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JAMA. 2006;295(5):499-507 (doi:10.1001/jama.295.5.499)

http://jama.ama-assn.org/cgi/content/full/295/5/499

Relapse of Major Depression During Pregnancy in Women Who Maintain or Discontinue Antidepressant Treatment

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Context Pregnancy has historically been described as a time of emotional well-being, providing "protection" against psychiatric disorder. However, systematic delineation of risk of relapse in women who maintain or discontinue pharmacological treatment during pregnancy is necessary.

Objective To describe risk of relapse in pregnant women who discontinued antidepressant medication proximate to conception compared with those who maintained treatment with these medications.

Design, Setting, and Patients A prospective naturalistic investigation using longitudinal psychiatric assessments on a monthly basis across pregnancy; a survival analysis was conducted to determine time to relapse of depression during pregnancy. A total of 201 pregnant women were enrolled between March 1999 and April 2003 from 3 centers with specific expertise in the treatment of psychiatric illness during pregnancy. The cohort of women was recruited from (1) within the hospital clinics, (2) self-referral via advertisements and community outreach detailing the study, and (3) direct referrals from the community. Participants were considered eligible if they (1) had a history of major depression prior to pregnancy, (2) were less than 16 weeks' gestation, (3) were euthymic for at least 3 months prior to their last menstrual period, and (4) were currently or recently (<12 weeks prior to last menstrual period) receiving antidepressant treatment. Of the 201 participants, 13 miscarried, 5 electively terminated their pregnancy, 12 were lost to follow-up prior to completion of pregnancy, and 8 chose to discontinue participation in the study.

Main Outcome Measure Relapse of major depression defined as fulfilling Structured Clinical Interview for *DSM-IV* [*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*] Diagnosis (SCID) criteria.

Results Among the 201 women in the sample, 86 (43%) experienced a relapse of major depression during pregnancy. Among the 82 women who maintained their medication throughout their pregnancy, 21 (26%) relapsed compared with 44 (68%) of the 65 women who discontinued medication. Women who discontinued medication relapsed significantly more frequently over the course of their pregnancy compared with women who maintained their medication (hazard ratio, 5.0; 95% confidence interval, 2.8-9.1; $P<.001$).

Conclusions Pregnancy is not "protective" with respect to risk of relapse of major depression. Women with histories of depression who are euthymic in the context of ongoing antidepressant therapy should be aware of the association of depressive relapse during pregnancy with antidepressant discontinuation.

JAMA. 2006;295:499-507 www.jama.com

PREGNANCY HAS HISTORICALLY been described as a time of emotional well-being, providing "protection" against psychiatric disorder.[1,2] However, systematic data to support this impression are sparse. A prospective community-based study described similar rates of depression in gravid and nongravid women[3] and, more recently, a second study noted the persistence of depressive symptoms during pregnancy.[4]

The high risk of depressive relapse following discontinuation of maintenance antidepressant therapy in nongravid patients treated with antidepressants has been well established.[5] The determination of risk of relapse following discontinuation of antidepressants during pregnancy or in those women who maintain treatment with these medications during pregnancy has not been previously investigated. Clinicians need such information to collaborate effectively with patients to tailor careful risk-benefit assessments with regard to antidepressant drug use for

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women who are pregnant or planning to conceive. Such assessments take into account prenatal exposure to antidepressants on one hand vs the risk of untreated affective disorder on the other.

Accumulating data from case series and prospectively derived samples over the last several decades support the absence of increased risk of major congenital malformations associated with first trimester exposure to older and newer antidepressants.[6-10] Recently, several unpublished reports describing data accumulated from both a large health maintenance organization database and the Swedish Medical Birth Registry (http://www.gsk-us.com/news/paroxetine/paxil_letter_e3.pdf) have raised concerns about a putative 1.5- to 2.0-fold increased risk for cardiovascular malformations (ventricular and atrial septal defects) associated with first trimester exposure to the selective serotonin reuptake inhibitor (SSRI) paroxetine. This has prompted the US Food and Drug Administration to issue an alert to health care professionals regarding the safety of prenatal use of paroxetine (http://www.fda.gov/cder/drug/InfoSheets/HCP/paroxetineHCP.htm). While these new findings are inconsistent with previous reports regarding the reproductive safety of paroxetine,[10,11] these new data may reflect a signal for increased teratogenic risk of paroxetine in need of confirmation by future systematic study. Several investigators have also described symptoms of neonatal jitteriness and transient neonatal distress associated with peripartum exposure to antidepressants, particularly the active SSRIs.[12-17] Informed clinical decisions require taking into account risks of fetal exposure to medication,[7,18-20] the potential impact of untreated maternal depression during pregnancy on neonatal outcome,[21-24] and potential risks of neonatal syndromes associated with certain antidepressants.

If pregnancy has a salutary effect on major depressive disorder, then women receiving maintenance antidepressant treatment may successfully discontinue their medication around conception without particular concern about relapse. However, if pregnancy does not have a "protective" effect on risk of depressive relapse, some women with a history of major depression, particularly those with highly recurrent disease, may elect to continue taking antidepressants during pregnancy to avoid the morbidity associated with depressive relapse. Similarly, the delineation of time to relapse has additional clinical importance. For example, if relapse of major depression occurs frequently following antidepressant discontinuation during pregnancy but is rare in the initial months following discontinuation, this serves as a potential clinical guide to minimize fetal antidepressant exposure in early pregnancy. Avoiding medications in the first trimester is consistent with typical approaches to early pregnancy.

Our previous work indicated a nearly 50% rate of antidepressant reintroduction across pregnancy in women with histories of depression who discontinued or attempted discontinuation of these medications proximate to conception.[25] In that study, we hypothesized that rates of antidepressant reintroduction underestimated the actual risk of depressive relapse given women's concerns regarding potential known and unknown effects of prenatal medication exposure and their reluctance to reintroduce medication during pregnancy. In a small preliminary follow-up study of participants not included in the current report, we also noted that 75% of women with histories of major depression experienced depressive relapse associated with discontinuation (or discontinuation attempt) of antidepressants proximate to conception.[26]

The purpose of the current study was to describe the risk of relapse in pregnant women who discontinued or who attempted to discontinue antidepressant medication proximate to pregnancy compared with those who maintained treatment with these medications. Another goal of the study was to identify the time to relapse across these various groups with respect to specific trimester of relapse. We hypothesized that discontinuation of antidepressant medications proximate to conception would be associated with substantial risk of relapse and that relapse risk in those who discontinued treatment would exceed that seen in those who maintained antidepressant treatment during pregnancy. To test these hypotheses and to circumvent the ethical dilemma inherent in the randomization of pregnant women to a specific treatment group, the current study used a naturalistic prospective study of pregnant women with histories of major depression followed across a spectrum of treatment conditions.

METHODS

Sample Selection

A total of 201 pregnant women were enrolled in the prospective longitudinal study of depression during pregnancy. The participants were selected from 3 centers with specific expertise in the treatment of psychiatric illness during pregnancy (Perinatal and Reproductive Psychiatry Clinical Research Program, Massachusetts General Hospital, Boston; Women's Mood Disorders Research Program, University of California, Los Angeles (UCLA); and the Women's Mental Health Program, Emory University School of Medicine, Atlanta, Ga). The 3 centers participated in this collaborative, federally funded investigation based on their previously demonstrated ability to recruit a sample of pregnant women with histories of depression. All sites made deliberate efforts to include a broad spectrum of patients with diverse backgrounds, and all eligible patients were offered the opportunity to participate. The cohort was recruited from (1) women planning pregnancy who were previously seen in consultation; (2) self-referral via advertisements and community outreach detailing the study; and (3) direct referrals from community obstetrical practices.

Participants were considered eligible if they (1) had a history of major depression prior to pregnancy, (2) were less than 16 weeks' gestation, (3) were euthymic for at least 3 months prior to their last menstrual period (LMP), and (4) were currently or recently (<12

weeks prior to LMP) receiving antidepressant treatment. Patients were excluded if they (1) were actively suicidal; (2) met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for one of the following disorders: organic mental disorders, substance use disorders; bipolar disorder; schizophrenia; delusional disorder; or current psychotic disorders; (3) had a positive urine drug screen associated with use of toxic substances; (4) had a medical condition associated with depressive symptomatology, ie, hypothyroidism. All patients gave informed consent to participate in the study, and the study protocol was approved by the institutional review board at each of the 3 collaborating centers. Participants self-identified their racial and ethnic status. These data were obtained and tracked across the study in an effort to achieve racial and ethnic diversity of participants with the hope that enhanced diversity among the target sample would enhance the generalizability of the study findings.

The study was a prospective naturalistic investigation conducted from March 1999 until April 2003. Longitudinal psychiatric assessments were used to describe pregnant women who elected either to discontinue or to maintain antidepressant therapy. Participants were not randomized, and decisions about pharmacological treatment were made independent of study participation. However, to standardize the information about the risks and benefits of pharmacotherapy associated with prenatal exposure to antidepressants for participants across all the sites, participants were given an audiotape on enrollment into the study. The audiotape included a summary of available information regarding teratogenicity of antidepressants, risk of transient neonatal syndromes associated with peripartum exposure to antidepressants, and risk of depressive relapse associated with discontinuation of antidepressant therapy.

Assessments

A study physician assessed participants at baseline to determine study eligibility. The Structured Clinical Interview (SCID-I/P)[27] was administered at baseline to confirm a *DSM-IV* lifetime diagnosis of major depressive disorder and presence of comorbid psychiatric illness (if any). A longitudinal tracking sheet was also used to document pharmacological and nonpharmacological treatment received before and during pregnancy and was completed at baseline and at each study visit with changes (if any) noted. Information regarding variables that might influence risk of relapse was collected including demographic data, pharmacotherapy and psychotherapy across pregnancy, number of prior episodes, total duration of illness, family history of depression, histories of suicide attempts, time since the onset of last depressive episode, and length of time taking antidepressants. A research assistant blinded to the participant's treatment plan administered the 28-Item Hamilton Rating Scale for Depression (HAM-D),[28] the Structured Clinical Interview mood module for depression (SCID-I/P), and the Clinical Global Impressions Scale (CGI)[29] during monthly study visits (12, 16, 20, 24, 28, 32, and 36 weeks' gestation). For participants who enrolled in the study between 12 and 16 weeks' gestation (n=40), the SCID was administered at the time of enrollment. The SCID and study questionnaires were administered by highly trained clinical research assistants at the individual sites. All had received joint SCID training, supervised by one of the investigators (R.S.), and joint HAM-D ratings, supervised by one of the investigators (L.L.A.). All raters reviewed and rated 2 tapes of SCID interviews and 3 tapes requiring HAM-D ratings. Excellent interrater reliability was achieved for the diagnosis of depression (overall κ, 0.92) and HAM-D total scores (overall κ, 0.72).

Statistical Analysis

All analyses were conducted with SAS statistical software.[30] The sample was stratified based on participants' decisions regarding pharmacological therapy during the period ranging from 3 months prior to LMP to 16 weeks' gestation. Participants were divided into 4 groups with respect to pharmacological status: (1) maintained antidepressant therapy for the entire period, (2) discontinued taking antidepressants completely for a minimum of 1 week, (3) decreased their antidepressant from the optimal dose (dose that had afforded euthymia for a minimum of 3 months) and never increased above the optimal dose, (4) increased their antidepressant above the optimal dose for at least 1 week and never decreased below the optimal dose. Relapse was defined as fulfilling *DSM-IV* criteria on the SCID mood module. Study completers were defined as those who either relapsed or remained euthymic through the last study visit at 36 weeks' gestation.

We compared the distribution of background psychiatric history characteristics across the 4 patient groups to identify potential confounding factors associated with both medication discontinuation and depressive relapse. We used survival analysis to assess the influence of medication discontinuation on time to recurrence of depression. The exposure period, or the window in which women had the opportunity to discontinue their medication, was defined as 3 months prior to LMP through 16 weeks' gestation. The risk period for relapse of depression was defined as the temporal window between LMP and 36 weeks' gestation or last follow-up, whichever came first. Censored end points included live birth delivery, pregnancy termination, and lost to follow-up. Kaplan-Meier product-limit survival analyses were used to estimate the median time to an episode of depression for the whole sample and to make univariate comparisons between those women who maintained and discontinued their antidepressant medication.

Cox proportional hazards regression models[31] were used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) for the relationship between medication discontinuation and relapse of depression during pregnancy while adjusting for clinical

site and prior history of either prenatal or postpartum depressive episode. These models were also used to examine potential predictors of relapse of depression during pregnancy, including demographic and clinical variables such as depressive illness history. The analyses were time-dependent, proportional hazards in which only complete data for all time periods were used. With the Proportional Hazards Regression (PHREG) procedure in SAS (version 8.0), we used the "exact" option to handle a high proportion of ties as a result of imprecise measurement of event times.[30] $P<.05$ was set as the level of significance.

RESULTS

Characteristics of the Sample

Of the 201 women who were followed up across the study and who were eligible for analysis, 13 miscarried, 5 electively terminated their pregnancy, 12 were lost to follow-up prior to completion of pregnancy, and 8 chose to discontinue participation in the study. Race was the only significant factor distinguishing those who were lost to follow-up ($P=.002$) and those who continued in the study. While nonwhites had a higher dropout rate compared with whites, no particular race among nonwhites, including African Americans, Hispanics, and Asians, was more likely to be lost to follow-up.

TABLE 1 illustrates the demographic characteristics of all participants and then those who maintained, increased, decreased, or discontinued their medication over the course of their pregnancy. Overall, the mean age of participants was 34.1 years, but those enrolled from Emory University were somewhat younger than those enrolled at UCLA and Massachusetts General Hospital (data not shown). Approximately 90% of participants were married and more than half reported completing a college education. Marital status and clinical center were the only demographic factors associated with medication status over the course of the pregnancy.

Clinical characteristics of the sample associated with illness history and its severity are presented in TABLE 2. Data are presented for the sample stratified by medication status. The mean age at first onset of depression was 18.8 years (SD=6.8), with approximately half the sample reporting first onset of mood disorder prior to 18 years of age. Mean duration of depression was 15.4 years (SD=7.1). Approximately 20% of participants reported duration of illness exceeding 20 years, with 48% reporting illness duration as 14 years or less. Although inclusion into the study required only a past history of major depression, the women in the sample were noted to have highly recurrent depression, with 44% reporting 5 or more prior recurrent episodes (mean [SD], 7.0 [10.8]). Current or past history of comorbid psychiatric illness was noted in 93 women (53% of the sample). Anxiety and eating disorders were the most common comorbid diagnoses (62 [35%] and 29 [17%], respectively). Antidepressant therapy for at least 3 con-

Table 1. Demographic Characteristics of Pregnant Women With Histories of Major Depression Across Different Medication Treatment Conditions*

Variable	All (N = 201)	Maintained (n = 82)	Increased (n = 20)	Decreased (n = 34)	Discontinued (n = 65)
Age, y					
<32	50 (24.9)	20 (24.4)	5 (25.0)	10 (29.4)	15 (23.1)
32-34	63 (31.3)	28 (34.2)	7 (35.0)	7 (20.6)	21 (32.3)
35-37	46 (22.9)	16 (19.5)	4 (20.0)	12 (35.3)	14 (21.5)
>37	42 (20.9)	18 (22.0)	4 (20.0)	5 (14.7)	15 (23.1)
Race					
White	178 (89.9)	73 (90.1)	19 (95.0)	30 (88.2)	56 (88.9)
Nonwhite	20 (10.1)	8 (9.9)	1 (5.0)	4 (11.8)	7 (11.1)
Highest level of education					
Partial college/high school	77 (38.9)	33 (40.7)	5 (25.0)	15 (44.1)	24 (38.1)
College	86 (43.4)	37 (45.7)	12 (60.0)	14 (41.2)	23 (36.5)
Graduate school	35 (17.7)	11 (13.6)	3 (15.0)	5 (14.7)	16 (25.4)
Highest education of partner					
Partial college/high school	72 (39.6)	34 (44.7)	7 (35.0)	15 (46.9)	16 (29.6)
College	72 (39.6)	27 (35.5)	8 (40.0)	13 (40.6)	24 (44.4)
Graduate school	38 (20.9)	15 (19.7)	5 (25.0)	4 (12.5)	14 (25.9)
Marital status†					
Single	20 (10.2)	5 (6.2)	2 (10.0)	1 (2.9)	12 (19.0)
Married	177 (89.8)	75 (93.8)	18 (90.0)	33 (97.1)	51 (81.0)
Site†					
University of California, Los Angeles	55 (27.4)	15 (18.3)	2 (10.0)	7 (20.6)	31 (47.7)
Emory University	66 (32.8)	36 (43.9)	9 (45.0)	14 (41.2)	7 (10.8)
Massachusetts General Hospital	80 (39.8)	31 (37.8)	9 (45.0)	13 (38.2)	27 (41.5)

*Data are expressed as No. (%). Columns may not sum due to missing data.
†Fisher exact test P value <.05 (comparison across all 4 medication groups).

Table 2. Clinical Characteristics of Pregnant Women With Histories of Major Depression Across Different Medication Treatment Conditions*

Variable	All (N = 201)	Maintained (n = 82)	Increased (n = 20)	Decreased (n = 34)	Discontinued (n = 65)
Age at onset, y					
<14	44 (23.2)	19 (24.0)	3 (16.7)	7 (21.9)	15 (24.6)
14-17	45 (23.7)	19 (24.0)	5 (27.8)	4 (12.5)	17 (27.9)
18-25	50 (26.3)	19 (24.0)	7 (38.9)	11 (34.4)	13 (21.3)
>25	51 (26.8)	22 (28.0)	3 (16.7)	10 (31.2)	16 (26.2)
Duration of illness, y					
<5	24 (12.6)	9 (11.4)	2 (11.1)	4 (12.5)	9 (14.8)
5-14	67 (35.3)	27 (34.2)	9 (50.0)	14 (43.8)	17 (27.9)
15-20	61 (32.1)	28 (35.4)	4 (22.2)	10 (31.2)	19 (31.2)
>20	38 (20.0)	15 (19.0)	3 (16.7)	4 (12.5)	16 (26.2)
No. of prior episodes					
<3	46 (23.4)	18 (22.2)	4 (20.0)	8 (23.5)	16 (25.8)
3-4	64 (32.5)	31 (38.3)	5 (25.0)	9 (26.5)	19 (30.6)
5-6	45 (22.8)	16 (19.8)	5 (25.0)	9 (26.5)	15 (24.2)
>6	42 (21.3)	16 (19.8)	6 (30.0)	8 (23.5)	12 (19.4)
No. of episodes in prior pregnancies					
Never pregnant	49 (25.3)	20 (25.3)	4 (21.0)	12 (36.4)	13 (20.6)
None	96 (49.5)	37 (46.8)	11 (57.9)	11 (33.3)	37 (58.7)
>1	49 (25.3)	22 (27.8)	4 (21.0)	10 (30.3)	13 (20.6)
No. of prior postpartum episodes					
Never pregnant	49 (26.1)	20 (26.3)	4 (22.2)	12 (36.4)	13 (21.3)
None	84 (44.7)	38 (50.0)	6 (33.3)	11 (33.3)	29 (47.5)
>1	55 (29.3)	18 (23.7)	8 (44.4)	10 (30.3)	19 (31.2)
Duration of prior episode, wk					
1-6	43 (23.1)	13 (16.9)	5 (26.3)	9 (29.0)	16 (27.1)
7-12	48 (25.8)	21 (27.3)	4 (21.0)	7 (22.6)	16 (27.1)
13-36	49 (26.3)	22 (28.6)	7 (36.8)	8 (25.8)	12 (20.3)
>36	46 (24.7)	21 (27.3)	3 (15.8)	7 (22.6)	15 (25.4)
Time since onset of most recent episode, wk					
0-24	28 (15.3)	10 (13.0)	4 (21.0)	5 (16.1)	9 (16.1)
25-72	54 (29.5)	16 (20.8)	9 (47.4)	12 (38.7)	17 (30.4)
73-144	47 (25.7)	19 (24.7)	4 (21.0)	7 (22.6)	17 (30.4)
>144	54 (29.5)	32 (41.6)	2 (10.5)	7 (22.6)	13 (23.2)
No. of attempts to discontinue antidepressant medication					
0	49 (26.5)	21 (28.0)	3 (16.7)	13 (40.6)	12 (20.0)
1	57 (30.8)	23 (30.7)	3 (16.7)	9 (28.1)	22 (36.7)
2	35 (18.9)	17 (22.7)	5 (27.8)	5 (15.6)	8 (13.3)
>2	44 (23.8)	14 (18.7)	7 (38.9)	5 (15.6)	18 (30.0)
History of suicide attempts					
No	154 (81.9)	64 (82.0)	16 (88.9)	27 (84.4)	47 (78.3)
Yes	34 (18.1)	14 (18.0)	2 (11.1)	5 (15.6)	13 (21.7)
Comorbidity					
No	82 (46.9)	30 (42.9)	7 (41.2)	17 (56.7)	28 (48.3)
Yes	93 (53.1)	40 (57.1)	10 (58.8)	13 (43.3)	30 (51.7)
Family history of depression					
No	36 (19.6)	15 (19.5)	3 (16.7)	6 (18.8)	12 (21.0)
Yes	148 (80.4)	62 (80.5)	15 (83.3)	26 (81.2)	45 (79.0)
Baseline antidepressants					
TCA	28 (13.9)	9 (11.0)	5 (25.0)	3 (8.8)	11 (16.9)
SSRI/SNRI	142 (70.6)	66 (80.5)	13 (65.0)	22 (64.7)	41 (63.1)
Combination	22 (11.0)	5 (6.1)	2 (10.0)	9 (26.5)	6 (9.2)
Other monotherapy	9 (4.5)	2 (2.4)	0 (0.0)	0 (0.0)	7 (10.8)

Abbreviations: SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
*Data are expressed as No. (%). Columns may not sum due to missing data.

Table 3. Relapse of Major Depression During Pregnancy

Relapse Status	All Women	Medication Status			
		Maintained	Increased	Decreased	Discontinued
No relapse	115 (57.2)	61 (74.4)	11 (55.0)	22 (64.7)	21 (32.3)
Relapse by trimester					
All	86 (42.8)	21 (25.6)	9 (45.0)	12 (35.3)	44 (67.7)
First	44 (51.2)	11 (52.4)	7 (77.8)	5 (41.7)	21 (47.7)
Second	31 (36.0)	9 (42.9)	2 (22.2)	3 (25.0)	19 (43.2)
Third	11 (12.8)	1 (4.8)	0 (0.0)	4 (33.3)	4 (9.1)

tinuous months prior to conception or medication discontinuation or discontinuation attempt was necessary to meet inclusion criteria for the study. The large majority of participants (184 [92%]) were noted at baseline to receive therapy predominantly with SSRIs or dual-action antidepressants either alone or in combination with other antidepressants. Patients were treated with the following SSRI/serotonin norepinephrine reuptake inhibitor (SNRI) medications: paroxetine (n=24), sertraline (n=45), citalopram (n=20), escitalopram (n=1), venlafaxine (n=25), fluoxetine (n=70), fluvoxamine (n=3); bupropion was also used (n=20), although mostly as an adjunct treatment (n=15) vs monotherapy (n=5). Monotherapy with tricyclic antidepressants was far less common (n=7 [4%]). Combination antidepressant therapy was used by 22 participants (14%), while 4 of the participants (2%) were treated with other antidepressant monotherapy, ie, monoamine oxidase inhibitor or nefazodone.

Severity of mood disorder measured by factors such as duration of illness ($\chi^2_9=6.15$, $P=.72$), number of previous episodes ($\chi^2_9=3.54$, $P=.94$), and frequency of comorbid psychiatric illness ($\chi^2_9=1.88$, $P=.60$) was not associated with choosing to maintain or discontinue medication over the course of the pregnancy. However, women who maintained their medication therapy during pregnancy were more likely to be receiving an SSRI regimen than those who chose to alter their medication regimen either proximate to or shortly following conception (Fisher exact test, $P=.01$).

Relapse of Depression During Pregnancy

The proportion of the sample that relapsed across pregnancy is shown in TABLE 3. Forty-three percent of women in the sample relapsed during pregnancy, and half of those relapsed during the first trimester. Among women who maintained their medication throughout the pregnancy, 26% relapsed compared with 68% of those who discontinued their medication. Women who increased or decreased their medication had a rate of relapse between those who maintained and those who discontinued their medication (45% and 35%, respectively). Mean HAM-D scores at the time of relapse for those who discontinued or maintained their antidepressant therapy were 23.7 (SD=7.4) and 20.8 (SD=7.5), respectively. No participants attempted suicide during the course of the study. For those who discontinued (n=65) or decreased their antidepressant (n=34) from their optimum dose at baseline, 60 participants (61%) reintroduced antidepressant therapy during pregnancy.

We used a life-table approach to assess time to relapse as a consequence of medication status over the course of the pregnancy. As shown in the FIGURE, women who increased or discontinued their medication had a more rapid time to relapse than those who maintained or decreased their medication. The magnitude of this difference is shown in TABLE 4 using Cox proportional hazards. After adjustment for the main effects of clinical center, marital status, number of prior episodes, and type of medication used at the start of pregnancy with no interactions, women who discontinued their medication had a 5-fold increased risk of relapse over the course of their pregnancy compared with women who maintained their medication. To determine if this association was driven by those women who miscarried or electively terminated their pregnancies, or by those who were lost to follow-up or chose to discontinue participation in the study, we restricted the sample to only those women who were followed up until delivery. We found that the association was even stronger in this smaller sample. Last, in the Figure we note that among women who discontinued their antidepressant, medication reintroduction attenuated the risk of relapse, but this risk was still substantially greater than that seen in women who maintained their current medication status.

Predictors of Relapse of Depression

We examined whether certain demographic and clinical variables were associated with relapse of depression during pregnancy. No statistically significant association was noted between race, educational status of partner, and baseline antidepressant treatment and depressive relapse during pregnancy. However, there was a trend for married patients to be somewhat protected against relapse of depression compared with single patients (HR, 0.4; 95% CI, 0.1-1.3; $P=.13$). Women who were older than 32 years were noted to have a 60% reduction in the rate of relapse compared with younger women (<32 years) (HR, 0.4; 95% CI, 0.2-0.8; $P=.01$). Given the extent to which duration of depressive illness and number of previous episodes of depression predict risk of recurrent depression,[32-34] we also investigated the association between these variables and relapse of depression during pregnancy adjusting for all other demographic and clinical variables (age, race, education, education of partner, marital status, baseline antidepressant therapy) and medication change (if any) (ie, discontinuation or increase of antidepressant). Both duration of depres-

sive illness (>5 years) and history of more recurrent depressive illness (>4 episodes) were associated with a significant increase in risk of depressive relapse during pregnancy (HR, 2.7; 95% CI, 1.5-4.7; $P = .009$; HR, 3.6; 95% CI, 1.9-7.0; $P < .001$).

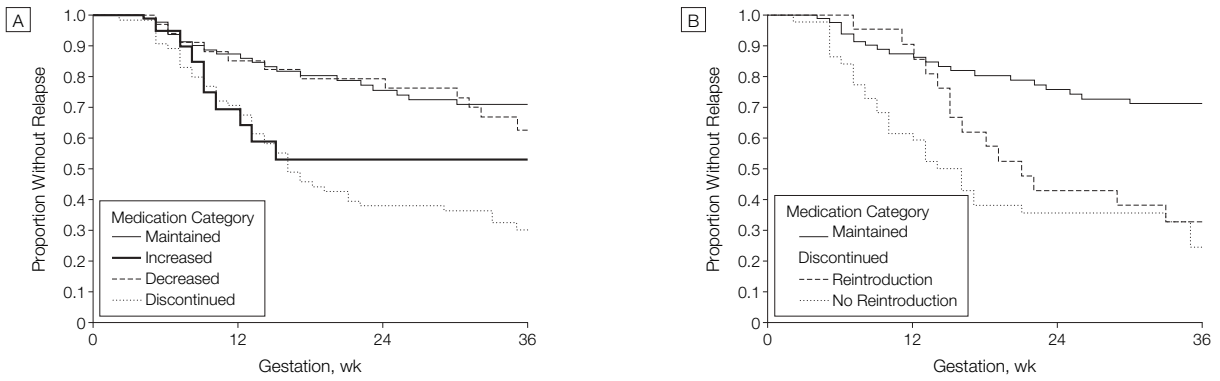
COMMENT

There has been a common belief that characteristic hormonal changes associated with pregnancy are inherently "protective" with respect to new onset of depression or risk of depressive relapse and that discontinuation of psychiatric medications should be almost uniformly pursued given concerns regarding prenatal exposure to these agents. Our data suggest that this is not the case. To our knowledge, there are no other data available regarding risk of relapse across pregnancy in women with histories of recurrent depression derived from clinical settings. O'Hara and colleagues[3] describe similar prevalence rates of depression in pregnant and nongravid women, and another community-based study has noted significant levels of depressive symptoms across pregnancy.[4]

Among the reasons for conducting the current study was to more systematically quantify risk of relapse of depression in pregnant women with histories of depression who are treated with antidepressants and who plan to conceive or who inadvertently conceive. Given the prevalence of depression in reproductive-age women, the prevalence of antidepressant use in this population, and the frequency of unplanned pregnancy, the ability to inform patients about risk of depressive relapse if either discontinuation or maintenance of treatment is pursued as a clinical course has significant implications. Our data suggest that women with histories of even highly recurrent depressive illness are likely to discontinue antidepressant use during attempts to conceive or after conception. However, such changes in treatment should proceed while patients are informed not only about the risk of prenatal exposure to medication, but also the risk of relapse associated with changes in ongoing pharmacological therapy.

In the current study, we noted that 68% of the women who discontinued antidepressant treatment proximate to conception relapsed during pregnancy; of those who relapsed, approximately 50% did so in the first trimester of pregnancy and 90% experienced recurrence of depression by the end of the second trimester. This is compared with the 26% of women who re-

Figure. Kaplan-Meier Curves Illustrating the Time to Relapse by the 4 Medication Categories and Medication Reintroduction Categories



No. at Risk				
Maintained	82	63	49	28
Increased	20	13	9	4
Decreased	34	29	26	13
Discontinued	65	46	23	11

No. at Risk				
Maintained	82	63	49	28
Discontinued				
Reintroduction	21	19	9	3
No Reintroduction	44	27	14	8

Table 4. Cox Proportional Hazard Ratios for Risk of Relapse of Major Depression Over the Course of Pregnancy by Medication Status*

	Medication Status			
	Maintained	Increased	Decreased	Discontinued
All women (N=201)				
Hazard ratio (95% confidence interval)*	1.0	2.8 (1.2-6.3)	1.2 (0.6-2.5)	5.0 (2.8-9.1)
P value		.02	.60	<.001
Women who did not miscarry, electively terminate pregnancy, or drop out of the study before 36 wk (n = 163)				
Hazard ratio (95% confidence interval)*	1.0	3.5 (1.5-8.3)	1.0 (0.4-2.5)	6.6 (3.4-12.6)
P value		.003	.92	<.001

*Adjusted for clinical center, marital status, number of prior depression episodes, and type of medication therapy (selective serotonin reuptake inhibitor vs other).

lapsed while sustaining preconception dosages of antidepressant (at least up until 16 weeks' gestation) where again approximately half of those who relapsed did so in the first trimester. These reported rates of relapse among pregnant women who either discontinued or maintained antidepressant treatment are strikingly similar to those reported by Kupfer and colleagues in nongravid samples.[5] It is also noteworthy that 60% of the women who discontinued antidepressant treatment in the current study at the beginning of pregnancy reintroduced antidepressant therapy during pregnancy. This was consistent with our earlier findings.[25] Differences in time to relapse between those who discontinued and those who maintained antidepressant treatment during pregnancy were also significantly different, with a 5-fold difference noted in risk of depressive relapse.

The risk of relapse among patients who either increased their medication during the time interval permissible for inclusion in the analysis or who decreased their antidepressant from the optimal dose that had afforded at least 3 months of euthymia deserves comment. Patients who increased their antidepressant typically did so at least once early on in pregnancy and often continued that intensity of treatment. However, others frequently increased antidepressant on multiple occasions across pregnancy (data not shown). Presumably, such increases in antidepressant somatotherapy would have been instituted in response to subsyndromal symptoms not initially reaching the proportion of major depression but in situations where such symptoms were considered to be a harbinger of frank depressive relapse. Thus, those women who increased their antidepressant appear quite distinct from a clinical perspective than those who maintained their antidepressant treatment across the entire exposure period (12 weeks before LMP until 16 weeks' gestation), a difference that is also reflected in the nearly 3-fold higher risk of depressive relapse between the 2 groups.

With respect to those who decreased their medication dose from a previous optimal dose, relapse risk was only modestly higher compared with those who maintained consistent antidepressant therapy across pregnancy. Common clinical scenarios for the women in this group included lowering the dose of SSRI from a previous dose or discontinuation of one antidepressant from a combination regimen.

These findings have important clinical implications. While some women may experience affective well-being during pregnancy, the current study suggests that pregnancy is not uniformly protective with respect to risk of relapse of major depression. Women with histories of depression who are euthymic in the context of ongoing antidepressant therapy should be aware of the risk of depressive relapse during pregnancy following antidepressant discontinuation. With this information, some women with histories of recurrent depressive illness may choose to maintain antidepressant therapy during attempts to conceive and during pregnancy. Such a treatment option might be particularly understandable given the growing amount of reproductive safety information available for commonly used antidepressants, including tricyclic antidepressants, SSRIs, and dual-action antidepressants (SNRIs).[19,20,35]

Conversely, the knowledge that half of the women who discontinue antidepressant treatment proximate to conception do not relapse early in pregnancy might prompt others to pursue medication discontinuation to avoid prenatal exposure during a critical period of organogenesis such as the first 12 weeks of gestation. It is noteworthy that as some of these patients might reintroduce antidepressant therapy in the second trimester, our data (Figure) suggest that reintroduction of antidepressant therapy during pregnancy attenuated risk of depressive relapse, but not entirely. It appears that although antidepressant reintroduction attenuates risk of depressive relapse, depression is still noted more frequently in those who elect this clinical course than among patients who sustain treatment with these medications.

Several limitations of the current study should be noted. First, the current investigation used a nonrandomized design. A randomized design with respect to antidepressant use during pregnancy was not considered ethical. However, differences among the 4 medication groups were controlled for in the analysis. Another limitation of the study relates to the highly recurrent nature of depression in those women who participated. It is possible that the risk of relapse associated with antidepressant discontinuation in patients with less severe depression might be lower than that noted for the participants in the current investigation or among women from regions of the country not represented in the current sample. Another limitation of the current findings derives from the possibility of misclassification of the temporal sequence between relapse and antidepressant discontinuation. Although data regarding changes in pharmacotherapy and relapse were obtained prospectively, it is possible that depressive relapse had begun before the discontinuation of the antidepressant.

Nonetheless, our findings help to refine the risk-benefit decision for those women with major depression who are treated with antidepressant medications. These women must weigh concerns about prenatal exposure to these medications ranging from risk of malformations to risk of obstetrical and perinatal complications.[15] These women should also consider the risks of depressive relapse during pregnancy and the effects of untreated depression on fetal and maternal well-being.[36] Depression is a highly prevalent illness in women and frequently has its onset during the childbearing years.[37] With greater awareness and increasing treatment of depression in the community, growing numbers of women may face a clinical decision regarding use of antidepressant medication during pregnancy. Navigating this clinical course can be facilitated by the accurate de-

lineation of the relative risks of prenatal exposure to medication on the one hand and the risk of relapse of psychiatric disorder on the other. Quantification of these risks affords clinicians the opportunity to make collaborative treatment decisions consistent with individual needs and wishes. Such information can also help to refine treatment guidelines for women with a history of depression who are planning to conceive or who experience mood disorders during pregnancy.

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Author Contributions: Dr Cohen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Cohen, Altshuler, Harlow, Nonacs, Viguera, Reminick, Stowe.
Acquisition of data: Cohen, Harlow, Nonacs, Newport, Viguera, Suri, Burt, Hendrick, Reminick, Loughhead, Stowe.
Analysis and interpretation of data: Cohen, Harlow, Nonacs, Newport, Viguera, Reminick, Vitonis, Stowe.
Drafting of the manuscript: Cohen, Altshuler, Harlow, Viguera, Burt, Reminick, Loughhead, Vitonis, Stowe.
Critical revision of the manuscript for important intellectual content: Cohen, Altshuler, Nonacs, Newport, Viguera, Suri, Hendrick, Reminick, Stowe.
Statistical analysis: Harlow, Vitonis.
Obtained funding: Cohen, Altshuler, Viguera, Suri, Stowe.
Administrative, technical, or material support: Altshuler, Newport, Viguera, Burt, Hendrick, Reminick, Loughhead, Stowe.
Study supervision: Cohen, Altshuler, Harlow, Nonacs, Viguera, Stowe.
Financial Disclosures: Dr Newport has served on the speakers bureaus for GlaxoSmithKline, Lilly, and Pfizer. Dr Stowe has served on the speakers bureaus for GlaxoSmithKline, Wyeth, and Pfizer; has received grants from GlaxoSmithKline and Wyeth; and has served on advisory boards for Bristol-Myers Squibb and GlaxoSmithKline. None of the other authors reported disclosures.
Funding/Support: This work was funded by multiinstitutional collaborative grants from the National Institute of Mental Health (MH 56420-05, MH 56492-04, MH 56555-01A2).
Role of the Sponsor: The National Institute of Mental Health had no role in the design and conduct of the study; in the collection, analysis, interpretation of the data; or in the preparation, review, or approval of the manuscript.

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CORRECTION

Incomplete Financial Disclosure: In the Original Contribution entitled "Relapse of Major Depression During Pregnancy in Women Who Maintain or Discontinue Antidepressant Treatment" published in the February 1, 2006, issue of *JAMA* (2006;295:499-507), financial disclosures were omitted. The complete disclosure statement follows: Dr Altshuler is a consultant to Abbott Laboratories, Eli Lilly, Forest Pharmaceuticals, Janssen Pharmaceutica, Pfizer, Solvay, and Bristol-Myers Squibb; receives grant support from Abbott, Eli Lilly, Forest, GlaxoSmithKline, and Solvay; has received honoraria from Abbott, Bristol-Myers Squibb, Eli Lilly, Forest, and GlaxoSmithKline; and is on the speakers bureaus and/or advisory boards of Abbott, Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Pfizer, Wyeth, and Solvay. Dr Burt is a consultant for Eli Lilly, GlaxoSmithKline, Bristol-Myers Squibb, and AstraZeneca, and has received honoraria from and is on the speakers and/or advisory boards for Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, AstraZeneca, Forest, and Pfizer. Dr Cohen has received grant support from AstraZeneca Pharmaceuticals, Berlex Laboratories, Eli Lilly, Forest, GlaxoSmithKline, Janssen Pharmaceuticals, Sepracor, and Wyeth-Ayerst; is a consultant for Eli Lilly, GlaxoSmithKline, Janssen, Ortho-McNeil Pharmaceuticals, Novartis Pharmaceuticals, and Wyeth-Ayerst; and is on the speakers bureau of AstraZeneca, Berlex, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pfizer, and Wyeth-Ayerst. Dr Hendrick is a member of the speakers bureaus for GlaxoSmithKline, Forest, and Pfizer. Dr Newport has served on the speakers bureaus for GlaxoSmithKline, Lilly, and Pfizer. Dr Nonacs is on the speakers bureau of GlaxoSmithKline. Dr Stowe has served on the speakers bureaus for GlaxoSmithKline, Wyeth, and Pfizer; has received grants from GlaxoSmithKline and Wyeth; and has served on advisory boards for Bristol-Myers Squibb and GlaxoSmithKline. Dr Suri has received an honorarium for a speaking engagement with Pfizer. Dr Viguera is on the speakers bureau of GlaxoSmithKline.

One writes such a story not out of the leaves of trees still to be observed, nor by means of botany and soil-science; but it grows like a seed in the dark out of the leaf-mold of the mind: out of all that has been seen or thought or read, that has long ago been forgotten, descending into the deeps. No doubt there is much selection, as with a gardener: what one throws on one's personal compost-heap; and my mold is evidently made largely of linguistic matter.
—J. R. R. Tolkien (1892-1973)

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