

Nulliparous Women with Recurrent Pregnancy Loss Have Increased Anxiety and Depression Scores During a Subsequent Pregnancy

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ABSTRACT

Study question: In nulliparous mothers with an ongoing pregnancy, do those with history of recurrent pregnancy loss (RPL) have a higher prevalence of symptoms of anxiety and depression than those without history of RPL?

Summary answer: History of RPL is associated with higher anxiety and depression scores during a subsequent pregnancy in nulliparous women.

What is known already: Sporadic pregnancy loss and recurrent pregnancy loss is associated with increased anxiety and depression, which can last for several months following a miscarriage.

Study design, size, duration: We conducted a secondary analysis of a prospective longitudinal cohort study between October 1, 2010, to September 30, 2013, including 9,481 participants.

Participants/materials, setting, methods: This is a secondary analysis of a prospective cohort study (NuMom2b) in which nulliparous women at eight medical centers across the United States were enrolled in their first trimester of a live singleton pregnancy. We stratified this cohort by RPL status defined as the presence of two or more miscarriages prior to the current pregnancy. Data were collected at visit 1 (between 6 weeks' gestation and 13 weeks and 6 days' gestation) and visit 3 (between 22 weeks' and 29 weeks and 6 days' gestation).

Results: During the first trimester, the median (interquartile range [IQR]) score for the State-Trait Anxiety Inventory (STAI-T) in women with RPL (34 [29,42]) was significantly higher than women without RPL (32 [27,39], $p < 0.001$). After adjusting for covariates, a history of RPL was significantly associated with an increase in anxiety (1.39 ± 0.38 , $p < 0.01$). The median score for the Edinburgh Postnatal Depression Score (EPDS) was also significantly higher in women with RPL in both early (6 [3,9] and later in pregnancy (5 [3,9]) compared with women without RPL (early 5 [3,8], later 5 [2,8] respectively, both $p < 0.001$). Similarly, after adjusting for covariates, participants who experienced RPL had significantly greater depression scores at visit 1 (0.50 ± 0.17 , $p < .01$) and visit 3 (0.60 ± 0.18 , $p < .01$) when compared to nulliparous mothers without history of RPL. The distribution of anxiety and depression severity significantly differed between women with RPL and those without RPL.

MeSH Terms: Abortion, Spontaneous; Abortion, Habitual; Anxiety / psychology*; Depression / psychology*; Female; Pregnancy

1. Introduction

Miscarriage is the most common complication in early pregnancy, affecting at least 15% of confirmed pregnancies¹. Recurrent pregnancy loss (RPL) affects 1-3% of couples of reproductive age and is defined by the American Society of Reproductive Medicine (ASRM) as two or more failed clinical pregnancies documented by ultrasonography or histopathological examination^{2,3}. The risk of subsequent pregnancy loss increases with the number of prior miscarriages⁴.

Although patient experiences of miscarriage vary widely, spontaneous pregnancy loss can be an unexpected and devastating diagnosis. Profound psychological sequelae have been documented following miscarriage, including grief, depression, anxiety and post-traumatic stress symptoms^{5,6}. These effects may persist for several months after the loss⁷. Individuals who have experienced miscarriage may worry about their ability to achieve and carry a subsequent pregnancy. During subsequent pregnancies, individuals with a history of pregnancy loss report higher levels of anxiety and depression in the first trimester, when uncertainty is greatest⁸. In the setting of recurrent pregnancy loss, this effect may be amplified, reflecting a cumulative psychological burden in which repeated losses reinforce fear of recurrence and anticipatory anxiety. However, data specifically examining mental health outcomes during an ongoing pregnancy among women with history of RPL remain limited.

The aim of the present study was to investigate the prevalence of trait anxiety and depression during an ongoing pregnancy in patients who have reported RPL compared with those who have not experienced RPL.

2. Materials and Methods

This study is a secondary analysis of nuMoM2b, a prospective cohort study. The methods have been previously described⁹. Briefly, the nuMoM2b study was conducted at eight medical centers across the United States from October 1, 2010, to September 30, 2013. NuMoM2b enrolled nulliparous women in their first trimester of a live singleton pregnancy and followed them at four timepoints through delivery: (Visit 1 [V1]) from 6 weeks 0 days to 13 weeks 6 days gestation; (V2) from 16 weeks 0 days to 21 weeks 6 days; (V3) from 22 weeks 0 days to 29 weeks 6 days; (V4) at delivery. Patients were excluded due to incomplete surveys, resulting in an overall sample size of 9,481. The study was approved by each study site's local institutional review board and all patients provided written informed consent.

The secondary retrospective analysis included patients enrolled in nuMoM2b who were previously diagnosed with RPL. RPL was defined as the presence of two or more miscarriages (loss of a fetus before 20-weeks 'gestation) prior to the current pregnancy.

Demographic data was collected at visit 1. An anxiety score was collected at visit 1 using the State-Trait Anxiety Inventory-Trait (STAI-T), a 20-item scale that rates each item on a 4-point Likert scale: (1) not at all; (2) somewhat; (3) moderately so; (4) very much so (10). Total scores range from 20 to 80 and were interpreted as: low anxiety (20-37), moderate anxiety (38-44) and high anxiety (45-80).

The Edinburgh Postnatal Depression Scale (EPDS) was collected at visits 1 and 3. EPDS scores were categorized into minimal, mild and probable clinical depression¹¹.

Demographic characteristics were described as mean (SD) and median [Q1, Q3] as applicable for continuous variables and frequencies for categorical variables. Statistical analysis was performed using Wilcoxon rank-sum test, Chi-square and analysis of variance tests as appropriate to evaluate if demographic characteristics were statistically significant between participants with and without history of RPL. Univariable and multivariable linear regression models were developed to evaluate the association of RPL with anxiety and depression scores. Multivariable analyses were a priori adjusted for potential confounders including maternal age, education (less than high school, high school or equivalent, some college or bachelor's and above), body mass index, marital status and presence of a mood disorder at baseline. A subgroup analysis was conducted among participants with RPL to assess whether outcomes varied according to prior pregnancy losses (2, 3 or ≥ 4). Significance was determined at $p < 0.05$. Analyses were conducted using R version 4.4.2.

3. Results

A total of 9,481 participants were included. Of these, 611 reported a history of RPL. 8,870 participants did not have history of RPL. Among participants with RPL, 82.2% had experienced 2 prior miscarriages. In contrast, most participants without RPL (79.8%) reported no prior pregnancy loss, although 20.2% had experienced 1 miscarriage previously.

3.1. Demographics

Demographics are reported in (Table 1). The mean (SD) age of participants with RPL was 28.7 years (6.0) versus 26.8 (5.6) in patients without history of RPL ($p < 0.001$). Participants with RPL had higher mean BMI (26.0 [22.5, 30.7] vs. 24.6 [21.9, 39.1], $p < 0.001$) when compared to participants without RPL. Marital status significantly differed between participants with and without history of RPL ($p < 0.001$). More participants with RPL were single and never married (52.5% vs. 38.5%), divorced (1.5% vs. 0.9%) or separated (0.5% vs. 0.2%) when compared to those without RPL. Participants who had not experienced RPL were more likely to be married when compared to RPL participants (60.4% vs. 45.5%, respectively).

3.2. Anxiety

Participants with history of RPL had greater trait anxiety scores in first trimester of pregnancy (adjusted $\beta \pm \text{SE}$ 1.39 $\pm$ 0.38, $p < 0.001$). Additionally, the distribution of STAI-T scores (low, moderate and high categories) differed by RPL status ($p < 0.001$). The proportion of moderate or high anxiety (scores 38 and higher) was 29.6% for participants without RPL and 37.0% in those with RPL.

3.3. Depression

Participants with RPL had greater depression scores at visit 1 (adjusted $\beta \pm \text{SE}$ 0.50 0.17 $\pm$, $p = 0.004$) and visit 3 (adjusted $\beta \pm \text{SE}$ 0.60 0.18 $\pm$, $p < 0.001$) when compared to patients without history of RPL. The distribution of EPDS scores differed between women who experienced RPL and those who had not at Visit 1 ($p = 0.009$) and Visit 3 ($p = 0.010$). Scores indicating probable clinical depression (13 or higher) were greater among participants with history of RPL when compared to those without at Visit 1 (first trimester; 10.5% vs. 7.3%) and Visit 3 (second/early third trimester; 9.6% vs. 6.5%).

Table 1: Maternal demographics stratified by RPL status.

	Overall (N = 9,481)	Non-RPL (n = 8,870)	RPL (n = 611)	p-value
Number of prior pregnancy losses				<0.001
0	7075 (74.6%)	7075 (79.8%)	0 (0.0%)	
1	1795 (18.9%)	1795 (20.2%)	0 (0.0%)	
2	502 (5.3%)	0 (0.0%)	502 (82.2%)	
3	82 (0.9%)	0 (0%)	82 (13.4%)	
4+	27 (0.3%)	0 (0.0%)	27 (4.4%)	
Maternal Age	27.0 (5.6)	26.8 (5.6)	28.7 (6.0)	<0.001
Mother's Race				<0.001
Non-Hispanic White	5,772 (60.9%)	5,483 (61.8%)	289 (47.3%)	
Non-Hispanic Black	1,316 (13.9%)	1,177 (13.3%)	139 (22.7%)	
Hispanic	1,538 (16.2%)	1,405 (15.8%)	133 (21.8%)	
Asian	380 (4.0%)	361 (4.1%)	19 (3.1%)	
Other	475 (5.0%)	444 (5.0%)	31 (5.1%)	
Mother's Education				<0.001
Less than High School	763 (8.0%)	724 (8.2%)	39 (6.4%)	
High School/GED	1,097 (11.6%)	1,012 (11.4%)	85 (13.9%)	
Some College	2,768 (29.2%)	2,556 (28.8%)	212 (34.7%)	
Bachelor's and Above	4,853 (51.2%)	4,578 (51.6%)	275 (45.0%)	
Mother's BMI	24.7 [22.0, 29.2]	24.6 [21.9, 29.1]	26.0 [22.5, 30.7]	<0.001
Data presented as mean (SD), median		[Q1, Q3] or n (%) as applicable		

BMI = body mass index

3.4. Anxiety and Depression Scores Among Women with RPL

Among women who experienced RPL, anxiety scores at Visit 1 were similar regardless of the number of prior pregnancy losses (adjusted $\beta \pm SE$ -0.62 0.79 $\pm$, $p=0.433$). Similarly, we found no evidence of an association between depression scores at visits 1 and 3 and the number of prior pregnancy losses the participant previously experienced (V1 adjusted $\beta \pm SE$ -0.25 $\pm$ 0.36, $p=0.493$; V3 adjusted $\beta \pm SE$ 0.34 0.37 $\pm$, $p=0.366$).

4. Discussion

The current study evaluated the prevalence of self-reported symptoms of trait anxiety and depression in RPL patients who participated in a large, prospective, multi-center cohort. We found that RPL participants reported higher rates of anxiety and depressive symptoms in early pregnancy when compared to those without history of RPL. Depressive symptoms remained statistically significantly greater for RPL participants as pregnancy progressed. These associations were maintained after adjusting for maternal age, education, marital status, body mass index and presence of a mood disorder at baseline.

Our results are consistent with previous studies that have demonstrated increased levels of anxiety and stress following pregnancy loss^{5,6,12} and, specifically, recurrent pregnancy loss^{13,14}. However, these studies were conducted in a non-pregnant population. Studies conducted at a single time point in pregnancy have demonstrated that history of pregnancy loss and RPL are associated with anxiety and depression in the first trimester of a subsequent pregnancy^{15,16}. Few studies have investigated the association of prior pregnancy loss and anxiety and depression using a longitudinal study design throughout pregnancy and no longitudinal study investigated RPL¹⁷⁻¹⁹. Our findings extend the current literature by demonstrating that the psychological impact

of recurrent pregnancy loss persists beyond the post-loss period and into a subsequent pregnancy in a diverse US population.

There is evidence of progressive attenuation of psychophysiological stress responses and improvement in psychological well-being with advancing gestation in an uncomplicated pregnancy^{20,21}. In contrast, we observed that women with RPL maintained higher depression scores when compared to women without RPL. This finding persisted from early pregnancy (V1) to the late second/early third trimester (V3). This finding aligns with recent prospective data from a smaller cohort demonstrating that women with a history of pregnancy loss did not exhibit a decrease in stress or improvement in mood throughout their pregnancy, unlike women without history of miscarriage²². This pattern reflects ongoing psychological vulnerability as pregnancy progresses.

Interestingly, a subgroup analysis of only participants who experienced RPL found that anxiety and depression scores did not significantly vary by the number of prior losses experienced. In contrast, a recent study found that a greater number of spontaneous miscarriages was significantly associated with higher risks of depression and anxiety in a non-pregnant population¹⁴. The discrepancy in our findings may reflect the differences in our population and study design. We examined anxiety and depression scores in a pregnant population in their first trimester and depression score later in pregnancy, whereas Hu et al. assessed a cohort of non-pregnant women over a median 12-year follow-up period¹⁴. Additionally, most of our participants experienced 0-2 pregnancy losses and the small sample sizes in higher-loss categories may have attenuated the dose-response relationship between number of pregnancy losses and anxiety and depression in a subsequent pregnancy.

These findings have clinical implications. Prenatal anxiety and depression are associated with maternal and fetal adverse

outcomes. Interestingly, as the pregnancy progresses beyond the time of their pregnancy loss, the depression scores were still elevated in women with RPL when compared to women without RPL. Prenatal anxiety and depression are associated with poorer obstetric outcomes, including increased rates of low birth weight and spontaneous preterm birth²³. Maternal prenatal anxiety and depression are associated with poorer child and adolescent development across multiple domains, including social-emotional, cognitive and motor²⁴. Therefore, psychological counseling and support are recommended for couples who experience RPL. Existing studies on improving care following pregnancy loss demonstrate that RPL patients have unique needs and may require extra sensitivity and tailoring to current reproductive status when provided medical care²⁵. Given the persistence of depressive symptoms in later pregnancy demonstrated in our study, mental health screening should be performed regularly throughout an ongoing gestation. Integrating psychological support into care models for patients with RPL may help address the emotional burden of subsequent pregnancies and improve patient-centered outcomes. Future studies should investigate targeted psychological interventions and their impact on anxiety, depression and maternal and child outcomes.

This study is not without limitations. This study was conducted as a secondary analysis of a prospective cohort study and variables were pre-collected. Length of time since most recent miscarriage was unknown and thus could not be adjusted for, despite evidence that suggests that shorter interpregnancy intervals are associated with increased anxiety and depression in a pregnancy following loss^{15,16}. Additionally, participants went through multiple levels of screening. One of the initial screening criteria was exclusion of participants with history of 3 or more spontaneous abortions. However, these participants were not ultimately excluded from participating in the cohort if this information was reported after enrollment. Thus, our sample includes participants who were not screened out, but who reported a history of more than 2 spontaneous miscarriages. The number of participants excluded due to multiple pregnancy losses is unknown. Prior pregnancy losses and mood symptoms were self-reported, which may introduce reporting bias. Lastly, anxiety was not assessed beyond Visit 1 and neither anxiety nor depression scores were collected in the late third trimester or postpartum.

In conclusion, individuals with a history of RPL experience higher levels of trait anxiety and depression during a subsequent ongoing pregnancy and experience persistently higher levels of depressive symptoms as the pregnancy progresses. These findings highlight the importance of proactive and sustained mental health screening and support as an integral component of prenatal care for patients with history of RPL.

5. Acknowledgements

5.1. Funding

None.

5.2. Conflict of interest

None.

5.3. Limitations, reasons for caution

This secondary analysis was performed on pre-collected data, limiting adjustment for additional factors. Assessment

of psychological symptoms was limited to two predetermined time points. Consequently, data were unavailable for later third trimester and postpartum.

5.4. Wider implications of the findings

Recurrent pregnancy loss is associated with higher rates of anxiety and depression in an ongoing pregnancy for a nulliparous patient. This highlights the importance of continued psychological support for RPL patients throughout the prenatal period. These findings extend the current literature by demonstrating that the psychological impact of recurrent pregnancy loss persists beyond the post-loss period and into a subsequent pregnancy.

5.5. Trial registration number

NCT0132259 (primary study).

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