Posttraumatic stress, anxiety and depression following miscarriage and ectopic pregnancy

OBSTETRICS

Posttraumatic stress, anxiety and depression following miscarriage and ectopic pregnancy: a multicenter, prospective, cohort study

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BACKGROUND: Early pregnancy losses are common, but their psychologic sequelae are often overlooked. Previous studies have established links between miscarriage and early symptoms of anxiety and depression. However, the incidence of posttraumatic stress symptoms and the psychologic response specifically to ectopic pregnancies have not been investigated.

OBJECTIVE: The purpose of this study was to investigate levels of posttraumatic stress, depression, and anxiety in women in the 9 months after early pregnancy loss, with a focus on miscarriage and ectopic pregnancy. Morbidity at 1 month was compared with a control group in healthy pregnancy.

STUDY DESIGN: This was a prospective cohort study. Consecutive women were recruited from the early pregnancy and antenatal clinics at 3 London hospitals and received emailed surveys that contained standardized psychologic assessments that included the Hospital Anxiety and Depression Scale and Posttraumatic stress Diagnostic Scale, at 1, 3, and 9 months after loss. Control subjects were assessed after a dating scan. We assessed the proportion of participants who met the screening criteria for posttraumatic stress and moderate/severe anxiety or depression. We used logistic regression to calculate adjusted odds ratios.

RESULTS: Seven hundred thirty-seven of 1098 women (67%) with early pregnancy loss (including 537 miscarriages and 116 ectopic pregnancies) and 171 of 187 control subjects (91%) agreed to participate. Four hundred ninety-two of the women with losses (67%) completed the Hospital Anxiety and Depression Scale after 1 month; 426 women (58%) completed it after 3 months, and 338 women (46%) completed it after 9 months. Eighty-seven control subjects (51%) participated. Criteria for posttraumatic stress were met in 29% of women with early pregnancy loss after 1 month and in 18% after 9 months (odds ratio per month, 0.80; 95% confidence interval, 0.72—0.89). Moderate/severe anxiety was reported in 24% after 1 month and in 17% after 9 months (odds ratio per month, 0.69; 95% confidence interval, 0.50—0.94). Moderate/severe depression was reported in 11% of the women after 1 month and 6% of the women after 9 months (odds ratio per month, 0.87; 95% confidence interval, 0.53—1.44). After miscarriage, proportions after 9 months were 16% for posttraumatic stress, 17% for anxiety, and 5% for depression. Corresponding figures after ectopic pregnancy were 21%, 23%, and 11%, respectively. In contrast, among control women with viable pregnancies, 13% reported moderate-to-severe anxiety (odds ratio loss at 1 month vs controls: 2.14; 95% confidence interval, 1.14—4.36), and 2% reported moderate-to-severe depression (odds ratio loss at 1 month vs control subjects: 3.88; 95% confidence interval, 1.27—19.2).

CONCLUSION: Women experience high levels of posttraumatic stress, anxiety, and depression after early pregnancy loss. Distress declines over time but remains at clinically important levels at 9 months.

Key words: Hospital Anxiety and Depression Scale, pregnancy, psychology

Early pregnancy loss is one of the most common reasons women of reproductive age are seen in both primary and secondary care, with >250,000 miscarriages and 10,000 ectopic pregnancies estimated to take place each year in the United Kingdom.[1,2] It represents not only the loss of a much desired child but also may challenge an individual's sense of control over life and pose a threat to plans of parenthood. Both miscarriage and ectopic pregnancy may involve significant pain or bleeding and hospital admission or emergency procedures. They may also lead to prolonged periods of uncertainty while awaiting diagnosis or resolution. For many women, an early pregnancy loss will be the most traumatic event that has happened in their lives.

Reactions such as sadness, frustration, and grief are expected. However, there is evidence to suggest that a proportion of women will experience severe psychologic sequelae in the aftermath of miscarriage, such that they meet diagnostic thresholds for recognized disorders that include anxiety, depression, and posttraumatic stress disorder (PTSD).[3,4] Anxiety and depression have also been demonstrated in a subsequent pregnancy, with almost twice the odds of experiencing sadness or low mood and excessive worry, compared with those women without a previous loss.[5,6] Research to date has been variable in quality, with some studies using a self-selected population[4,7] and others not specifying the derivation of participants.[8–10] Most studies lack large cohorts with prolonged follow up or have not assessed for the impact of intercurrent losses or successful pregnancies.[3,11] High proportions of participants drop out over the course of studies in this field. Notably, there are very little data on ectopic pregnancies, which

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AJOG at a Glance

Why was this study conducted?

Early pregnancy losses affect up to 1 in every 2 women in their lifetime; however, to date, the psychologic consequences have not been a major focus of research or treatment.

Key findings

One month after early pregnancy loss, 29% of women met criteria suggestive of posttraumatic stress, 24% of women met criteria suggestive of moderate-severe anxiety, and 11% of women met criteria suggestive of moderate-severe depression. Posttraumatic stress, anxiety, and depression decline over time in those women without further losses or pregnancies, but they remain at clinically important levels at 9 months. Posttraumatic stress, anxiety, and depression symptoms were high after both ectopic pregnancies and miscarriage.

What does this add to what is known?

After early pregnancy loss, there is a high incidence of psychologic morbidity, particularly posttraumatic stress, in women after both ectopic pregnancy and miscarriage.

perhaps reflects the clinical focus on treating a potentially critical acute condition or their relative rarity in comparison to miscarriage.[12] Furthermore, only small studies or those also including stillbirth have assessed for posttraumatic stress.[4] The majority of relevant studies are also mostly over a decade old.

In this study, our aims were (1) to assess the proportion of women who met screening criteria for posttraumatic stress, anxiety, and depression at 1, 3, and 9 months after an early pregnancy loss, (2) to compare prevalence of anxiety and depression after 1 month with a control group of women with viable pregnancies, and (3) to compare the reactions to miscarriage and ectopic pregnancy.

Materials and Methods

Study design

This is the first report from the Psychological Impact of Early Pregnancy Events prospective cohort study. Ethical approval of the study protocol was granted by the Research Ethics Service of South-West Exeter, reference 11/SW/0052. The main goals of Psychological Impact of Early Pregnancy Events study are longitudinal assessment of psychologic morbidity in women and partners after early pregnancy loss and investigation of potential risk factors. This study reports on longitudinal morbidity in women.

Consecutive recruitment of women with losses took place in the Early Pregnancy Assessment Units at 3 central London hospitals (Queen Charlottes and Chelsea, St. Mary's, and Chelsea and Westminster) between November 13, 2013, and March 15, 2016, on days on which the study investigators were available. Women could be recruited at diagnosis of a nonviable pregnancy or at any point during routine follow-up evaluation, provided it was within 1 month of diagnosis. If women with early pregnancy loss consented, their partners were also approached. Women with viable pregnancies were recruited consecutively from antenatal clinic on 28 mornings between November 23, 2013 and February 9, 2016. The determination of the target sample size of 734 women is described in Appendix A.

All women with any losses were sent a link to a survey by email message at months 1, 3, and 9 after diagnosis. Women with viable pregnancies (control group) were sent a questionnaire at the earliest opportunity after confirmation of viability on their routine 11- to 14-week dating scan. Email communication always included a reminder that they were free to withdraw from the study without providing a reason for doing so. A lack of response without active withdrawal prompted up to 2 reminder email messages at weekly intervals. In cases of passive nonresponse, women were emailed the questionnaire at the subsequent time points, if applicable.

Participants

Inclusion and exclusion criteria are listed in Table 1. Women who were eligible for participation in the early pregnancy loss group had received a diagnosis of a miscarriage (a small proportion of whom ultimately were diagnosed with a molar pregnancy) or an ectopic pregnancy or were classified as having a resolving or persistent pregnancy of unknown location. Women were recruited into the control group after booking routine antenatal care: if a dating scan had not already taken place (between 11 and 14 weeks in the United Kingdom), hospital records were checked to ensure later confirmation of viability (with exclusion if this was not evident).

Women with an early pregnancy loss were offered treatment in line with local protocols. Those women with a diagnosis of miscarriage (unless complete) were offered the clinically appropriate options of expectant, medical (misoprostol administered by the patient at home), or surgical treatment (under general anesthesia). Women with ectopic pregnancy were offered expectant treatment, methotrexate, or surgical intervention (usually laparoscopic salpingectomy) depending on symptoms, ultrasound findings, and serum human chorionic gonadotropin concentrations. Women with pregnancy of unknown location, after a resolving trend in human chorionic gonadotropin concentration had been established, were asked to confirm that a urine pregnancy test was negative after a further 2 weeks. Women with a diagnosis of a molar pregnancy (confirmed on histologic assessment approximately 2 weeks after surgical management of miscarriage) were referred to the regional trophoblastic center. Those women with viable pregnancies continued routine antenatal care.

TABLE 1
Inclusion and exclusion criteria

Inclusion criteria
Early pregnancy loss group: diagnosis of early pregnancy loss (miscarriage that includes molar pregnancy, failing pregnancy of unknown location, or ectopic pregnancy)
Control group: booked for antenatal care and viable pregnancy on 11−14 week scan
Exclusion criteria
Age <18 years
Gestation >20 weeks
Lack of proficiency in the English language
Inability to give informed consent
Review after voluntary termination of pregnancy
Already a participant of study from previous loss

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Demographic and background information

For participants with early pregnancy losses, details of the clinical encounter were collected: the date of their last menstrual period, the onset and type of any symptoms, the dates and outcomes of any scans, and the dates and outcomes of any active management. A record was also made of whether the pregnancy was conceived by in vitro fertilization (IVF) and whether the woman had previously had children or had experienced past losses.

As part of the first questionnaire, all respondents were asked to provide demographic information, symptoms, views on the pregnancy loss and on the health care that they received. A summary of all data collected, including data not used for this analysis, is listed in Appendix B.

Measures

Participants were asked to complete a number of psychometric screening questionnaires presented in the same order. For the purposes of this article, we have limited our analysis to anxiety, depression, and post traumatic stress in women.

Hospital Anxiety and Depression Scale

All participants were asked to complete the Hospital Anxiety and Depression Scale (HADS), which is a 14-item (7 questions related to anxiety and depression each) questionnaire.[13] Each subscale measures symptom severity (the score ranges between 0 and 21, a score ≥11 indicates moderate-to-severe symptoms). HADS has good psychometric properties, with mean Cronbach's α coefficient of internal consistency 0.83 for anxiety, and 0.82 for depression,[14] and has been used frequently in the miscarriage population.[12]

Posttraumatic Stress Diagnostic Scale

The Posttraumatic Stress Diagnostic Scale (PDS) is a well-validated self-report questionnaire to screen for posttraumatic stress.[15] It contains 17 items that are based on the Diagnostic and Statistical Manual of Mental Disorders−Fourth Edition (DSM-4) diagnostic criteria for PTSD, which are clusters of reexperiencing, avoidance, and hyperarousal symptoms. It assesses for a probable diagnosis of PTSD in response to an identified trauma (in this case, the pregnancy loss), and also provides a score of symptom severity (ranging between 0 and 51). A number of scoring methods to diagnose cases have been proposed and used. We used scoring proposed by Ehring et al[16] in which participants (1) met each of 3 symptom clusters as originally proposed by Foa et al[15] (1 reexperiencing, 3 avoidance, and 2 hyperarousal symptoms), (2) showed interference of activity (overall functioning, or ≥2 areas of interference), and (3) had an overall PDS severity score of at least 18. This has been found to maximize overall accuracy in the diagnosis of current PTSD based on structured interviews, with a sensitivity of 82% and specificity of 89% (in 522 individuals who were exposed to motor vehicle accidents or physical or sexual assault).[16]

We will use the term posttraumatic stress rather than PTSD in this study to acknowledge that our criteria focus on screening for probable PTSD.

Statistical analysis

We compared demographic data and psychometric scores at month 1 between nonrespondents (no response at month 1, month 3, and month 9), dropouts (last response at month 1 or month 3) and nondropouts (last response at month 9). For this, we considered a response to be present if the participant had completed HADS, which was the first psychometric screening questionnaire presented.

We used multivariable logistic regression with Firth bias correction to compare proportions of moderate/severe anxiety and depression between the loss group at month 1 and the control group. The adjusted odds ratio of moderate/severe symptoms for the loss vs control groups was reported with its 95% confidence

interval, with the use of the following prespecified variables as covariates: maternal age (years), IVF pregnancy (yes/no), previous children (yes/no), and a history of any early pregnancy loss.

We used generalized linear mixed models to investigate moderate/severe anxiety, moderate/severe depression, and posttraumatic stress over time in the early pregnancy loss group. The model included random intercepts and random slopes for time. The following prespecified covariates were used: maternal age (years), history of any early pregnancy loss, IVF pregnancy (yes/no), time since loss (months after loss), previous children (yes/no), whether a further loss was experienced during the study period, and whether the patient was pregnant when filling in the questionnaire. The last 2 variables are time-varying (ie, could take on different values at different time points). We used the method of decomposition to handle time-varying covariates.[17] In a second step, similar models were fitted using only the cases of miscarriage and ectopic pregnancy. The following additional covariates were added: loss type (miscarriage vs ectopic pregnancy) and an interaction between time and loss type. Because of variability in the exact time of filling in the questionnaire, time was quantified as the exact time rather than as the target time (months 1, 3, or 9). Appendix C provides more detailed information on these multivariable models.

Among patients who completed HADS and/or PDS at least once, 19 women had a missing value for history of early pregnancy loss, and 1 woman had a missing value for previous children. These missing values were imputed with the use of single stochastic imputation based on the method of fully conditional specification.[18] Variables that were used in the imputation procedure were age, loss type, IVF pregnancy, HADS depression and anxiety scores, and PDS score at all time points (months 1, 3, and 9). We did not impute missing values in longitudinal outcomes, for example because of dropout. Instead, we used direct likelihood as the estimation method, which is valid when longitudinal outcomes are 'missing at random'.

All statistical analyses were performed using R software (version 3.4.3) and SAS software (version 9.4; SAS Institute Inc, Cary, NC).

Results

As shown in Figure 1, 1396 women (1201 with early pregnancy losses and 195 with viable pregnancies) were invited to participate across 3 sites. One hundred eleven women were ineligible for recruitment: 84 of the women (7%) with losses and 8 of the control subjects (4%) did not speak sufficient English to take part in the study; 18 women (1%) with losses had been recruited previously in a previous pregnancy, and 1 woman with loss did not have capacity to consent. Three hundred seventy-nine of the women with losses (34%) and 16 of the control subjects (9%) actively declined participation or requested time to consider but did not return the consent form. Of those with an early pregnancy loss who provided a reason for not taking part, most of the women (34/77) explained that they wished to avoid reminders of the event; an additional 14 women reported that the pregnancy had been unplanned (on which they did not wish to dwell). The remainder cited time constraints or lack of access to a private email address.

The background details of those who consented to take part are given in Table 2.

Nonresponse and drop out

Response rates and withdrawal data are given in Figure 1. Overall, of the group with losses, 303 of 737 women (41%) responded to HADS at all 3 time points; 530 of 737 women (72%) responded at least once; 492 of 737 women (67%) with losses completed HADS at month 1; 426 of 737 women (58%) responded at month 3, and 338 of 737 women (46%) responded at month 9. Eighty-seven of 171 women (51%) of the control group responded to HADS. A small number of women completed HADS (which was presented first), but not PDS, at each time point (5 at month 1, 8 at month 3, and 2 at month 9).

Nonrespondents, dropouts, and nondropouts were broadly similar in terms of background characteristics (age, previous losses, IVF pregnancy; Appendix D, Table D1). There was a tendency that dropouts, after month 3, were less often trying to conceive at month 3 than participants who continued to month 9 (29% vs 43%). Month 1 HADS and PDS scores were similar, irrespective of whether they continued to month 9 (Appendix D, Table D2). Of those women with moderate/severe depression at month 1, 55% (29/53) completed month 9, compared with 67% (296/443) of those with no/mild depression. Of those with moderate/severe anxiety at month 1, 62% (74/120) completed month 9, compared with 67% (251/376) of those with no/mild anxiety. Of those with posttraumatic stress at month 1, 66% (92/139) completed month 9, compared with 65% (225/348) without posttraumatic stress.

In the control group, respondents were broadly similar to nonrespondents in terms of age, IVF pregnancy, history of losses, and number of existing children (Appendix D, Table D3)

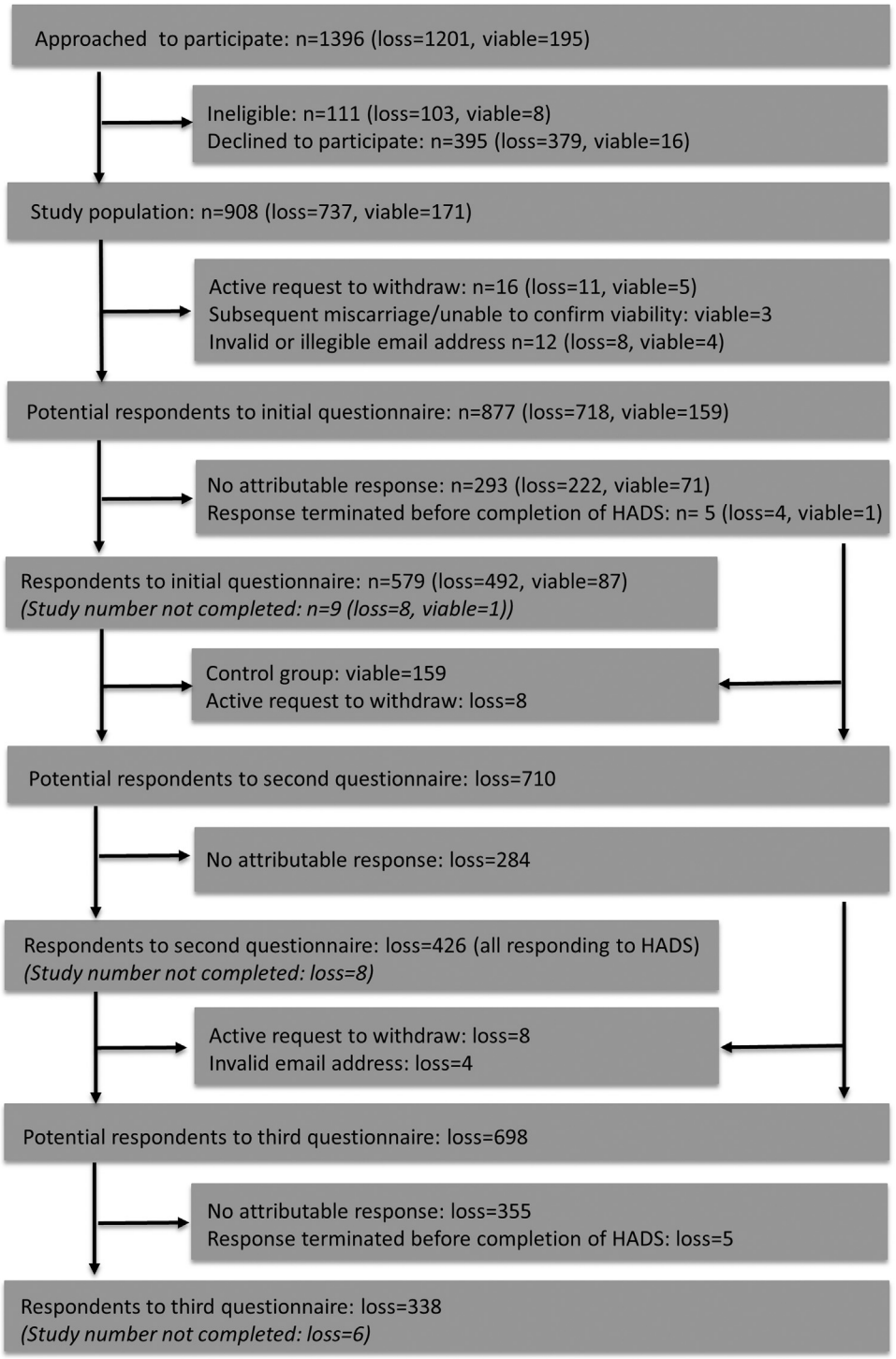
Response timing

Responses to the first questionnaire (month 1; sent 30 days after diagnosis of loss) were a mean of 40 days after diagnosis (standard deviation, 12; interquartile range, 32−45); responses to the second questionnaire (month 3; sent 90 days after loss) were a mean of 101 days after diagnosis (standard deviation, 19; interquartile range, 91−105), and responses to the final questionnaire (month 9; sent 270 days after diagnosis of loss) were a mean of 280 days after diagnosis (standard deviation, 15; interquartile range, 271−285).

Posttraumatic stress, anxiety, and depression at month 1 for early pregnancy loss and control subjects

At month 1, 139 of 487 women with early pregnancy loss (29%) met the criteria for posttraumatic stress; 119 of 492 women (24%) reported moderate/severe anxiety, and 53 of 492 women (11%) reported moderate/severe depression (Table 3). In the control group, 11 of 87 women (13%) met the

FIGURE 1
Flowchart



Flowchart of recruitment and response rates (response defined here as completion of the first self-report measure [the Hospital Anxiety and Depression Scale]), subdivided by group (early pregnancy loss group and control group with viable pregnancies).

HADS, Hospital Anxiety and Depression Scale.

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TABLE 2
Background details of those women who consented to participate[a]

Variable	Women with early pregnancy losses (n=737)	Control subjects (n=171)
Age, y[b]	34.9±5.4 (19–54)	32.1±4.9 (19–49)
Obstetric history, n/N (%)		
Miscarriage		
Any	237/737 (32)	49/171 (25)
>1	112/737 (15)	13/171 (8)
Unknown	25/737 (3)	0/171
Ectopic pregnancy		
Any	36/737 (5)	2/171 (1)
>1	7/737 (1)	1/171 (1)
Unknown	25/737(3)	0/171
Live births		
Any	316/737 (43)	52/171 (30)
>1	106/737 (14)	9/171(5)
Unknown	24/737 (3)	0/171
Index pregnancy		
Mean gestation at recruitment (control subjects only), d[b]	N/A	70.1±22.7 (30–161; 10 missing)
Gestation at diagnosis of early pregnancy loss, d[b,c]	65.4±20.0 (2–138; 131 missing)	N/A
In vitro fertilization pregnancy, n/N (%)	50/737 (7)	12/171 (7)
Any early pregnancy issues/scans (control subjects only), n/N (%)	N/A	81/171 (47)
Reason for referral, n/N (%)		N/A
Pain/bleeding	522/737 (71)	N/A
Incidental finding on scan	95/737 (13)	N/A
Clear passage of pregnancy	6/737 (1)	N/A
Other[d]	111/737 (15)	N/A
No clear reason documented	3/737 (0)	N/A
Final diagnosis, n/N (%)		
Miscarriage	537/737 (73)	N/A
Ectopic pregnancy	116/737 (16)	N/A
Failed pregnancy of unknown location	58/737 (8)	N/A
Persistent pregnancy of unknown location	5/737 (1)	N/A
Molar pregnancy	21/737 (3)	N/A
Fetal heart pulsations previously seen on scan (intrauterine only), n/N (%)		
Yes	125/558 (22)	N/A
Yes with concerns[e]	7/558 (1)	N/A
No	422/558 (76)	N/A
Unknown	4/558 (1)	N/A

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TABLE 2
Background details of those women who consented to participate[a] *(continued)*

Variable	Women with early pregnancy losses (n=737)	Control subjects (n=171)
Final management, n/N (%)		
No active intervention necessary	244/737 (33)	N/A
Medical management of miscarriage	51/737 (7)	N/A
Surgical management of miscarriage	330/737 (45)	N/A
Methotrexate for ectopic pregnancy	22/737 (3)	N/A
Salpingectomy for ectopic pregnancy	66/737 (8)	N/A
Salpingotomy for ectopic pregnancy	5/737 (1)	N/A
Other surgical intervention	7/737 (1)	N/A
Lost to follow-up	12/737 (2)	N/A
Emergency surgical management, n/N (%)[f]	124/409 (30)	N/A
Emergency admission, n/N (%)	110/737 (14)	N/A
Blood transfusion, n/N (%)	18/737 (2)	N/A

‡Persistent pregnancy of unknown location defined as requiring >2 blood tests to confirm resolution; 1 of 5 required 2 doses of methotrexate; the remainder were treated conservatively.

[a] Women with early pregnancy losses and control subjects with viable pregnancies; [b] Data are given as mean±standard deviation (range); [c] From self-reported last menstrual period, where known (for in vitro fertilization pregnancies, 19 days added to date of transfer to calculate gestation [assuming day 5 embryo transfer, unless otherwise specified] or molar pregnancies, date of diagnosis considered to be date of diagnosis of nonviability [as histopathologic diagnosis of molar pregnancy is often delayed]); [d] Includes a reduction in pregnancy symptoms, medical reasons (eg, exposure to illness or medication in early pregnancy), spontaneous rupture of membranes, or referral from termination clinic; [e] concerns include bradycardia, or a smaller than expected for gestation fetus; these concerns are explained to the patient to manage their expectations, and a repeat scan is booked; [f] Surgical management considered "emergency" rather than "elective" if the patient is admitted as an inpatient for a procedure to be completed as soon as possible, because of preceding or future risk of significant hemorrhage

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criteria for anxiety, and 2 of 87 women (2%) met the criteria for depression.

The unadjusted odds ratio (OR) for the presence of moderate/severe anxiety at month 1 for those women with losses compared with those with a viable pregnancy was 2.20 (95% confidence interval [CI], 1.18−4.51). The adjusted OR was 2.14 (95% CI, 1.14−4.36; Appendix E. For moderate/severe depression, the unadjusted OR was 5.13 (95% CI. 1.56−31.7), and the adjusted OR was 3.88 (95% CI, 1.27−19.2).

Trajectory of posttraumatic stress, anxiety, and depression for all women with early pregnancy loss

Among women with early pregnancy losses, the proportion screening positive decreased over time for all 3 conditions (Table 3). At month 3, 86 of 418 women (21%) met criteria for posttraumatic stress; 96 of 426 women (23%) reported moderate/severe anxiety, and 32 of 426 women (8%) reported moderate/severe depression. At month 9, 59 of 336 women (18%) met criteria for posttraumatic stress; 58 of 338 women (17%) reported moderate/severe anxiety, and 21 of 338 women (6%) reported moderate/severe depression. With the use of multivariable logistic regression (Table 4), the odds ratio was 0.80 per month for meeting posttraumatic stress criteria (95% CI, 0.72−0.89), 0.69 per month for moderate/severe anxiety (95% CI, 0.50−0.94), and 0.87 per month for moderate/severe depression (95% CI, 0.53−1.44). With respect to other covariates in these models, a history of early pregnancy loss and a further loss during the study follow-up period increased the odds of meeting the screening criteria. The other covariates had mixed or unclear results.

Endorsement of individual Posttraumatic Diagnostic Scale clusters (reexperiencing, avoidance, and hyperarousal symptoms) and interruption caused by these symptoms on specific activities are given in Appendix F. The most commonly endorsed cluster of symptoms, by 91% respondents at month 1, was reexperiencing symptoms. Equal proportions of the women (60%) met criteria for avoidance and hyperarousal symptoms. The most common interruption of activity was reported as sex life (49%), closely followed by general satisfaction with life (48%). By month 3, an interruption of general satisfaction with life was the most commonly endorsed (50%).

Posttraumatic stress, anxiety, and depression after miscarriage vs ectopic pregnancy

For those who had a miscarriage, 109 of 363 women (30%) met the criteria for posttraumatic stress at month 1 (Table 3), which decreased to 60 of 308 women 19% at month 3 and 41 of 249 women 16% at month 9. Moderate/severe anxiety was reported by 93 of 366 women (25%) at month 1, 70 of 315 women (22%) at month 3, and 43 of 249 women (17%) at month 9. Moderate/severe depression was reported by 45 of 366 women (12%) at month 1, 23 of 315 women (7%) at month 3, and 13 of 249 women (5%) at month 9. According to the multivariable models that included type of loss Appendix G

TABLE 3
The number of available observations in every group at each time point (N), the mean and standard deviation (SD) of anxiety, depression and post-traumatic stress scores, and the number (n) and percentage of patients with moderate to severe anxiety and depression, and with posttraumatic stress

Month	Control subjects	All early pregnancy losses	Miscarriage	Ectopic pregnancy	Resolved pregnancy of unknown location	Molar
Sample size, n						
1	87	492	366	75	35	16
3	—	426	315	68	29	14
9	—	338	249	53	22	14
Anxiety score, Hospital Anxiety and Depression Scale[a]						
1	6.0 (3.4)	6.9 (4.5)	7.1 (4.5)	6.3 (4.5)	5.5 (4.2)	7.1 (5.4)
3	—	6.8 (4.5)	6.9 (4.5)	7.5 (4.7)	5.2 (4.1)	6.5 (3.9)
9	—	6.3 (4.5)	6.3 (4.6)	6.6 (4.1)	3.9 (2.9)	7.2 (5.0)
Moderate/severe anxiety, percentage, % (95% confidence interval)						
1	13 (7–21)	24 (21–28)	25 (21–30)	21 (14–32)	17 (8–33)	25 (10–49)
3	—	23 (19–27)	22 (18–27)	31 (21–43)	10 (4–26)	14 (4–40)
9	—	17 (14–22)	17 (13–22)	23 (13–36)	5 (1–22)	14 (4–40)
Depression score, Hospital Anxiety and Depression Scale[a]						
1	3.5 (2.6)	4.5 (4.4)	4.7 (4.5)	3.7 (4.2)	3.5 (3.6)	4.2 (4.3)
3	—	4.1 (3.9)	4.1 (4.0)	4.8 (4.2)	2.9 (3.4)	3.1 (2.8)
9	—	3.6 (3.8)	3.6 (3.8)	3.8 (4.2)	2.1 (2.5)	3.6 (4.4)
Moderate/severe depression, % (95% confidence interval)						
1	2 (1–8)	11 (8–14)	12 (9–16)	7 (3–15)	3 (1–15)	13 (3–36)
3	—	8 (5–10)	7 (5–11)	12 (6–22)	3 (1–17)	0 (0–22)
9	—	6 (4–9)	5 (3–9)	11 (5–23)	0 (0–15)	14 (4–40)
Posttraumatic diagnostic scale score[a,b]						
1	—	13.1 (10.5)	13.7 (10.6)	11.7 (10.1)	8.6 (7.8)	15.6 (12.6)
3	—	10.8 (9.2)	10.6 (9.4)	11.9 (8.9)	8.7 (7.7)	12.2 (8.6)
9	—	9.1 (9.4)	9.0 (9.4)	9.8 (8.6)	5.7 (7.1)	14.9 (13.0)
Posttraumatic stress, % (95% confidence interval)[b]						
1	—	29 (25–33)	30 (26–35)	23 (15–34)	15 (6–30)	50 (28–72)
3	—	21 (17–25)	19 (15–24)	28 (19–40)	10 (4–26)	29 (12–55)
9	—	18 (14–22)	16 (12–22)	21 (12–34)	10 (3–29)	36 (16–61)

[a] Data are given as mean±standard deviation; [b] The number of early pregnancy loss cases was 487 at month 1, 418 at month 3 and 336 at month 9 because of a small proportion of participants who completed the Hospital Anxiety and Depression Scale but not posttraumatic diagnostic scale.

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(Table G), the odds of meeting the criteria for posttraumatic stress criteria decreased by 23% each month (OR, 0.77; 95%, CI 0.68–0.87), of moderate/severe anxiety by 35% each month (OR, 0.65; 95% CI, 0.44–0.94), and of moderate/severe depression by 34% each month (OR, 0.66; 95% CI, 0.32–1.35; Figure 2).

TABLE 4
Results for the multivariable models for the early pregnancy loss group

Predictor variable	Odds ratio (95% confidence interval)		
	Moderate/severe anxiety	Moderate/severe depression	Posttraumatic stress
Time per month since loss	0.69 (0.50–0.94)	0.87 (0.53–1.44)	0.80 (0.72–0.89)
Maternal age per year	0.98 (0.91–1.06)	0.98 (0.90–1.08)	0.95 (0.86–1.04)
History of any early pregnancy loss (yes vs no)	4.03 (1.79–9.06)	6.40 (2.24–18.3)	5.13 (1.92–13.8)
In vitro fertilization pregnancy (yes vs no)	0.26 (0.05–1.22)	0.97 (0.18–5.15)	1.05 (0.19–5.87)
Previous children (yes vs no)	0.91 (0.42–1.96)	1.36 (0.55–3.37)	0.36 (0.14–0.94)
Further pregnancy (yes vs no)[a]	1.52 (0.54–4.30)	1.58 (0.37–6.64)	0.26 (0.08–0.83)
Further loss (yes vs no)[a]	13.2 (2.27–76.7)	13.4 (1.50–120.1)	14.7 (3.63–59.2)
Between-patient differences			
Patient median odds ratio[b]	10.55	23.08	37.56
Time per month since loss[c]	0.47–1.01	0.62–1.22	NA

NA, not applicable.

[a] Time-varying measurements that were scored in each of the 3 questionnaires: such events, although not very common, may have strong impact on the outcomes; hence, they were included as covariates, irrespective of the width of the confidence intervals; [b] Median odds ratio between a randomly selected subject at higher risk of the outcome and a randomly selected subject at lower risk of the outcome, with the same covariate values, which shows how the outcome risk differs between patients; [c] The interval for the individual time effect that covers the middle 80% of patients, which shows how the effect of time differs between patients, after adjustment for covariates.

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For women who had an ectopic pregnancy, 17 of 74 women (23%) met the criteria for posttraumatic stress at month 1, 19 of 67 women (28%) met the criteria at month 3, and 11 of 52 women (21%) met the criteria at month 9 (Table 3). Moderate/severe anxiety was reported by 16 of 75 women (21%) at month 1, by 21 of 68 women (31%) at month 3, and by 12 of 53 women (23%) at month 9. Moderate/severe depression was reported by 5 of 75 women (7%) at month 1, by 8 of 68 women (12%) at month 3, and by 6 of 53 women (11%) at month 9. According to the multivariable models that included type of loss, the odds of meeting posttraumatic stress criteria decreased by 16% each month (OR, 0.84; 95% CI, 0.69–1.03); moderate/severe anxiety decreased by 20% each month (0.80; 95% CI, 0.59–1.10), and moderate/severe depression decreased by 4% each month (OR, 0.96; 95% CI, 0.57–1.61; Figure 2).

Proportions that met criteria for posttraumatic stress, anxiety, and depression decreased more strongly after miscarriage vs ectopic pregnancy, although confidence intervals were very wide (Figure 2). In multivariable analysis, the *P* values for a different evolution of morbidity after miscarriage vs ectopic pregnancy (interaction loss type x time) were .43 (posttraumatic stress), .14 (anxiety), and .07 (depression).

Posttraumatic stress, anxiety, and depression after molar pregnancy or pregnancy of unknown location

The number of patients with these conditions was small (35 women with a pregnancy of unknown location at month 1 and 16 women with a molar pregnancy). Morbidity rates are presented in Table 3 but are subject to large levels of uncertainty.

Comment

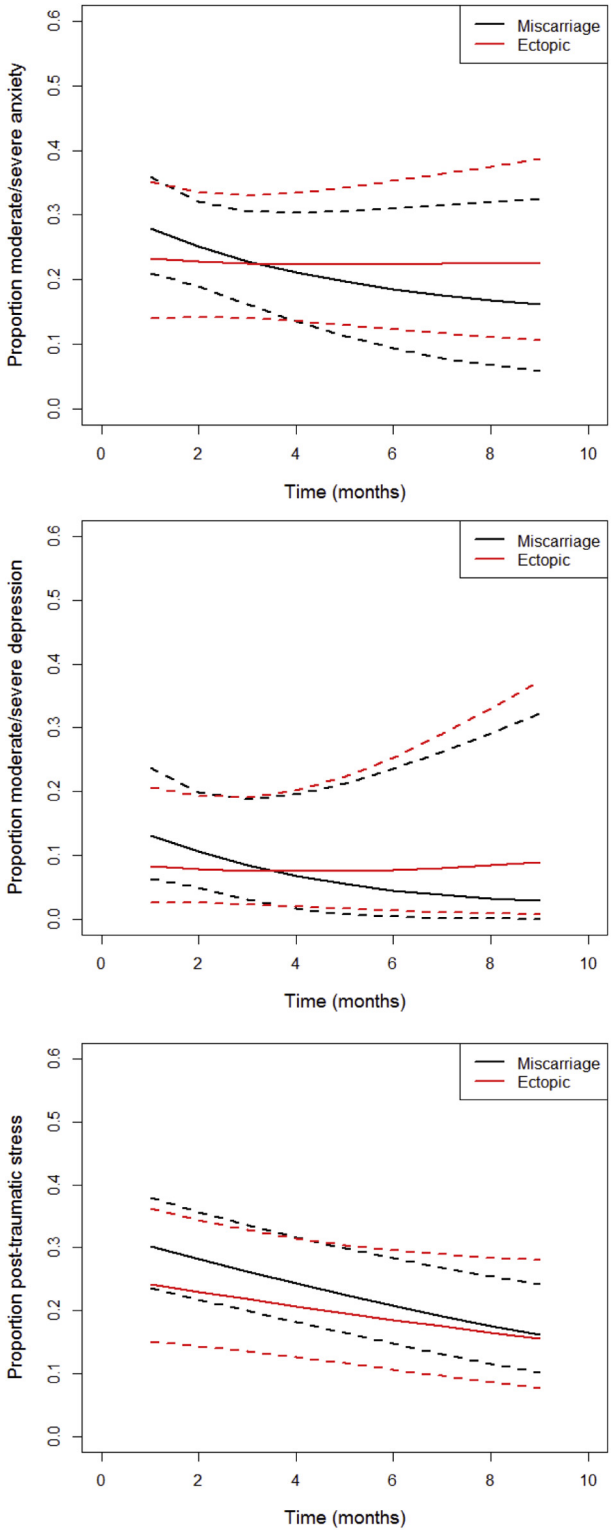
Principal findings of the study

One month after early pregnancy loss, we observed high proportions of women who met the criteria for posttraumatic stress (29%), moderate/severe anxiety (24%), and moderate/severe depression (11%). Although the prevalence of each disorder declined over time, observed proportions remained high 9 months after early pregnancy loss (18% for posttraumatic stress, 17% for moderate/severe anxiety, 6% for moderate/severe depression). In viable pregnancies after 1 month, 13% of the women reported moderate/severe anxiety, and 2% of the women reported moderate/severe depression. Prevalence was high after both miscarriage and ectopic pregnancies. Confidence intervals were too wide for a robust comparison of how morbidity for miscarriage and ectopic pregnancy changes over time.

Strengths and weaknesses

This is the largest study published to date to assess posttraumatic stress, anxiety, and depression on consecutive women at set times after an early pregnancy loss. A further strength is the use of a comparison group of women with a viable pregnancy. We have also modelled the decline in symptoms over time and controlled for further losses and further pregnancies, which has not been investigated before and is likely to be integral to the recovery process. To our knowledge, it is the first study to assess these conditions after ectopic pregnancy outside the context of an interventional study.

FIGURE 2
Predicted anxiety, depression, and posttraumatic stress rates over time



Predicted anxiety, depression, and post-traumatic stress rates over time (with 95% prediction intervals) for the average individual with miscarriage and ectopic pregnancy, based on a mixed effects model that contains an interaction effect between the type of loss and time. We assume no further loss or pregnancy during the follow-up period and average values for maternal age (35 years), history of any early pregnancy loss (0.407), in vitro fertilization pregnancy (0.082), and existing children (0.443).

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The main weakness of the study was the drop-out rate. Accordingly, the possibility of selection and participation bias must be considered when the data are interpreted. Reassuringly, full respondents, partial respondents, and nonrespondents were broadly similar, and there was no observed tendency for those who screened positive for psychologic illness at the outset to more often continue participation. There may also have been an unintended therapeutic benefit of taking part in the study, and also some participants who independently accessed psychological support. This would lead us to underestimate the level of psychopathology in a population who did not access any intervention.

A second weakness was that the timing of the assessment in the control group was not standardized; it took place at the earliest moment between the dating scan and 20 weeks gestation.

Third, despite this being the largest study on the subject to date, the number of ectopic pregnancies was modest, which hampered a strong comparison of the evolution of psychopathology after miscarriage vs ectopic pregnancy.

A final limitation is that screening questionnaires, rather than the gold standard of individualized assessment by a trained professional, were used in this study. The large sample size of the study was at the cost of reduced accuracy, as is usually the case in such research. Since commencing the study, the Post-traumatic Diagnostic Scale has been updated to reflect the changing

diagnostic criteria for PTSD brought on by the introduction of DSM-V. The updated DSM-V criteria has omitted the "intense fear, helplessness, and horror" from Criterion A along with the symptom "foreshortened future," and separated the "avoidance and emotional numbing" criteria into 2 separate clusters ("avoidance" and "changes in cognition and mood"), thereby giving more weight to negative mood and risk-taking behavior. Although it is not possible to establish exact PTSD rates with the use of the updated DSM-V criteria from the Posttraumatic Diagnostic Scale, cohort studies that have compared the diagnostic prevalence rates from the DSM-IV and DSM-V criteria has remained largely the same.[19,20]

Rates of anxiety and depression are broadly similar to those reported by other articles over the past 3 decades.[12] Rates of posttraumatic stress appear higher than in the study by Engelhard et al[4]: 29% vs 25% at 1 month and 21% vs 6% at 3 and 4 months, respectively. This is likely to reflect the different scoring methods used. It may also reflect societal change over the past 17 years.

Implications of the work

The fact that such a high proportion of women experience symptoms that are suggestive of PTSD and that these symptoms persist over time is important. It is recognized that PTSD in other contexts can have a significant impact on work, social interaction, healthcare utilization, and risks in future pregnancies. Given annual incidences of miscarriage and ectopic pregnancy (which may rise further if the trend towards later childbearing continues), this points to a significant public health issue.

Our clinical management must be more sensitive to the psychologic implications of early pregnancy loss. Women often experience long waiting times for review or treatment and insensitive communication or treatment. We should strive to provide access to specialist early pregnancy assessment care where expert advice is available and an awareness of the potential psychologic response and need for appropriate treatment. Work is needed to evaluate strategies to effectively identify and treat affected women with these specific psychopathologies. This is likely to be more efficacious than nonspecific counselling for all women, which, given the large proportion of women without psychopathology, has unsurprisingly been found to be unhelpful.[21]

Importantly, although we have adhered to strict definitions of case in the presentation of these results, it should be acknowledged that those women with scores that fall beneath the thresholds are also likely to have important symptoms that will benefit from understanding, support, or potential formal treatment. Such considerations should be at the forefront of any clinician's mind when a patient is approached after an early pregnancy loss. ■

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Appendices

Appendix A Determination of sample size

To arrive at a meaningful sample size, the following calculation was performed after a pilot study by the statistician of that study.[1] Anxiety was chosen as the parameter from which to calculate the sample size for a comparison to the control group.

To detect a 20% difference in the rate of moderate and severe anxiety cases between early pregnancy losses at 1 month and control subjects, assuming 10% in control subjects and 30% in losses at 1 month after pilot study results, with significance level .05 and power 0.80 and assuming a 1:3 ratio of control subjects to cases, we needed 176 participants: 132 women with losses and 44 control subjects.

A second calculation was performed for the risk factor aim of the Psychological Impact of Early Pregnancy Events study to have sufficient data for most risk factors to perform an informative analysis. Based on the results of the pilot study, a total of 440 women with losses would need to complete part 1 of the study to demonstrate a 20% difference in prevalence of posttraumatic stress between women with assisted reproduction and those without (chosen as an uncommon potential risk factor of interest) with power 0.80 and significance level .05 and assuming a frequency of 1:7 women having had assisted reproduction. The 20% difference was operationalized as 40% posttraumatic stress in women with losses after natural conception vs 60% posttraumatic stress in women with losses after assisted reproduction because this would maximize the sample size. Assuming that the response rate at 1 month would be 60%, the total sample size equals 734 (440 divided by 0.6).

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Appendix B Summary of data collected

TABLE B
Information collected on each participant with early pregnancy loss

Variable	Explanation
Data prospectively collected from clinical records	
Background	Date of birth
	Previous miscarriage/ectopic pregnancy/pregnancy of unknown location/stillbirth/termination
	Living children
Clinical	Date of last menstrual period
	In vitro fertilization pregnancy
	Date of presentation
	Reason for presentation
	Date of diagnosis
	Number of scans for diagnosis
	Diagnosis
	1st, 2nd and 3rd line management (if applicable)
	Elective or emergency surgical management (if performed)
	Admission
	Blood transfusion
	Date of discharge
Questionnaire data collected at month 1	
Demographics	Highest level of education
	Annual household income
	Marital status
	Time with current partner
	Religion
	Ethnic origin
Medical and surgical history	Severe medical condition requiring treatment in hospital
	Previous emergency surgery
	Diagnosis and/or treatment of psychiatric condition
Details of current pregnancy loss	Time taken to conceive
	Severity of abdominal pain
	Amount of bleeding
	Worry for own well-being
	Time for physical symptoms to resolve
Obstetric and gynecologic history	Previous pregnancy complications
	Previous termination of pregnancy
	Previous live births
	Past diagnosis of chlamydia

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TABLE B
Information collected on each participant with early pregnancy loss *(continued)*

Variable	Explanation
Attitude to pregnancy	How much the pregnancy was desired
	How distressed they are about loss
	Extent to which they feel responsible for loss
Views on support	Given clear information by healthcare professionals
	Felt emotionally supported by healthcare professionals
	How satisfied they were with health care they received
	Whether counselling was desired or offered
Psychometric scales	Hospital Anxiety and Depression Scale
	Posttraumatic Stress Diagnostic Scale
	Self-compassion scale
	Rumination Response Scale
Questionnaire data collected at 3 and 9 months	
Change in status since last response	Change in relationship status
	New medical conditions
	Whether received any counselling and, if so, whether it had been helpful
	Attempts to conceive again
	Further pregnancies
Psychometric scales	Hospital Anxiety and Depression Scale
	Posttraumatic Stress Diagnostic Scale
	Norbeck Social Support Questionnaire
	Self-compassion scale
	Rumination Response Scale

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Appendix C Statistical methods for multivariable models of the evolution of morbidity among women with early pregnancy losses

We fitted 6 multivariable models. First, there were 3 morbidity outcomes (measured after about 1, 3, and 9 months after the loss): moderate/severe anxiety, moderate/severe depression, and posttraumatic stress according to the Ehring criteria.[1] For each of these 3 outcomes, we fitted 1 model for all women with losses and 1 model for women with miscarriage or ectopic pregnancy only. The latter model allowed us to investigate the evolution of morbidity after miscarriage and ectopic pregnancy separately.

All models were conceived as mixed effects logistic models with repeated measurements, which included a random intercept and random slope (for the evolution over time).

For the models based on all women with early losses, we included the prespecified covariates maternal age (years), history of any early pregnancy loss (yes/no), in vitro fertilization pregnancy (yes/no), time (continuous), previous children (yes/no), whether a further loss was experienced (binary, time-varying), and whether the patient was pregnant when filling in the questionnaire (binary, time-varying). Further loss was conceived as "any further pregnancy loss since start of follow-up." Current pregnancy was conceived per measurement.

For the models based on only women with a miscarriage or ectopic pregnancy, we included the same prespecified covariates but added type of loss (miscarriage vs ectopic pregnancy) and the interaction between time and type of loss as extra covariates. This allowed us to examine the evolution over time by loss type.

This approach can use all available data, is valid under the assumption that missing outcomes are "missing at random" conditional on the covariates in the model,[2] and can deal with repeated measurements that are not taken at fixed time points. When fitting the model, all available observations were used. There were 3 measurement moments: 1 month after the event, 3 months after the event, and 9 months after the event. However, there was substantial variability in the exact time when patients filled out the questionnaire. Therefore, we quantified time as the exact time since the loss.

Because further loss and current pregnancy could change over time, there is not only variability between patients but also within patients. To obtain an accurate effect estimate of becoming pregnant again and further loss on a woman's risk of the outcome, the within-patient effect of the time-varying covariate will be estimated by adjustment for the patients' proportion of measurement points with any pregnancy loss since follow-up evaluation and any new pregnancy to prevent bias.

More specifically, let us define the following quantities:

- FUP_i=the mean of the different values of "further pregnant" of individual i
- $FUPc_{ij}=FUPregnant_{ij}-FUP_i$ (the values of "further pregnant" of individual i at time point j minus the mean of the different values of "further pregnant" of individual i)
- FUL_i=the mean of the different values of "further loss" of individual i
- $FULc_{ij}=FULoss_{ij}-FUL_i$ (the values of "further loss" of individual i at time point j minus the mean of the different values of "further loss" of individual i)

This way, FUP_i and FUL_i are constant within individuals and capture the between subject variability (further pregnant [between] and further loss [between], respectively), and $FUPc_{ij}$ and $FULc_{ij}$ capture the within subject variability (further pregnant [within] and further loss [within], respectively). The effects of interest are the effects of $FUPc_{ij}$ and $FULc_{ij}$ because they indicate the effects on the evolution of anxiety and depression when an individual experiences further loss or pregnancy during follow up.

More formally, we fitted the following generalized linear models using all women with losses:

- $Y_{ij}|b_{1i},b_{2i} \sim Bin(\pi_{ij})$, with Y_{ij} being the anxiety or depression indicator for individual i at time j
- $Logit(P[Y_{ij}=1|b_i,b_{2i}])=\beta_0+b_{1i}+\beta_1 \times Time_{ij}+b_{2i}\times Time_{ij}+\beta_2\times age_i+\beta_3 \times AnyPrevLoss_i+\beta_4\times IVF_i+\beta_5\times PrevChild_i+\beta_6\times FUP_i+\beta_7 \times FUPc_{ij}+\beta_8\times FUL_i+\beta_9\times FULc_{ij}$

We fitted the following generalized linear models using only women with a miscarriage or ectopic pregnancy:

- $Y_{ij}|b_{1i},b_{2i} \sim Bin(\pi_{ij})$, with Y_{ij} being the anxiety or depression indicator for individual i at time j
- $Logit(P[Y_{ij}=1|b_i,b_{2i}])$ $\beta_0+b_{1i}+\beta_1\times Time_{ij}+b_{2i}\times Time_{ij}+\beta_2 \times group_i+\beta_3\times Time_{ij}\times group_i+\beta_4\times age_i+\beta_5\times AnyPrevLoss_i+\beta_6\times IVF_i+\beta_7 \times PrevChild_i+\beta_8\times FUP_i+\beta_9 \times FUPc_{ij}+\beta_{10}\times FUL_i+\beta_{11}\times FULc_{ij}$

The models were fitted with the use of adaptive Gaussian quadrature and 15 quadrature points to approximate the likelihood. Quasi-Newton was used as the optimizer. For posttraumatic stress, however, there were computational difficulties for the random slopes. Therefore, for this outcome only, we pragmatically deleted the random slopes (ie, b_{2i} set to 0).

Here is a summary of observations for each model:

- All women with early pregnancy losses, anxiety: 1256 observations from 530 women
- All women with early pregnancy losses, depression: 1256 observations from 530 women
- All women with early pregnancy losses, posttraumatic stress: 1241 observations from 525 women
- Miscarriage/ectopic pregnancy only, anxiety: 1126 observations from 474 women

- Miscarriage/ectopic pregnancy only, depression: 1126 observations from 474 women
- Miscarriage/ectopic pregnancy only, posttraumatic stress: 1113 observations from 470 women

Of the 530 individuals who data were used in the analysis for depression and anxiety, 311 women did not experience any previous loss; 200 women did experience previous loss. Nineteen individuals did not have information about previous losses, and 1 individual did not have information on existing children. For those individuals, single imputation was used based on their age, type of loss, in vitro fertilization pregnancy, (imputed) depression, anxiety and Posttraumatic Stress Diagnostic Scale scores (all 3 measurement moments), previous losses, and previous children.

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Appendix D Results according to response status

TABLE D1
Baseline data and month 1 and 3 responses regarding pregnancy status according to response status[a]

Variable	Nonresponders (n=207)	Missing, n (%)	Dropout (last response on month 1/month 3, n=192)	Missing, n (%)	No dropout (last response on month 9, n=338)	Missing, n (%)
Background demographic and clinical data						
Type of loss						
Miscarriage (including molar pregnancy), n (%)	147 (71)	0	148 (77)	0	263 (79)	0
Ectopic pregnancy, n (%)	36 (17)	0	27 (14)	0	53 (16)	0
Resolved pregnancy of unknown location, n (%)	24 (12)	0	17 (9)	0	22 (7)	0
Age[b]	33±6	0	34±5	0	35±5	0
In vitro fertilization pregnancy, n (%)	8 (4)	0	16 (8)	1 (1)	26 (8)	0
Past miscarriage or ectopic pregnancy (any/none), n (%)	62 (34)	24 (12)	71 (37)	1 (1)	120 (36)	0
Proportion with children, n (%)	92 (50)	23 (11)	85 (45)	1 (1)	139 (41)	0
Month 1 responses						
Desire for pregnancy (Likert scale 1, not at all; 4, very much), n (%)[b]	N/A		3.7±0.6[b]	21 (11)	3.7±0.6[b]	13 (4)
Distress about loss (Likert scale 1, not at all; 5, extremely), n (%)	N/A		4.1±1.0[b]	21 (11)	3.9±1.0[b]	13 (4)
Satisfaction with health care (Likert scale 1, not at all; 5, very excellent), n (%)	N/A		4.1±0.9[b]	27 (14)	4.2±0.9[b]	17 (5)
Highest level of education, n (%)						
A-levels or lower	N/A		49 (28)	19 (10)	49 (15)	12 (4)
University degree			93 (54)		182 (56)	
Postgraduate degree/doctorate			31 (18)		95 (29)	
Annual income, n (%)						
<£25000	N/A		49 (28)	19 (10)	48 (15)	12 (4)
£25–50 000			48 (28)		64 (20)	
£50–100 000			48 (28)		118 (36)	
>£100 000			28 (16)		96 (29)	

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TABLE D1
Baseline data and month 1 and 3 responses regarding pregnancy status according to response status[a] *(continued)*

Variable	Nonresponders (n=207)	Missing, n (%)	Dropout (last response on month 1/month 3, n=192)	Missing, n (%)	No dropout (last response on month 9, n=338)	Missing, n (%)
Psychiatric disorder, n (%)						
No	N/A		141 (82)	19 (10)	249 (77)	15 (4)
Yes currently (<6 mo)			8 (5)		13 (4)	
Yes in past (>6 mo)			24 (14)		61 (19)	
Time taken to conceive, n (%)						
<3 Mo/unplanned	N/A		108 (63)	21 (11)	206 (63)	13 (4)
3–12 Mo			32 (19)		68 (21)	
>12 Mo			31 (18)		51 (16)	
Previous termination of pregnancy, n (%)	N/A		54 (32)		68 (21)	
Month 3 responses						
Trying to conceive, n (%)						
Pregnant	N/A		20 (18)	80 (42)	38 (12)	25 (7)
Further early pregnancy loss			3 (3)		7 (2)	
Not trying to conceive			57 (51)		132 (42)	
Trying to conceive			32 (29)		136 (43)	

N/A, not available.

[a] Nonresponders vs last information at months 1 or 3 vs last information at month 9; [b] Data are given as mean±standard deviation.

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TABLE D2
Psychometric scale scores, and proportion meeting specified criteria, at month 1 according to response status

	Last information					
Variable at month 1	Month 1 (n=79)	Missing, n	Month 3 (n=113)	Missing, n	Month 9 (n=338)	Missing, n
Hospital Anxiety and Depression Scale						
Depression score[a]	4.7±4.5	0	5.2±4.8	21	4.2±4.2	17
Depression score ≥11, n (%)	10 (13)	0	14 (15)	21	29 (9)	17
Anxiety score[a]	7.1±4.4	0	7.8±4.7	21	6.6±4.5	17
Anxiety score ≥ 11. N (%)	17 (22)	0	29 (32)	21	73 (23)	17
Posttraumatic Stress Diagnostic Scale						
Total score[a]	12.2±10.9	2	14.4±11.0	22	12.9±10.3	19
Caseness, n (%)	20 (26)	2	27 (30)	22	92 (29)	19

[a] Data are given as mean±standard deviation.

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TABLE D3
Comparison of respondents vs nonrespondents within the control group

Variable	Nonrespondents (n=81)	Respondents (n=87)
Mean age, y	31.2	32.9
Miscarriage, n/N (%)		
Any	23/81 (28)	18/87 (21)
>1	6/81 (7)	6/87 (7)
Ectopic pregnancy, n/N	0/87	1/87 (1)
Live births, n/N (%)		
Any	27/81 (33)	22/87 (25)
>1	4/81 (5)	3/87 (3)
Mean gestation at recruitment, d	66.8	73.8
In vitro fertilization pregnancy, n/N	4/81	7/87
Any early pregnancy issues/scans, n/N (%)	44/81 (54)	36/87 (41)

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Appendix E Multivariable model to compare women with early pregnancy loss with the control group

TABLE E
Multivariable models to compare women with early pregnancy loss with the control group

	Odds ratio (95% confidence interval)	
Predictor variable	Moderate/severe anxiety	Moderate/severe depression
Early pregnancy loss vs control	2.14 (1.14–4.36)	3.88 (1.27–19.2)
Maternal age (per year)	0.98 (0.94–1.02)	1.00 (0.94–1.06)
In vitro fertilization pregnancy (yes vs no)	0.73 (0.30–1.59)	1.32 (0.47–3.27)
History of any early pregnancy loss (yes vs no)	2.12 (1.41–3.19)	2.79 (1.57–5.05)
Previous children (yes vs no)	1.07 (0.70–1.61)	1.11 (0.61–1.97)

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Appendix F Posttraumatic stress results by symptom cluster

Reference

1. Ehring T, Kleim B, Clark DM, Foa EB, Ehlers A. Screening for post-traumatic stress disorder: what combination of symptoms predicts best? J Nerv Ment Dis 2007;195:1004-1012.

TABLE F
Mean score, proportion of women who met overall criteria, and criteria of each symptom cluster (subdivided by severity and method of scoring)[a]

Variable	Month 1 (N=487), n (%)	Month 3 (N=418), n (%)	Month 9 (N=336), n (%)
Helpless	361/484 (75)	329 (79)	264 (79)
Terrified	246/484 (51)	209 (50)	181 (54)
Helpless or terrified	384/484 (79)	345 (83)	275 (82)
Proportion meeting each symptom cluster[b]			
Reexperiencing	441 (91)	349 (83)	244 (73)
Avoidance	290 (60)	213 (51)	138 (41)
Hyperarousal	290 (60)	228 (55)	173 (51)
All 3 clusters	233 (48)	162 (39)	117 (35)
Interruption of activities			
Work	189 (39)	137 (33)	93 (28)
Household chores	151 (31)	105 (25)	72 (21)
Relationships with family	154 (32)	136 (33)	84 (25)
Relationships with friends	164 (34)	151 (36)	100 (30)
Fun and leisure activities	191 (39)	146 (35)	96 (29)
Sex life	240 (49)	171 (41)	107 (32)

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TABLE F
Mean score, proportion of women who met overall criteria, and criteria of each symptom cluster (subdivided by severity and method of scoring)[a] *(continued)*

Variable	Month 1 (N=487), n (%)	Month 3 (N=418), n (%)	Month 9 (N=336), n (%)
General satisfaction with life	234 (48)	208 (50)	134 (40)
Overall level of functioning	175 (36)	145 (35)	93 (28)
Any interruption of activities	342 (70)	264 (63)	174 (52)
≥2 activities interrupted or interruption of overall level of functioning	291 (60)	223 (53)	145 (43)
Score ≥18	146 (30)	92 (22)	63 (19)
Total proportion meeting criteria proposed by Ehring[1] (all 3 clusters; interruption ≥2 activities; score ≥18): posttraumatic stress	139 (29)	86 (21)	59 (18)

[a] According to the Posttraumatic Diagnostic Scale, in women with losses, at 3 time points after early pregnancy loss; [b] Endorsed to meet criteria (ie, reexperiencing, ≥1 positive responses to 5 questions; avoidance, ≥3 positive responses to 7 questions; hyperarousal, ≥2 positive responses to 5 questions.

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Appendix G

TABLE G
Results for the multivariable models for miscarriages or ectopic pregnancies[a]

	Odds ratio (95% confidence interval)		
Predictor variable	Moderate/severe anxiety	Moderate/severe depression	Posttraumatic stress
Effects of early pregnancy loss and time			
Miscarriage vs ectopic pregnancy at month 1	1.61 (0.54–4.79)	2.61 (0.53–12.8)	2.20 (0.53–9.11)
Time (per month since loss) for miscarriage	0.65 (0.44–0.94)	0.66 (0.32–1.35)	0.77 (0.68–0.87)
Time (per month since loss) for ectopic pregnancy	0.80 (0.59–1.10)	0.96 (0.57–1.61)	0.84 (0.69–1.03)
Other predictor variables			
Maternal age (per year)	0.96 (0.89–1.05)	0.98 (0.89–1.09)	0.96 (0.86–1.06)
History of any early pregnancy loss (yes vs no)	4.20 (1.76–10.0)	6.57 (2.10–20.6)	4.83 (1.66–14.0)
In vitro fertilization pregnancy (yes vs no)	0.30 (0.06–1.53)	1.25 (0.20–7.73)	1.30 (0.21–8.18)
Previous children (yes vs no)	0.85 (0.37–1.91)	1.20 (0.43–3.30)	0.31 (0.11–0.89)
Further pregnancy (yes vs no)[b]	1.50 (0.47–4.76)	2.07 (0.40–10.7)	0.33 (0.10–1.16)
Further loss (yes vs no)[b]	20.0 (2.60–153)	19.2 (1.55–237)	12.3 (2.76–55.0)
Between-patient differences			
Patient (median odds ratio)[c]	10.61	21.71	44.17
Time (per month since loss) for miscarriage[d]	0.50–1.30	0.62–1.46	NA
Time (per month since loss) for ectopic pregnancy[d]	0.40–1.04	0.43–1.00	NA

NA, not available.

[a] Because we included an interaction term between time and early pregnancy loss, these 2 variables were represented by indicating the effect of loss type at month 1 and the effect of time in each loss group; [b] Time-varying measurements that were scored in each of the 3 questionnaires; [c] Median odds ratio between a randomly selected subject at higher risk of the outcome and a randomly selected subject at lower risk of the outcome, with the same covariate values, which shows how the outcome risk differs between patients; [d] The interval for the individual time effect covering the middle 80% of patients, which shows how the effect of time differs between patients, after adjustment for covariates.

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