black, white, Hispanic, other); and maternal education (high school or less, some college, college graduate). (The categorical variables were entered as "dummy" variables.) All reported odds ratios were adjusted for these covariates.

Event categories, event valence, and patient subgroups. Individual events on the checklist occurred rarely, thereby precluding evaluation of their separate contribution to any observed associations. However, exploratory analyses were feasible for each of the seven broad groupings (described above) based on the area of social life affected and the person central to the event. In addition, we examined the data for evidence of a dose-response relation between chromosomally normal loss and negative events as a function of number of negative events (0, 1, 2, and ≥ 3) and of event severity. (For the latter analysis, events were dichotomized at the median of the magnitude ratings into moderately stressful and severely stressful.)

To test the specificity of the associations between negative events and chromosomally normal loss, analyses were repeated for positive events (0 vs. ≥ 1). The association between life events and chromosomally normal loss within each payment group was also examined.

Results were judged statistically significant when the p value was less than 0.05.

Sample characteristics

Of the 192 eligible and interviewed women aged 18–42 years, 111 had had a chromosomally normal loss and 81 had had a chromosomally abnormal loss. As anticipated, the two groups differed somewhat with regard to sociodemographic and reproductive history variables. Women with chromosomally normal losses were younger, were less often white, and had fewer years of formal education than women with chromosomally abnormal losses (table 1). Average length of gestation at expulsion was greater in women with normal losses than in women with abnormal losses. Seventy percent of the women were interviewed at time 1. In each group, the life event interview covered approximately the 4–5 months prior to spontaneous abortion.

By payment status, differences between women with chromosomally normal and chromosomally abnormal losses were either absent or less pronounced. One third of the women were private patients, and of these, 43 percent had chromosomally normal losses. Among private patients, women with chromosomally normal and chromosomally abnormal losses were similarly distributed according to sociodemographic and reproductive characteristics (table 1). Among public patients, 66 percent had chromosomally normal losses, and women with normal and abnormal losses differed somewhat with regard to sociodemographic characteristics.

In the total sample, 63 percent of subjects reported experiencing one or more negative events prior to the spontaneous abortion (table 2).

TABLE 1. Selected characteristics of women with chromosomally normal and chromosomally abnormal spontaneous abortions

	Total sample† (*n* = 192)		Private patients† (*n* = 69)		Public patients† (*n* = 123)	
	Chromosomally normal (*n* = 111)	Chromosomally abnormal (*n* = 81)	Chromosomally normal (*n* = 30)	Chromosomally abnormal (*n* = 39)	Chromosomally normal (*n* = 81)	Chromosomally abnormal (*n* = 42)
Mean age (years)	28.4 (6.1)‡	31.2*** (5.9)	32.2 (4.2)	33.6 (5.6)	27.0 (6.1)	29.0* (5.3)
Ethnic group (%)						
White	24.3	42.0**	73.3	82.1	6.2	4.8
Black	24.3	18.5	10.0	7.7	29.6	28.6
Hispanic	36.9	34.6	6.7	5.1	48.1	61.9
Other	14.4	4.9	10.0	5.1	16.0	4.8
Education (%)						
≤High school	55.0	39.5*	13.3	12.8	70.4	64.3
Some college	24.3	29.6	23.3	23.1	24.7	35.7
≥4 years of college	20.7	30.9	63.4	64.1	4.9	
Marital status (%)						
Not married	32.4	28.4	10.0	2.6	40.7	52.4
Married	57.7	60.5	90.0	94.9	45.7	28.6
Cohabiting	4.5	7.4		2.6	6.2	11.9
Separated	5.4	3.7			7.4	7.1
No. of children (%)						
0	38.7	35.8	50.0	53.8	34.6	19.0
1	24.3	32.1	20.0	28.2	25.9	35.7
2	19.8	19.8	20.0	10.3	19.8	28.6
≥3	14.4	12.3	10.0	7.7	19.6	16.7
No. of previous spontaneous abortions (%)						
0	65.8	67.9	66.7	59.0	65.4	76.2
1	23.4	22.2	23.3	23.1	23.5	21.4
≥2	10.8	9.9	10.0	17.9	11.1	2.4
Mean no. of days' gestation at abortion	112.0 (34.7)‡	83.6*** (20.4)	105.0 (31.3)	81.1*** (16.1)	114.5 (35.7)	86.0*** (23.7)
Recall period (mean no. of days)	161.3 (16.7)	157.3 (19.4)	156.4 (18.2)	154.4 (20.5)	163.1 (15.9)	160.0 (18.1)

* $p < 0.10$; ** $p < 0.05$; *** $p < 0.01$.

† Significance tests pertain to differences in parameter estimates between the column with the asterisk(s) and the adjacent column to its left.

‡ Numbers in parentheses, standard deviation.

RESULTS

Total sample

Events in the entire recall period prior to spontaneous abortion. In the total sample, for the entire recall period preceding spontaneous abortion, 70 percent of women with chromosomally normal losses reported experiencing one or more negative events, whereas 52 percent of women with chromosomally abnormal losses reported one or more negative events. The adjusted odds ratio for exposure to negative events was 2.6 (table 2). The small increase in the point estimate of the odds ratio derives from minor sociodemographic differences between groups. The magnitude of the association of chromosomally normal loss with negative life events did not vary significantly between women with and without a history of spontaneous abortion.

Events in the pre-/periconception and postconception periods. In the pre-/periconception period, chromosomally normal loss was not associated with negative events. Thirty-seven percent of women with chromosomally normal losses and 40 percent of women with chromosomally abnormal losses reported one or more negative events (adjusted odds ratio (OR) = 1.2) (table 2). Since the pre-/periconception recall period was greater for women with chromosomally abnormal losses, adjustment for differences between study groups in number of pre-/periconception days of recall produced an increase in the point estimate of the odds ratio. In the postconception pe-

TABLE 2. Association of chromosomally normal spontaneous abortion with one or more recent negative life events

Timing of event(s)	No. and % of women reporting one or more negative events				Crude odds ratio	95% CI*	Adjusted† odds ratio	95% CI
	Chromosomally normal (n = 111)		Chromosomally abnormal (n = 81)					
	No.	%	No.	%				
Entire recall period	78	70.3	42	51.9	2.2	1.2–4.6	2.6	1.3–5.2
Pre- or periconception‡	40	37.4	32	39.5	0.9	0.5–1.7	1.2	0.6–2.3
Postconception§	60	54.0	23	28.4	3.0	1.6–5.4	1.9	0.9–3.8

* CI, confidence interval.

† Adjusted for duration of recall (continuous), payment status (private/public), maternal age (continuous), ethnicity (black, white, Hispanic, other), and education (less than or equal to high school, some college, college graduate).

‡ The pre-/periconception recall period extended from the beginning of the recall period to the last menstrual period plus 28 days. For four women, all with chromosomally normal losses, recall was limited to the postconception period.

§ The postconception recall period extended from the 29th day after the last menstrual period to the date of spontaneous abortion.

riod, 54 percent of women with chromosomally normal losses reported one or more negative events, as compared with 28 percent of women with chromosomally abnormal losses. The adjusted odds ratio was elevated (OR = 1.9), and the 95 percent confidence interval included 1 ($p < 0.09$). Since the postconception recall period was greater for women with a chromosomally normal loss, adjustment for differences between study groups in number of postconception days of recall resulted in a decrease in the point estimate of the odds ratio.

Event categories, number, and severity

The adjusted odds ratio for criminal/legal events pertaining to the woman, her partner, or her child was 1.8 (95 percent confidence interval (CI) 0.9–3.6). For reproductive losses occurring among the woman's relatives, friends, or important others, the adjusted odds ratio was 1.7 (95 percent CI 1.0–2.8); for deaths among family, friends, or important others, it was 1.6 (95 percent CI 1.0–2.6). The odds ratios for the remaining event categories were all below 1.4; none approached statistical significance. Neither the odds ratios associated with 1, 2, and ≥3 events nor those associated with moderately stressful events as compared with severely stressful events afforded clear, consistent evidence of dose-response relations with chromosomally normal loss.

Event valence

Chromosomally normal loss was not associated with positive events (data not shown). Sixty-seven percent of women with chromosomally normal losses reported one or more positive events, and 69 percent of women with chromosomally abnormal losses did so (adjusted OR = 0.9, 95 percent CI 0.5–1.9).

Variation by payment status

The magnitude of the association of chromosomally normal loss with negative events did not vary significantly between private and public patients, either for events taking place during the entire recall period ($p < 0.34$) or for events occurring in the postconception period ($p < 0.14$). Nonetheless, the pronounced socioeconomic differences that marked private and public patients, and their derivation from distinct hospital services, prompted further analyses within each payment group separately.

Among private patients, 73 percent of women with chromosomally normal losses reported experiencing one or more negative events in the 4–5 months before spontaneous abortion, whereas 46 percent of women with chromosomally abnormal losses did so (adjusted OR = 4.2) (table 3). For events taking place in the pre-/periconception period, the adjusted odds ratio approximated 1; for events occurring in the postconception period, the adjusted odds ratio was 3.2.

Among public patients, 69 percent of women with chromosomally normal losses reported one or more negative events in the 4–5 months before spontaneous abortion; 57 percent of women with chromosomally abnormal losses reported one or more negative events (adjusted OR = 1.9). For events occurring in the pre-/periconception period, the adjusted odds ratio approached 1; for events in the postconception period, it was 1.4.

DISCUSSION

In accord with the a priori hypothesis of this study, recent negative life events were associated with chromosomally normal spontaneous abortion. In the total sample, the odds ratio associated with the occurrence of one or more events in the 4–5 months prior to

TABLE 3. Association of chromosomally normal spontaneous abortion with one or more recent negative life events, by payment status (private vs. public)

Timing of event(s)	No. and % of private patients reporting one or more events				Crude odds ratio	95% CI*	Adjusted† odds ratio	95% CI
	Chromosomally normal (n = 30)		Chromosomally abnormal (n = 39)					
	No.	%	No.	%				
Entire recall period	22	73.3	18	46.2	3.2	1.2–2.2	4.2	1.3–13.4
Pre- or periconception‡	9	31.0	13	33.3	0.9	0.3–2.5	1.1	0.4–3.6
Postconception§	17	56.7	8	20.5	5.1	1.8–14.3	3.2	0.9–11.8
	No. and % of public patients reporting one or more events							
	Chromosomally normal (n = 81)		Chromosomally abnormal (n = 42)					
	No.	%	No.	%				
Entire recall period	56	69.1	24	57.1	1.7	0.8–3.6	1.9	0.8–4.8
Pre- or periconception‡	31	39.7	19	45.2	0.8	0.4–1.7	1.1	0.5–2.6
Postconception§	43	53.1	15	35.7	2.0	1.0–4.4	1.4	0.6–3.5

* CI, confidence interval.

† Adjusted for duration of recall (continuous), maternal age (continuous), ethnicity (black, white, Hispanic, other), and education (less than or equal to high school, some college, college graduate).

‡ The pre-/periconception recall period extended from the beginning of the recall period to the last menstrual period plus 28 days. For one private patient and three public patients, all with chromosomally normal losses, recall was limited to the postconception period.

§ The postconception recall period extended from the 29th day after the last menstrual period to the date of spontaneous abortion.

spontaneous abortion was 2.6. Analyses restricted to postconception events afford the more stringent test of the hypothesized association, because, as noted above, these events can neither generate chromosomal abnormalities nor perceptibly influence the risk of in utero demise. In the entire sample, the odds ratio for postconception events was elevated (OR = 1.9), although it did not achieve a conventional level of statistical significance ($p < 0.09$). Equally interesting, pre-/periconception events did not appear to contribute to the odds of chromosomally normal loss.

In post hoc analyses, odds ratios were highest for legal problems involving the woman and for deaths and reproductive losses among the woman's friends, relatives, or important others. The absence of a dose-response relation between increasing number or severity of negative events and chromosomally normal loss should be accepted only provisionally, given the relatively small numbers of subjects who reported multiple events or severe events.

Positive events exhibited no association with chromosomally normal loss.

These findings cannot have arisen from recall bias, since karyotype was unknown at the time of interview and the two types of losses—chromosomally normal and abnormal—were indistinguishable to subjects and to study personnel; nor is selective recruitment of study subjects—for example, recruitment of women with both chromosomally normal loss and atypically high life event frequencies—a plausible explanation. The findings for postconception events satisfactorily address any suggestion, however unlikely, that our results derive from a protective effect of negative events on the genesis of chromosomal abnormalities.

The pregnant women who served as controls in the antecedent case-control study were also asked about life events occurring in the 6 months preceding their interview. Although these controls were excluded from the analysis a priori because of concern about possible recall bias, comparison of life event frequencies between the pregnant women and the women with spontaneous abortions is of interest post hoc. The mean number of days of recall for the women with spontaneous abortions was 160, beginning approximately 3 weeks prior to the interview date (table 1). Among pregnant women, 49 percent reported one or more events for the same duration of time and analogous time frame, as compared with 52 percent of women with chromosomally abnormal losses and 70 percent of women with chromosomally normal losses. These results suggest that our principal findings derive from an elevated life event frequency among women with chromosomally normal losses rather than from an atypical deficit of events among women with abnormal losses.

These features of design and specificity of study results as regards both event valence and timing render these findings compatible with a causal relation be-

tween recent negative life events and risk of chromosomally normal loss. The fact that events involving death and loss among friends and relatives appear to be especially implicated in these associations concurs with extensive literature showing an increase in mortality and morbidity following bereavement (16, 17). On the other hand, it is noteworthy that major positive events, which also often require substantial physical and psychological adjustment, were not associated with chromosomally normal loss. Environmental and adaptive challenges per se, therefore, do not appear to influence risk of pregnancy loss.

Associations between negative events and chromosomally normal loss appeared to be stronger for private patients than for public patients. Among private patients, the odds ratio for one or more negative events in the 4–5 months preceding spontaneous abortion was 4.2; the corresponding odds ratio among public patients was 1.9. Attenuated associations among public patients, if confirmed, might reflect our inability to detect the impact of discrete events against a background of pervasive chronic stress, the presence of better mechanisms for dealing with certain types of stressors among public patients, or possibly reduced reliability of recall by less educated individuals (18, 19). However, at present, the most credible explanation for these variations in odds ratios is sampling variability, since the strength of the associations did not differ significantly by payment group.

Disruption of pregnancy by stressful events is biologically plausible, given the manifold endocrinologic and immunologic effects of chronic and acute stress (20); the complex, if incompletely understood, hormonal requirements of pregnancy in primates (21, 22); and the possible role of maternal immunologic rejection of the embryo in spontaneous abortion (1). In lower mammals, a variety of stressors—e.g., overcrowding, social subordination (23), handling (24), novel environments, and exposure to predators—have been implicated in pregnancy termination (21). However, empirical demonstration of these effects in lower primates is usually indirect (25, 26), and it remains unsatisfactory in humans.

In the past 35 years, at least 20 prospective perinatal epidemiologic investigations have examined the relations between stressful life events and adverse human reproductive outcomes. Typically, these studies focused on late pregnancy complications, with low birth weight and preterm birth receiving particular attention. Of these studies, less than half reported significant, direct associations between exposure to stressful events and adverse reproductive outcomes (8, 27–31). Most of the other studies failed to find any association (8, 32–36), whereas two studies reported protective effects (37, 38). Whether these inconsistent results reflect unrecognized deficiencies in study design, inadequate control for residual confounding, associations that appear only among special population subgroups represented in varying degrees in different study samples, or the true absence of effects is not known.

The current study is the first, to our knowledge, to have tested the possibility of a link between stressful life events and spontaneous abortion. Our findings afford some evidence that recent negative life events increase the risk of spontaneous abortion of chromosomally normal conceptuses. Nonetheless, any recommendations for prevention or clinical care must await replications designed to elucidate the characteristics of events that are most pathogenic and the physiologic pathways by which such events may disrupt an ongoing pregnancy.

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