Anxiety Disorders Following Miscarriage

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Background: Several previous studies have established that miscarriage is a risk factor for depressive symptoms and disorder. By contrast, research on miscarriage as a possible risk factor for anxiety symptoms is inconclusive, and for anxiety disorders, sparse and uninformative. The current study examines the incidence of and relative risk for 3 DSM-III anxiety disorders (obsessive-compulsive disorder [OCD], panic disorder, and phobic disorders) within the 6 months following miscarriage. Adequate diagnostic data on other anxiety disorders were not available.

Method: Using a cohort design, we tested whether women who miscarry are at increased risk for a first or recurrent episode of an anxiety disorder in the 6 months following loss. The miscarriage cohort consisted of women attending a medical center for spontaneous abortion (N = 229); the comparison group was a population-based cohort of women drawn from the community (N = 230).

Results: Among miscarrying women, 3.5% experienced a recurrent episode of OCD, compared with 0.4% of community women (relative risk [RR] = 8.0; 95% confidence interval [CI] = 1.0 to 63.7). The relative risk for noncomorbid panic disorder was substantial (RR = 3.6), albeit not statistically significant (95% CI = 0.8 to 17.2). There was no strong evidence for increased risk for phobic disorders or agoraphobia, combined or considered separately, in the 6 months following loss. Relative risk for all 3 disorders combined was 1.5 (95% CI = 0.9 to 2.3).

Conclusion: In this first miscarriage cohort study using a concurrent frequency-matched comparison group, miscarriage was a substantial risk factor for an initial or recurrent episode of OCD. Given statistical power limitations of this investigation, the current findings do not preclude a possible contribution of miscarriage to risk for other anxiety disorders.

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For many women, miscarriage constitutes an unanticipated, stressful experience associated with considerable pain, fear, sadness, and discomfort.[1,2] Clinical attention in the early weeks after loss may help to offset later, more serious psychological and psychiatric consequences. In order to develop appropriate clinical screening and treatment protocols, empirical evaluation of the specific mental health consequences of miscarriage is necessary. Although much research has established that miscarriage is a risk factor for depressive reactions ranging from depressive symptoms to major and minor depressive disorders,[3–10] systematic study of anxiety as a psychiatric consequence of miscarriage has been rare. The fact that miscarriage can represent a stressful life event,[11,12] together with a growing literature reporting increased anxiety disorders postpartum[13–15] (for a review, see Shear and Mammen[16]), raises the possibility that the psychiatric sequelae of miscarriage may include increased risk for anxiety as well as depression.

A number of studies provide evidence suggesting elevated anxiety symptoms following pregnancy loss (e.g., references 7, 9, 11, 17–20). Among studies that included comparison groups unexposed to loss, Thapar and Thapar,[9] for example, used the Hospital Anxiety and Depression Scale (HAD) and found that miscarrying women reported significantly greater anxiety at both 24 hours (p < .001) and 6 weeks (p < .01) following loss, compared

with an antenatal clinic group.[9] Using the State-Trait Anxiety Inventory, Beutel and colleagues[17] found that the anxiety scores assessed shortly after miscarriage were significantly increased above those of age-matched, pregnant comparison women who were in their first 20 weeks of an uncomplicated pregnancy (p < .001). At a 6-month follow-up, however, the anxiety scores of the miscarrying women were no longer elevated significantly above those of the comparison group.

Some studies indicate that anxiety symptoms may be more prominent or more elevated than depressive symptoms postmiscarriage.[19–21] Lee et al.[19] compared frequency of anxiety and depressive symptoms assessed with the HAD in a sample of 60 women at 1 week and 4 months following miscarriage with previously reported estimates for community samples. At 1 week postmiscarriage, 35.9% of their sample had elevated levels of anxiety symptoms and 7.7% had elevated levels of depressive symptoms. At 4 months postmiscarriage, 28.2% of their sample had elevated levels of anxiety symptoms, and 5.1% had elevated levels of depressive symptoms, with anxiety scores remaining significantly above those in the community samples.[19] Although a comparison group was not employed, Prettyman et al.,[20] using the HAD, found that 41% of 65 miscarrying women had significant levels of anxiety within the first week after miscarriage, whereas only 22% showed significant levels of depressive symptoms during the same time period. Twelve weeks after miscarriage, frequency of anxiety symptoms remained greater than frequency of depressive symptoms (i.e., 32% versus 6%, respectively). Nikcevic et al.[21] found anxiety symptoms elevated in 45%, whereas depressive symptoms (both measured by the HAD) were elevated in only 15% of women after miscarriage. In that study, women were assessed at a median time of 187 days after the loss. There was no significant association between the time interval since the miscarriage and symptomatology.[21] However, at least 2 investigations,[22,23] albeit lacking comparison groups, failed to find any apparent elevation of anxiety symptoms following miscarriage.

Research on risk for anxiety disorders following miscarriage has been quite limited. Of the 2 studies published, Wisner et al.[15] investigated the natural history of pregnancy and the postpartum period in a series of women (N = 22) with preexisting panic disorder over 5 years. Two of the women miscarried and had an onset of panic disorder in the immediate postmiscarriage period. Lee et al.[24] report that 6 weeks after miscarriage, 1.3% of 150 miscarrying women received a DSM-III-R diagnosis of anxiety disorder not otherwise specified using the Structured Clinical Interview for DSM-III-R (SCID). However, the absence of a comparison group in both studies precludes clear interpretation of these findings. In sum, studies of increased risk for development of anxiety symptoms following miscarriage have found mixed re-

sults, and studies of anxiety disorders are sparse and uninformative on the question of increased risk.

The current study is the first investigation to date to examine the incidence of anxiety disorders following miscarriage in a rigorously designed cohort study with a concurrent frequency-matched comparison group. Specifically, we compare the risk for developing 1 of 3 DSM-III anxiety disorders (i.e., obsessive-compulsive disorder [OCD], panic disorder, or phobic disorders)[25] among miscarrying women as assessed with a structured clinical interview within the 6 months following loss with the risk among women in the community free of recent reproductive loss or childbirth. Adequate diagnostic data on other anxiety disorders were not available.

METHOD

Study Design

Phase 1. The current study comprises a hospital-based miscarriage cohort and a comparison cohort of women drawn directly from the community assessed between 1984 and 1987. The miscarriage cohort consisted of women attending a New York City hospital for a miscarriage, with most seen on an outpatient basis. Miscarriage is defined as the involuntary termination of a nonviable intrauterine pregnancy before 28 completed weeks of gestation with the conceptus dead on expulsion. This cohort was derived from miscarrying women participating in an antecedent case-control study of spontaneous abortion.[26,27] After the study protocol was described to potential participants, written informed consent was obtained for those agreeing to participate. At the conclusion of the case-control interview, participants who were at least 18 years of age, English- or Spanish-speaking, and accessible by telephone were invited to enter phase 1 of the present investigation. All eligible women were targeted to be interviewed at 3 timepoints: 2 weeks, 6 weeks, and 6 months after loss. Among eligible miscarrying women, 73% (N = 382) were assessed at 1 or more of these time points[4] using the Center for Epidemiologic Studies Depression scale (CES-D).[28]

The community cohort comprised women from the same community as the miscarrying women but who had not been pregnant in the preceding 12 months. The community group served as an unexposed cohort, allowing estimation of the frequency of psychiatric disorders in the absence of any recent reproductive event (including childbirth, which itself may be associated with increased levels of anxiety). Women for the community cohort were located by random-digit dialing of telephone numbers based on the same telephone area codes and exchanges as the interviewed miscarrying women. Community women were frequency-matched to the miscarrying women on age, education, language of interview (English or Spanish), and season of interview. Of known eligible community women, 82% (N = 318) were interviewed during

phase 1. Within the miscarriage and community cohorts, interviewed and uninterviewed women were similar in age, ethnicity, education, language, season of interview, and depressed mood.[4,5]

Phase 2. Following phase 1, women in the miscarriage and community cohorts were invited to enter phase 2, comprising a single psychiatric diagnostic assessment. Among study-eligible participants, 60% (N = 229) of miscarrying women and 72% (N = 230) of community women were assessed in phase 2.[6] Within the miscarriage cohort, women interviewed and not interviewed did not differ substantially on reproductive history. However, women who were white, had higher education, and were married were overrepresented among those interviewed. Interviewed and uninterviewed community women were similar on all major sociodemographic and reproductive history variables.[6]

Phase 1 included a measure of anxiety symptoms,[29] which allowed us to compare the level of anxiety symptoms of those who agreed and refused to complete the Diagnostic Interview Schedule (DIS). Among the miscarriage and community cohorts considered separately, the mean anxiety symptom scores of those who did and did not complete the DIS were nearly identical in unadjusted and adjusted analyses. These findings suggest that anxiety symptom levels among women who completed the DIS were representative of all women invited to participate in phase 2 of the study within each cohort.

Measurement of Psychiatric Disorder: The Diagnostic Interview Schedule

Psychiatric disorders in the 2 study cohorts were measured with the DIS, a structured interview developed for the National Institute of Mental Health Epidemiologic Catchment Area (ECA) studies to obtain psychiatric diagnoses in population samples using lay interviewers.[30–32] The DIS employs a fixed sequence of standardized questions and response options to secure information on the presence, severity, and distribution of psychiatric symptoms over time. The DIS used in the current study, comprising data collected in the mid-1980s, was necessarily based on DSM-III criteria. Diagnoses of panic disorder, specific phobic disorders, or OCD were assigned to those women meeting DSM-III criteria.[25] Agoraphobia is a specific phobia that can be associated with significant dysfunction and is accorded special clinical attention as an associated feature of panic disorder in current assessments.[33] Therefore, after investigating phobias generally, including agoraphobia, we examined agoraphobia as a separate diagnostic entity as well. The DIS version used in this study did not collect adequate data on symptoms or other diagnostic criteria (e.g., functional impairment) sufficient to derive diagnoses of generalized anxiety disorder or posttraumatic stress disorder, nor was systematic information available on pharmacologic interventions.

Table 1. Selected Sociodemographic and Reproductive History Characteristics of Women in the Miscarriage and Community Cohorts[a]

Characteristic	Miscarriage Cohort (N = 229) N	Miscarriage Cohort (N = 229) %	Community Cohort (N = 230) N	Community Cohort (N = 230) %
Sociodemographic				
Age, y				
18–24	49	21.4	55	23.9
25–34	122	53.3	122	53.0
> 34	58	25.3	53	23.1
Race/ethnicity				
White	97	42.4	85	37.0
Black	46	20.1	46	20.0
Hispanic	72	31.4	88	38.3
Other	14	6.1	11	4.8
Education				
< High school graduate	51	22.3	45	19.6
High school graduate	54	23.6	58	25.2
Some college	48	21.0	66	28.7
≥ College graduate	76	33.2	61	26.5
Annual income, $*[b]				
< 10,000	62	28.1	51	22.7
10,000–19,999	39	17.6	44	19.6
20,000–39,999	44	19.9	77	34.2
≥ 40,000	76	34.4	53	23.6
Marital status**				
Currently single	45	19.7	115	50.0
Married	157	68.6	80	34.8
Other	27	11.8	35	15.2
Reproductive				
No. of prior reproductive losses**[c]				
0	143	62.4	189	82.2
1	51	22.3	33	14.3
≥ 2	35	15.3	8	3.5
No. of elective abortions				
0	145	63.3	162	70.4
≥ 1	84	36.7	68	29.6
No. of living children**				
0	91	39.7	120	52.2
1	71	31.0	34	14.8
≥ 2	67	29.3	76	33.0
Time of gestation at loss[d]				
First trimester (< 14 wk)	156	68.1	...	...
Second trimester (14–26 wk)	72	31.4	...	...
Third trimester (> 26 wk)	1	0.4	...	...
Attitude toward the pregnancy				
Negative	25	10.9	...	...
Positive	204	89.1	...	...

[a]For each variable, differences in proportions between cohorts were evaluated using an overall chi-square test.
[b]Income data were missing for 3% of the women.
[c]Includes spontaneous abortions, fetal deaths, ectopic pregnancies, and neonatal deaths.
[d]Time from the last menstrual period to the date of expulsion of the conceptus.
*p < .05.
**p < .001.

Study Sample

The study sample included 459 women, 229 in the miscarriage cohort and 230 in the community cohort (Table 1). In both cohorts, approximately 50% of women were between 25 and 34 years of age at the start of the 6-month period. Roughly a third were white, a third were Hispanic, and 20% were black. Slightly over 50% had more than a high school education. Over two thirds of the women in

the miscarriage cohort experienced their loss in their first trimester of pregnancy. The miscarriage and community cohorts differed significantly on several sociodemographic and reproductive history characteristics. Miscarrying women were more likely to be married, have living children, and have a greater number of prior reproductive losses. None of the differences in sociodemographic or reproductive history characteristics between miscarrying and community cohorts were associated with risk for anxiety disorders, thereby precluding the need to control for these factors in the analyses.

Analytic Strategy

The data were screened for variables potentially confounding the association of miscarriage with each anxiety disorder individually (and with a combined category of "any anxiety disorder"). First, we examined the data for sociodemographic and reproductive history characteristics that both varied across cohorts and were associated with an outcome of study interest in the community cohort. Next, any such variable was judged to be a confounder if it changed the log odds ratio relating miscarriage to the anxiety disorder by more than four tenths of the standard error of the parameter estimate when entered into a logistic regression model.

Chi-square tests revealed that none of the variables that were distributed differently between the cohorts (i.e., marital status, number of living children, history of reproductive loss) were significantly associated with 6-month risk of OCD in the community cohort. Panic disorder was associated with both marital status and history of reproductive loss, and phobia was associated with number of living children. However, entry of these potential confounders in the corresponding logistic regression model changed the log odds ratio by less than four tenths of the standard error of the parameter estimate. Therefore, in the absence of evidence for confounding, we estimated the association between miscarriage and each anxiety disorder using unadjusted relative risks (RRs) and 95% confidence intervals (CIs).[34]

Relative risk is computed by dividing the 6-month total incidence rate of the anxiety disorder in the miscarriage cohort by that in the community cohort. For total incidence rates, the numerator includes women in the particular cohort who experienced 1 or more episodes of anxiety disorder during the 6 months of interest, whether a first lifetime episode or recurrent episode. The denominator includes all women in the particular cohort.

Our previous work has shown that miscarriage is associated with increased risk for both major and minor depressive episodes in the 6 months following reproductive loss.[3,6] To examine whether this relationship contributed to any observed association between miscarriage and anxiety disorders, we also conducted analyses with cases of comorbid anxiety and depression removed from the numerator and the denominator. Specifically, comorbidity was defined as having an episode of the anxiety disorder(s) in question and an episode of major or minor depression some time in the 6 months following miscarriage.

RESULTS

The 6-month total incidences for miscarrying and community women for a first or recurrent episode of any anxiety disorder under study (i.e., OCD, panic disorder, phobic disorders) were 15.7 and 10.9 per 100, respectively (RR = 1.5; 95% CI = 0.9 to 2.3) (Table 2).

Next, we calculated the relative risk for each anxiety disorder separately. In the 6 months following reproductive loss, miscarrying women were at significantly increased risk for a first or recurrent episode of OCD relative to community women (RR = 8.0; 95% CI = 1.0 to 63.7) (see Table 2). However, there was no strong evidence for increased risk of panic disorder (RR = 1.8; 95% CI = 0.5 to 5.9) or phobia (including agoraphobia) (RR = 1.3; 95% CI = 0.8 to 2.3) in the 6 months following miscarriage. When examined as a separate entity, the relative risk for agoraphobia was 2.5, but was not statistically significant (95% CI = 0.5 to 12.8).

Exclusion of Comorbid Cases

There were 6 cases of OCD in the miscarriage cohort and no cases in the community that were not comorbid with depressive disorder (see Table 2). Hence, the relative risk for OCD without comorbidity was not calculable. The proportion of miscarrying women with OCD (6/229) was significantly greater (p < .03) than the proportion of community women with OCD (0/230). The relative risk for panic disorder was 3.6 (95% CI = 0.8 to 17.2). For phobia (including agoraphobia), the relative risk was 1.0 (95% CI = 0.5 to 1.8), and for agoraphobia considered separately, the relative risk was 2.1 (95% CI = 0.4 to 11.2).

DISCUSSION

The results of our investigation reveal no overall increased risk for the 3 anxiety disorders combined following miscarriage. However, the risk of OCD appears increased in the 6 months following loss, even when the analysis is restricted to cases without a comorbid depressive disorder. (The 3 participants with OCD who were excluded due to co-occurring OCD and depression were the only 3 who also had a lifetime history of depressive disorder). Although no prior studies have examined frequency of OCD in relation to miscarriage, several previous clinical case series have studied frequency of OCD episodes in relation to pregnancy and the postpartum period. Overall, pregnancy and the postpartum period have been implicated in the risk of new onset or exacerbation of existing OCD. For example, Buttolph and Holland[35]

Table 2. Total Incidence and Relative Risk of Anxiety Disorders in a Cohort of Miscarrying (N = 229) and Community (N = 230) Women in the 6 Months Following Miscarriage[a]

Anxiety Disorder	No. of Cases	Incidence per 100 Participants	Relative Risk (95% confidence interval)
Any anxiety disorder (includes OCD, panic disorder, phobic disorders)			
All cases			
Miscarriage	36	15.7	1.5 (0.9 to 2.3)
Community	25	10.9	
Cases without comorbid depression[b]			
Miscarriage	26	11.9	1.3 (0.7 to 2.2)
Community	21	9.3	
OCD			
All cases			
Miscarriage	8	3.5	8.0 (1.0 to 63.7)
Community	1	0.4	
Cases without comorbid depression			
Miscarriage	6	2.7	Undefined[c]
Community	0	0.0	
Panic disorder			
All cases			
Miscarriage	7	3.1	1.8 (0.5 to 5.9)
Community	4	1.7	
Cases without comorbid depression			
Miscarriage	7	3.2	3.6 (0.8 to 17.2)
Community	2	0.9	
Phobic disorders (includes agoraphobia)			
All cases			
Miscarriage	28	12.2	1.3 (0.8 to 2.3)
Community	21	9.1	
Cases without comorbid depression			
Miscarriage	19	8.7	1.0 (0.5 to 1.8)
Community	20	8.9	
Agoraphobia			
All cases			
Miscarriage	5	2.2	2.5 (0.5 to 12.8)
Community	2	0.9	
Cases without comorbid depression			
Miscarriage	4	1.8	2.1 (0.4 to 11.2)
Community	2	0.9	

[a]Abbreviation: OCD = obsessive-compulsive disorder. Diagnoses based on an assessment using the Diagnostic Interview Schedule and the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition.
[b]Cases with a comorbid episode of major or minor depression in the 6 months following miscarriage were removed from the numerator and denominator.
[c]Undefined due to empty cell in the 2 × 2 table for this stratum.

studied 39 women diagnosed with OCD according to DSM-III-R criteria, of whom 59% reported an onset or worsening of OCD symptoms with pregnancy or childbirth, 15% having a first onset of OCD in the postpartum period. Neziroglu et al.[36] administered a questionnaire assessing life events associated with onset of OCD symptoms in 106 female patients who had a DSM-III-R diagnosis of OCD. Of the 59 women with children, 39% developed OCD during pregnancy, with half reporting symptom onset during their first pregnancy. Sichel et al.[37] reviewed the charts of 15 outpatient women with first onset of DSM-III-R OCD postpartum. They reported that the mean time to onset of OCD symptoms was 2.2 weeks postpartum and concluded that the puerperium might increase risk for the development of OCD.[37] Hertzberg et al.[38] reported a case of postpartum OCD that recurred after a subsequent pregnancy. Williams and Koran[14] re-

ported no postpartum onset in a sample of 57 women diagnosed with OCD, but an onset of OCD in pregnancy was observed in 13% of cases. Postpartum exacerbation was reported by 29% of the women with preexisting OCD who completed full-term pregnancies. Also, premenstrual worsening was described by 42% of the women, suggesting that OCD may in some cases be influenced by changes in gonadal hormones. Unfortunately, the absence of any comparison groups or other formal methods for comparing observed with expected values for the frequency of the outcome variable in these studies clouds interpretation of findings.

The OCD results may reflect the operation of a selection bias whereby miscarrying women with a history of OCD are more inclined than other women to seek medical attention for a miscarriage. As a consequence, women at increased risk for an episode of OCD would be overrepresented in the miscarriage cohort. This mechanism is an unlikely explanation for our findings for 2 reasons. First, we would expect this bias to operate most strongly with early first trimester loss and to be absent with later losses when medical attention is a virtual necessity. However, in our study, the magnitude of the odds ratio did not vary with length of gestation at time of loss. Second, we would expect the same type of selection bias to operate with the other anxiety disorders as well. Hence, the specificity of the OCD results also supports the argument against selection bias.

In our sample, all the women diagnosed with OCD were experiencing recurrent episodes. It is possible that pregnancy-related hormonal changes modifying serotonin neurotransmission play a role in the onset or recurrence of OCD.[39] A genetic transmission of vulnerability to OCD might be activated by the pregnancy or the event of the loss.[40] Furthermore, it has been hypothesized that psychosocial factors connected with pregnancy,[41] or more generic factors associated with acute stress and life events, could contribute to the recurrence of OCD.[42] However, research examining the relationship between general life stress and OCD relapse has been sparse. Interviewing a sample of 20 adolescents and children diagnosed with OCD about possible precipitating events, Thomsen[43] found that stressful family events (e.g., death of a family member) occurred prior to the onset or exacerbation of symptoms for 11 respondents. Examining the clinical

records of 72 children and adolescents diagnosed with OCD, Toro et al[44] found that in 53% of cases, a stress situation preceded the disorder. Given that these studies focused on nonadult samples, relied upon retrospective recall of events and archival data, and did not employ control groups, they shed little light on the current issue.

We found no significant association of panic disorder with miscarriage either when all cases of panic disorder were included in the analyses or when cases of comorbid panic and depression were removed. The one published study regarding episodes of panic disorder following miscarriage reports an increased risk.[15] However, this claim was not supported analytically by the use of a comparison group.

Findings of an association of pregnancy and/or the postpartum period with onset or exacerbation of panic disorder are highly varied.[15,16] Despite methodological insufficiencies in these studies, Shear and Mammen[16] suggest that, overall, panic symptoms tend to subside during pregnancy and to worsen during the first 3 months postpartum. The substantial point estimate of 3.5 for noncomorbid cases of panic disorder following miscarriage in the current study indicates that this area of panic disorder and the reproductive cycle warrant further research.

We found no evidence of elevated risk of first-onset or recurrent phobia (or agoraphobia considered separately) following miscarriage, with or without cases of comorbid depression. No other study published to date has examined the association of phobias with pregnancy, miscarriage, or the postpartum period.

The absence of a significant association between miscarriage and risk for panic disorder and phobia must be interpreted with caution. We investigated the total incidence of these anxiety disorders for a relatively limited period of time (i.e., 6 months) in a sample of fewer than 500 women. The statistical power to detect moderately increased risks associated with miscarriage therefore is very limited. It is also possible that the increased risk for anxiety symptoms observed postmiscarriage and postpartum does not translate to higher rates of anxiety disorders during this period. However, we did find that the proportion of miscarrying women with multiple anxiety disorder diagnoses (6/229) was greater than the proportion of community women with more than 1 anxiety disorder (1/230). The possible contribution of miscarriage to risk for the other anxiety disorders examined here, as well as to risk for generalized anxiety disorder and posttraumatic stress disorder, also merits further investigation in studies utilizing large sample sizes, unexposed cohorts, and more intensive monitoring of clinical outcomes.

Miscarriage is a significant risk factor for a first or recurrent episode of affective disorders including major depression and minor depression, as well as for depressive symptoms. The results of this cohort investigation suggest that miscarriage also is a significant risk factor for

a recurrent episode of OCD. Women should be monitored carefully postmiscarriage for worsening of their symptoms or for first onset of an affective disorder or OCD.

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