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TITLE PAGE

Factors associated with post-traumatic stress, anxiety and depression in women after early pregnancy loss: a multi-centre prospective cohort study

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Abstract

Objectives: To investigate prognostic factors for anxiety, depression and post-traumatic stress symptoms one month after early pregnancy loss (EPL).

Design: A prospective cohort study. Consecutive women were recruited, and demographic and clinical data collected. Surveys containing the hospital anxiety and depression scale (HADS) and posttraumatic stress diagnostic scale (PDS) were emailed one month after a loss. Univariable logistic regression was performed to link factors with caseness of anxiety, depression or post-traumatic stress (PTS) according to screening measures.

Setting: Early pregnancy units of three central London hospitals.

Participants: 737/1116 eligible women with an EPL were recruited. 492 responded to HADS and 487 to PDS.

Primary and secondary outcome measures: Primary outcome is the area under the curve (AUC) to predict any psychological morbidity (defined as moderate/severe anxiety or depression, or meeting screening criteria for PTS) for each variable. Further outcomes are explained variation (R-squared) and p-value for any morbidity, and AUC, explained variation, and p-value for each morbidity separately.

Results: Women who had a current or past diagnosis of a psychiatric condition were at higher risk of meeting criteria for anxiety, depression or PTS (75% for current versus 55% for past versus 30% for no diagnosis; AUC 0.61; R-squared 8.4%; $p<0.0001$), as were those with previous pregnancy loss (48% versus 30%; AUC 0.59; R-squared 4.3%; $p<0.0001$). Most of the assessed factors did not demonstrate potential utility in predicting psychological distress, including gestational age, overnight admission, time taken for diagnosis, pre-existing children, and the diagnosis itself (miscarriage versus ectopic versus other) (AUCs≤0.54; R-squared≤0.9%).

Conclusions: Women with a history of mental health problems, or those with previous losses, may be at higher risk of psychological illness one month after pregnancy loss. However, a high proportion of women with psychological distress will not have risk factors. All women should be considered at risk.

Article Summary

Strengths and weaknesses

- We have involved a large cohort of women to explore a wide variety of prognostic factors for psychological morbidity after early pregnancy loss.
- We included women with miscarriage, ectopic pregnancy and resolved pregnancy of unknown location: few studies have included groups other than miscarriage
- We have assessed for a relationship with anxiety, depression and post-traumatic stress, both as a combined outcome and individually. Post-traumatic stress has been found to be the most common response after early pregnancy loss, but has been little studied.
- A weakness is in the use of screening questionnaires for psychological morbidity
- A further weakness is the drop out of participants: 67% of those recruited responded to the questionnaire

Introduction

Evidence to date has confirmed that early pregnancy losses (EPLs) may be associated with a high likelihood of anxiety, depression and post-traumatic stress(Engelhard, van den Hout et al. 2001, Cumming, Klein et al. 2007, Farren, Jalmbrant et al. 2020). Given the high frequency of EPLs, and their impact at an important time in a woman's life (at work and at home), it is imperative that focus is given to ways to prevent or treat this psychological morbidity.

A Cochrane review, published in 2012, suggested that there was no evidence, from a total of 1001 participants across six studies, to support offering counselling in various formats to all women following early pregnancy loss (Murphy, Lipp et al. 2012). However, the predictive validity of those studies was deflated by a floor effect: they included all women with EPL rather than selecting women who were clinically distressed prior to the intervention and who therefore realistically could show improvement. It is probable that better results could be obtained by targeting treatment towards those who experience clinically significant symptoms of distress. Understanding what (if any) factors in a woman's history or clinical encounter put her at risk of psychological morbidity might enable treatment to be targeted at those at high risk, with better results.

A number of possible risk factors have been suggested by previous research, including childlessness (Neugebauer, Kline et al. 1992, Thapar and Thapar 1992), previous losses (Thapar and Thapar 1992, Engelhard, van den Hout et al. 2001), previous subfertility (Sham, Yiu et al. 2010), past psychiatric history (Friedman and Gath 1989, Walker and Davidson 2001, Nordal Broen, Moum et al. 2006, Cumming, Klein et al. 2007) and longer gestation (Janssen, Cuisinier et al. 1996, Engelhard, van den Hout et al. 2001). However, many of these have been identified on the basis of retrospective exploratory analyses for statistically significant differences between groups, and the degree to which they may actually be able to explain the variation in psychological morbidity between individuals remains obscure. Furthermore, limited research has been done linking potential factors to post-

traumatic stress symptoms, which, according to this group's recent study is the most common psychological response(Farren, Jalmbrant et al. 2020).

This explorative study aimed to assess whether, in a large cohort, a prospectively chosen set of potential factors could be used to reliably and usefully predict those with psychiatric morbidity. Increases in diagnostic thresholds for miscarriage in 2011 (in order to minimise the risk of a false positive diagnosis and inadvertent termination) have increased the proportion of inconclusive scans, and lengthened the duration of uncertainty (NICE 2012) . Of particular interest at the current time is whether these changes may be associated with increased psychological morbidity.

Methods

This is the third report from the Psychological Impact of Early Pregnancy Events (PIEPE) prospective cohort study. The first reported on anxiety, depression and post-traumatic stress (PTS) at one, three and nine months in women directly experiencing a loss and a control group in healthy pregnancy(Farren, Jalmbrant et al. 2020). The second reported on these symptoms in both women and their partners in a cohort of couples (Farren, Jalmbrant et al. 2021). This report focuses on exploring risk factors for morbidity reported at one month. Ethical approval was given by South-West Exeter National Research Ethics Service (reference 11/SW/0052).

Women with pregnancy losses before 20 weeks (miscarriage (including molar pregnancy), ectopic pregnancy, and resolved pregnancy of unknown location) were recruited from the Early Pregnancy Assessment Units (EPAUs) at three hospitals in central London (Queen Charlotte's and Chelsea, St Mary's, and Chelsea and Westminster Hospitals). Exclusion criteria were: age of participant <18 years, lack of proficiency in the English language (insufficient, based on the subjective assessment by the researcher, to complete the questionnaire without help or translation), inability to give informed consent, review following voluntary termination of a pregnancy, or if they were already a participant in the study following a previous loss.

Women were recruited consecutively, and could be recruited on the day of diagnosis of a loss or at follow-up within one month of diagnosis thereafter. The target sample size of 721 women with EPL was based on data from our pilot study, with the aim to assess for a 20% difference in PTS prevalence in those with IVF and without, taking into account a predicted 60% response rate at one month (with the aim to include 440 responders) (Farren, Jalmbrant et al. 2016).

The clinical care of women was unaltered by participation in the study. Those with a diagnosis of incomplete or missed miscarriage were offered the clinically appropriate options out of expectant, medical (misoprostol administered by the patient at home) or surgical (under general anaesthesia) management. Women with ectopic pregnancy (EP) were offered expectant management, methotrexate or surgical intervention (usually laparoscopic salpingectomy) depending on symptoms and clinical markers. Women with resolving pregnancy of unknown location (rPUL) were asked to check for a negative urine pregnancy test after two weeks. Women with a confirmed diagnosis of a molar pregnancy were referred to the regional trophoblastic centre.

Details of the encounter were prospectively collected, including, for the purposes of this analysis, the woman's age at diagnosis, the date of last menstrual period (LMP), the final diagnosis (miscarriage, ectopic, other (PUL and molar)), the dates and outcomes of any scans (including whether a fetal heart had previously been visible in women who were subsequently diagnosed with miscarriage), and number of nights admission. The length of time from the first scan to a diagnosis of loss was calculated. Management was also recorded: if multiple interventions were required (most commonly medical or expectant management followed by surgical), then the final definitive management was used. Record was made as to whether the pregnancy was conceived via in vitro fertilisation (IVF).

Women were sent a link to a confidential online survey (in which they were identified by a study number) by email one, three and nine months after diagnosis of their loss. Only data from the one-month questionnaire was included in this analysis. Reminders that they were free to withdraw from

the study were included in every communication. Without active withdrawal, two reminder emails at weekly intervals were sent to those who did not respond.

As part of the first questionnaire, respondents were asked their ethnicity, their past educational attainment, whether they had experienced past losses, past terminations of pregnancy (ToP), or had existing children. They were asked whether they had previously been diagnosed and/or received treatment for a psychiatric condition (currently, in the past, or no). They were also asked how long they had been trying to conceive. The methods by which this data was obtained, and the groupings used in both data collection and analysis are summarised in Supplementary Table 1.

Surveys included two psychometric screening questionnaires: the Hospital Anxiety and Depression Scale (HADS)), and the Post-traumatic Diagnostic Scale (PDS). Both have previously been used in the pregnancy loss population, and have been shown in multiple contexts to have good psychometric properties (Farren, Mitchell-Jones et al. 2018). Further discussion of these measures is included in our primary analysis(Farren, Jalmbrant et al. 2020). A woman was considered to meet criteria for anxiety or depression if their score fell within the moderate or severe range (>=11/21 for each). For PTS, a PDS score >= 18/51, along with endorsement of the required number of symptoms within each cluster (re-experiencing, avoidance and hyper-arousal), was required (Ehring, Kleim et al. 2007).

Exploration of the potential prognostic value of each factor was performed by univariable logistic regression, initially for any morbidity (defined as moderate/severe anxiety or moderate/severe depression or PTS), and then for each morbidity individually. The primary outcome was the area under the receiver operating characteristic curve (AUC) for any morbidity. Further outcomes were the Nagelkerke R-squared to quantify the explained variation in the outcome and the likelihood ratio p-value for any morbidity, and the AUC, R-squared and p-value for each morbidity separately. Because missing values were limited among responders at one month, individuals with a missing value were excluded from the analyses involving that predictor only. The goal was to explore which risk factors could be subject to further research for developing a multivariable prediction model.

All statistical analyses were performed using R 3.6.1.

Results

A flowchart of women approached, eligible, recruited and who responded is shown in **Figure 1.** Of the 737 women with early pregnancy loss who were recruited, 492 responded to the HADS questionnaire and 487 to the PDS. The questionnaires were sent one month after diagnosis, and responses were a mean of 40 days after diagnosis (standard deviation, 12; interquartile range, 32-45). Of those responding to HADS, 366 cases were miscarriage, 75 were EP, and 51 were other diagnoses (including resolved and persistent pregnancy of unknown location and molar pregnancy). Demographic, background clinical, and response data on all respondents is shown in **Table 1.** There was a small proportion of missing data for all variables except gestational age, for which 84 cases were omitted where this was unknown.

The variable with the highest AUC was past or current diagnosis of a psychiatric disorder (AUC 0.61, R-squared 8.4%, p<0.0001) (Table 2). 75% (15/20) of those with a self-reported current diagnosis of a psychiatric disorder met criteria for anxiety, depression or PTS, compared to 55% (45/82) of those with a past diagnosis, and 30% (115/382) in those without a past psychiatric history (Figure 2, Table 3). AUCs for each morbidity separately were 0.60 (anxiety), 0.64 (depression), and 0.61 (PTS) (Supplementary Table 2).

Those with past losses also appear to be at higher risk of any morbidity (AUC 0.59, R-squared 4.3%, p<0.0001): 48% (86/180) women with any previous loss met criteria for any disorder, compared to 30% (92/307) in the group without previous losses. AUCs for each morbidity separately were 0.59 (anxiety), 0.64 (depression), and 0.57 (PTS).

There is a modest suggestion of prognostic value for time to conceive (AUC 0.56, R-squared 2.2%, p 0.02) and ethnicity (AUC 0.57, R-squared 2.4%, p 0.07). 49% (40/81) women who had taken more than one year to conceive met criteria for any disorder, compared to 35% (105/296) in those taking <1 year, and 30% (33/110) in those in whom the pregnancy was unplanned. 40% (72/182) women of White

British ethnicity, 35% (17/48) of Asian ethnicity, 34% (17/50) of Black ethnicity, 29% (46/156) of other White ethnicities, and 51% (26/51) of any other ethnicities met criteria for any morbidity.

Factors with little to no evidence of potential prognostic value (AUC≤0.54, R-squared≤0.9%, p≥0.14): include: the diagnosis itself (miscarriage versus ectopic versus other), having seen the fetal heart on previous US imaging (miscarriage only), the woman's age, educational attainment, overnight admission, previous termination of pregnancy, previous children, IVF conception, duration of the time to diagnosis from first scan, and gestation at time of diagnosis (in those for whom this is known).

AUC, Nagelkerke R-squared and p values for each morbidity separately (anxiety, depression and PTS) were generally similar for each predictor variable: there was no suggestion that predictors would be valuable for certain conditions (Supplementary table 2).

Overall, even those factors likely to be associated with any morbidity (based on p-values) do not seem to have strong prognostic ability (based on the AUC and R-squared).

Discussion

Our principal finding was that psychological morbidity (post-traumatic stress, anxiety or depression) appears to be more common in those with past or current psychiatric history, and in those with a history of previous pregnancy loss. There is a modest suggestion of potential prognostic ability according to time taken to conceive and ethnicity. Individually, however, all factors have modest AUCs and explain little of the variation in the outcomes (even taking into consideration that R-squared values for binary endpoints tend to be modest in general). The most promising factors could be considered for inclusion in a prediction model in future research, but our results indicate that such model may be of limited utility. A considerable proportion of women with psychological morbidity will probably have none of the potentially prognostic factors from our study.

The strength of this study is in its large size relative to other studies in this area, and in the assessment of multiple, prospectively chosen potential risk factors. Another strength lies in its inclusion of women with ectopic pregnancy, which have not been the subject of any such analysis to date. Only one small study has previously assessed for risk factors for post-traumatic stress, which our group has found to be the most commonly endorsed condition(Engelhard, van den Hout et al. 2001).

A weakness is the considerable drop out between recruitment and response to the first questionnaire (though unavoidable in studies of this nature, and similar to other studies in this field). It was also necessary to use screening questionnaires rather than the gold-standard of individualised assessment by a trained professional.

A decision was made to assess for factors predictive of psychological morbidity at one month rather than at later time points because a) response rates were expected to be higher at one month, and b) this avoids the impact of further pregnancy (healthy or otherwise). However, arguably the most clinically important responses are those that persist over time, and therefore assessing for predictors of longer-term PTS could also be of value.

Another methodological decision was made to assess for factors which could predict any morbidity, and then each morbidity separately. This is because the diagnosis of any condition was considered to be the clinically important outcome to predict, as it is likely to warrant treatment. We did not find any evidence that predictors are different for different outcomes. PTSD is considered a type of anxiety response, and includes within its diagnostic criteria a requirement for negative alterations in mood: it is therefore unsurprising that the relationships seem consistent across the three pathologies, individually and as a combined outcome.

Previous studies have found higher anxiety and depression in women without children, and with reducing numbers of existing children (Neugebauer, Kline et al. 1992, Thapar and Thapar 1992, Sham, Yiu et al. 2010). This study did not suggest that the absence of previous children was able to predict those with morbidity. This may be in part due to methodological reasons. It is also possible that there have been cultural shifts over the past three decades: modern day women may be more susceptible to distress relating to the loss itself than concern over childlessness. Previous studies have also found that gestation may be associated with increased anxiety, depression and post-traumatic stress scores (Janssen, Cuisinier et al. 1996, Engelhard, van den Hout et al. 2001). In contrast to these studies, we did not include stillbirths. Moreover, the vast majority of included women experienced losses in the first 12 weeks of pregnancy (mean gestation 71 days for miscarriage (SD 17), and 46 days (SD 18) for ectopic pregnancies), limiting power to detect differences between the first and second trimester.

In this study, neither gestation nor overnight admission (which is likely to indicate severe pain, heavy blood loss, or the need for emergency surgery) seem to be prognostic of psychological distress. This sends an important message to clinicians: even diagnoses at very early gestations (often referred to as 'biochemical pregnancies'), and with clinically mild symptoms, may provoke significant psychological sequelae, and must be treated with compassion, and acknowledged as a potential cause of psychological illness.

In 2011, criteria for the diagnosis of miscarriage were changed in order to minimise the possibility of error and inadvertent termination(NICE 2012). As a result, the scan outcome of a 'pregnancy of uncertain viability', which requires a repeat scan 7-14 days later for confirmation, has become more common. It could be hypothesised that this longer delay to diagnosis (which might also increase the likelihood of unplanned passage of pregnancy tissue outside of hospital) could have psychological implications: it is reassuring that a longer delay to diagnosis does not seem to be predictive of morbidity. It is possible that appropriate counselling about the likely outcome, or the increased opportunity for discussion with healthcare professionals during follow-up, might ameliorate any negative impact of a delay.

Going forward, it is possible that screening for psychological morbidity after a loss will be a more appropriate way of targeting treatment than a predictive model. The optimal methods and timing of such screening, and its reliability, requires further research.

Conclusions

It is unlikely that a useful model to predict psychological distress in the aftermath of EPL can be developed. Clinicians should be particularly alert to the risk of morbidity in those with a past or current psychiatric history, and those with previous losses. However, it is imperative that staff working in early pregnancy are vigilant to the risk of disabling mental health conditions in all women after pregnancy loss, irrespective of their gestation, the details of their clinical encounter, or their previous obstetric history.

Ethics approval Ethical approval of the study protocol was granted by the NRES committee of South-West Exeter, reference 11/SW/0052.

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Competing interests None declared.

Author Contributions TB and MJ devised the original study protocol, which was amended by JF. JF, NMJ, ST, SB and MA recruited participants for the study. NF and BVC were responsible for statistical analysis of the results. JF, TB and MJ wrote the first draft of the manuscript that was then critically reviewed and revised by the other co-authors. DT commented on the drafts of the paper. All authors approved the final version of the manuscript for submission. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. TB is the guarantor, and affirms that the manuscript is an honest, accurate and transparent account of the study being reported; and that any discrepancies from the study as planned have been explained.

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Disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Data sharing statement Data are available upon reasonable request

Patient and public involvement A pilot study was used to confirm the acceptability of the study methodology, especially the recruitment of women at an acutely upsetting time. Feedback from women was used to optimise the participant information .

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List of Tables

List of Figures

Supplementary Material

Supplementary tables

Supplementary Table 1: *Table of predictor variables chosen, the method of data collection, the subgroups at measurement and the subgroups at analysis*

Supplementary Table 2 *AUC, Nagelkerke R2 and p value for each morbidity (anxiety, depression and post-traumatic stress) separately. Displayed in order or strength of prediction for any morbidity*

Supplementary material

REMARK Checklist

Tables

Table 1 *Prospectively chosen parameters chosen for inclusion, subdivided into data obtained prospectively from clinical records, and data obtained from questionnaire sent one month after diagnosis*

	All recruits		Respondents to questionnaire sent one month after diagnosis	
Variable	All (737)	Missings	All (492)	Missings
Data from clinical records				
Final diagnosis				
Miscarriage	537 (73%)	0 (0%)	366 (74%)	0 (0%)
Ectopic	116 (16%)	0 (0%)	75 (15%)	0 (0%)
Resolved PUL	84 (11%)	0 (0%)	51 (10%)	0 (0%)
Age (in years)	34 (5)	0 (0%)	35 (5)	0 (0%)
IVF this pregnancy	50 (7%)	0 (0%)	38 (8%)	0 (0%)
Gestation at diagnosis	65.4 (20.0)	130 (18%)	66.3 (19.5)	84 (17%)
Nights admission	0.3 (0.7)	12 (2%)	0.3 (0.7)	2 (0.4%)
Nights admission (yes vs. no)	163 (22%)	12 (2%)	100 (20%)	2 (0.4%)
Days from first scan to diagnosis	5.0 (7.7)	13 (2%)	5.1 (7.4)	6 (1%)
Final management				
Medical management	73 (10%)	12 (2%)	45 (9%)	2 (0.4%)
Surgical management	408 (56%)	12 (2%)	291 (59%)	2 (0.4%)
No treatment needed	244 (34%)	12 (2%)	154 (31%)	2 (0.4%)
Fetal heart (misc only)				
Yes	126 (23%)	4 (1%)	84 (23%)	3 (1%)
No	407 (76%)	4 (1%)	279 (77%)	3 (1%)
Data from first questionnaire				
Highest level of education				
No formal qualifications	6 (1%)	233 (32%)	6 (1%)	0 (0%)
GCSEs (or equivalent)	41 (8%)	233(32%)	41 (8%)	0 (0%)
A Levels (or equivalent)	52 (10%)	233(32%)	50 (10%)	0 (0%)
Uni degree/prof. qualif.	278 (55%)	233(32%)	271 (55%)	0 (0%)
Post graduate/PhD	127 (25%)	233 (32%)	124 (25%)	0 (0%)
Time taken to conceive				
Not planned	110 (22%)	240 (33%)	110 (22%)	0 (0%)
≤1 year	305 (61%)	240 (33%)	301 (61%)	0 (0%)
>1 year	82 (16%)	240 (33%)	81 (16%)	0 (0%)
Psych disorder				
Currently	21 (4%)	236 (32%)	20 (4%)	3 (1%)
In the past	86 (17%)	236 (32%)	83 (17%)	3 (1%)
No	394 (79%)	236 (32%)	386 (79%)	3 (1%)
Any previous pregnancy loss	264 (46%)	162 (22%)	182 (37%)	0 (0%)
Any previous termination	161 (23%)	25 (3%)	121 (25%)	0 (0%)
Any previous children	316 (44%)	24 (3%)	203 (41%)	0 (0%)
Ethnicity				
Asian	50	233 (32%)	48	0 (0%)
Black	53	233 (32%)	51	0 (0%)
Other	53	233 (32%)	52	0 (0%)
White British	187	233 (32%)	185	0 (0%)
White Other	161	233 (32%)	156	0 (0%)

Abbreviations: HADS – Hospital Anxiety and Depression Score; IVF – in vitro fertilization; PDS – posttraumatic stress diagnostic scale; PUL – pregnancy of unknown location

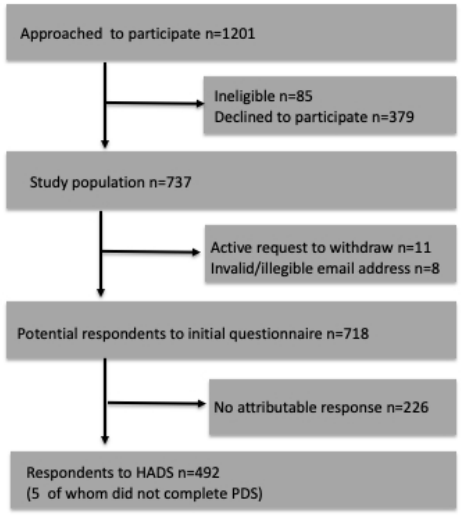
Table 2 *AUC, Nagelkerke R2 and p value in the prediction of any morbidity (anxiety, depression or post-traumatic stress) for each potential predictor variable, displayed in order of decreasing predictive probabilities*

Predictor	AUC (95% CI)	R2	p value
Psychiatric disorder (no, in past, currently)	0.61 (0.55;0.66)	0.084	<0.0001
Any previous pregnancy loss (no=0;yes=1)	0.59 (0.54;0.64)	0.043	<0.0001
Ethnicity (White British/White other/Black/Asian/ Other)	0.57 (0.52;0.63)	0.024	0.07
Time to conceive (unknown/<1year/>1 year)	0.56 (0.51 0.61)	0.022	0.02
Final diagnosis (miscarriage, ectopic, other)	0.54 (0.48;0.59)	0.009	0.19
Final management (surgical, medical, conservative)	0.54 (0.49;0.59)	0.008	0.23
Fetal Heart (no=0; yes=1) (Miscarriage only)	0.53 (0.47;0.59)	0.008	0.34
Age (in years)	0.53 (0.47;0.58)	0.001	0.53
Educational attainment (none; GCSE; A-level; University; Post-graduate degree)	0.52 (0.47; 0.57)	0.003	0.89
Overnight admission (no=0;yes=1)	0.52 (0.47;0.57)	0.003	0.29
Previous termination (no=0;yes=1)	0.52 (0.47;0.57)	0.002	0.37
Previous children (no=0;yes=1)	0.52 (0.47;0.57)	0.002	0.39
Days to diagnosis from first scan (days)	0.51 (0.46; 0.57)	0.000	0.95
IVF (no=0;yes=1)	0.50 (0.45;0.56)	0.000	0.70
Gestational age (days)	0.50 (0.44;0.56)	0.000	0.89

Abbreviations: AUC – Area Under Curve, CI – Confidence Interval

Table 3 *Descriptive statistics for the most important variables*

	Anxiety (%) (N=492)	Depression (%) (N=492)	PTS (%) (N=487)	Any (%) (N=487)
Psych Disorder				
No	76/386 (20%)	28/386 (7%)	86/382 (23%)	115/382 (30%)
Yes, in the past	29/83 (35%)	20/83 (24%)	39/82 (48%)	45/82 (55%)
Yes, currently	12/20 (60%)	4/20 (20%)	11/20 (55%)	15/20 (75%)
Missing	2/3 (67%)	1/3 (33%)	3/3 (100%)	3/3 (100%)
Any previous loss				
No	59/310 (19%)	20/310 (6%)	73/307 (24%)	92/307 (30%)
Yes	60/182 (33%)	33/182 (18%)	66/180 (37%)	86/180 (48%)
Ethnicity				
Asian	14/48 (29%)	5/48 (10%)	12/48 (25%)	17/48 (35%)
Black	15/51 (29%)	7/51 (14%)	13/50 (26%)	17/50 (34%)
Other	18/52 (35%)	14/52 (27%)	20/51 (39%)	26/51 (51%)
White British	49/185 (26%)	17/185 (9%)	56/182 (31%)	72/182 (40%)
White Other	23/156 (15%)	10/156 (6%)	38/156 (24%)	46/156 (29%)
Time to conceive				
Unknown/unplanned	20/110 (18%)	9/110 (8%)	24/110 (22%)	33/110 (30%)
>1 year	76/301 (25%)	30/301 (10%)	79/296 (27%)	105/296 (35%)
> 1 year	23/81 (28%)	14/81 (17%)	36/81 (44%)	40/81 (49%)



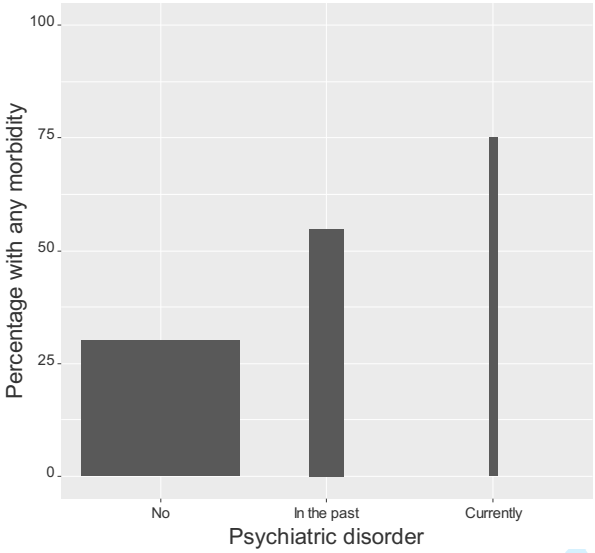
Abbreviations: HADS: Hospital Anxiety and Depression Scale, PDS: Post-traumatic Diagnostic Scale

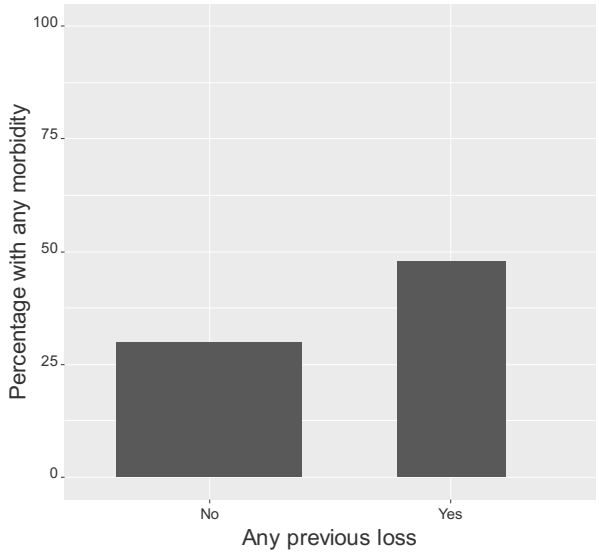
Figure 1: Flowchart of women approached, who agreed to participation, and who responded to the questionnaire

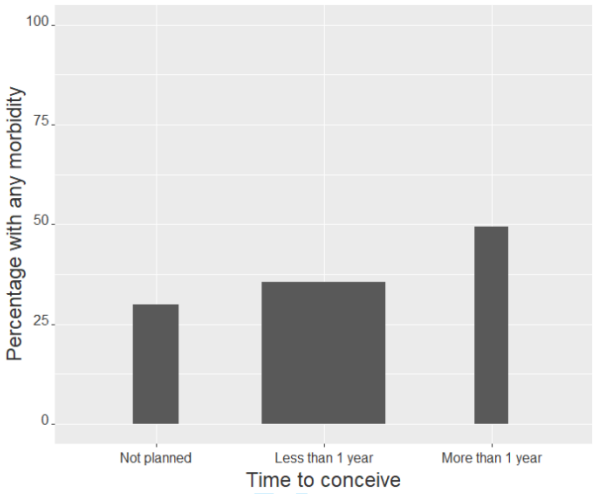
254x299mm (72 x 72 DPI)

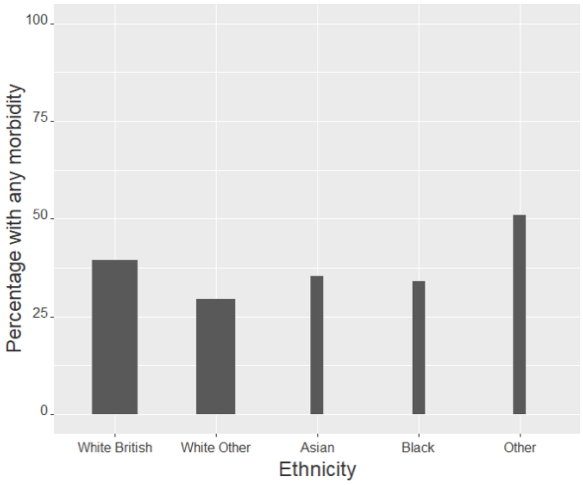
Figure 2

Figure 2: *Figures showing presence of any morbidity for the most important predictors. The width of the bars reflects the number of patients with that value for the predictor*









Supplementary Data

Supplementary Table 1: *Table of predictor variables chosen, the method of data collection, the subgroups at measurement and the subgroups at analysis*

Potential predictor	Source of data	Subgroups when measured	Subgroups when analysed
Final diagnosis	Clinical records	Miscarriage (including molar)/ Ectopic pregnancy/ Resolved PUL	Miscarriage (including molar)/ Ectopic pregnancy/ Resolved PUL
Age (in years)	Clinical records *Date of birth to date of diagnosis*	Continuous	Continuous
IVF this pregnancy	Clinical records	Yes/No	Yes/No
Gestation at diagnosis	Clinical records *Date of LMP (if known) or embryo transfer to date of diagnosis**	Continuous/ Unknown	Continuous/ Unknown
Nights admission	Clinical records	Continuous	Continuous
Days from first scan to diagnosis	Clinical records *Date of first scan to date of diagnosis**	Continuous	Continuous
Final management	Clinical records *If more than one management, final management used*	Conservative/ Medical management of miscarriage/ Medical management of ectopic or PPUL with methotrexate Surgical management of miscarriage/ Salpingectomy for ectopic/ Salpingostomy for ectopic/ Other surgical management for ectopic	Conservative/ Medical management of miscarriage or ectopic/ Surgical management of miscarriage or ectopic
Fetal heart (miscarriage only)	Clinical records	Yes/ Yes with concerns/ No	Yes/No
Highest level of education	Questionnaire	No formal qualifications/ GCSEs(or equivalent)/ A-levels (or equivalent)/ University degree or professional qualification/ Post-graduate or PhD	No formal qualifications/ GCSEs(or equivalent)/ A-levels (or equivalent)/ University degree or professional qualification/ Post-graduate or PhD

Time taken to conceive	Questionnaire	Not planned/ 1-3 months/ 3-6 months/ 6-12 months/ 13-18 months/ 19-24 months/ more than 2 years	Not planned/ <=1 year/ >1year
Psychiatric disorder	Questionnaire	Currently/ In the past/ No	Currently/ In the past/ No
Any previous pregnancy loss	Questionnaire	Types and numbers of losses previously encountered (stillbirth, miscarriage, ectopic, termination for fetal anomaly, PUL)	Yes/No
Any previous termination	Questionnaire	Yes/No	Yes/No
Any live children	Questionnaire	Yes – one/ Yes – two/ Yes- three/ Yes – four or more/ No	Yes/No
Ethnicity	Questionnaire	White British/ White Other/ South East Asian/ South Asian/ Asian Other/ Arab/ Black African/ Black Caribbean/ Black other/ Mixed	Asian/ Black/ Other/ White British/ White other

* Date of diagnosis as non-viable pregnancy: i.e. if diagnosed as molar on later histological diagnosis, date of scan confirming non-viability

Abbreviations: IVF – in vitro fertilisation

Supplementary Table 2 *AUC, Nagelkerke R2 and p value for each morbidity (anxiety, depression and post-traumatic stress) separately. Displayed in order of strength of prediction for any morbidity.*

Predictor	Anxiety			Depression			PTS		
	AUC	R2	P value	AUC	R2	P value	AUC	R2	P value
Psychiatric disorder (Ref = no)	0.60 (0.54;0.65)	0.062	<0.0001	0.64 (0.56;0.72)	0.077	<0.0001	0.61 (0.55;0.66)	0.076	<0.0001
Any previous losses (no=0;yes=1)	0.59 (0.53;0.65)	0.036	0.0006	0.64 (0.56;0.72)	0.063	<0.0001	0.57 (0.52;0.63)	0.027	0.0026
Ethnicity (5 categories)	0.60 (0.54;0.66)	0.039	0.01	0.64 (0.56;0.71)	0.061	0.005	0.56 (0.50;0.61)	0.015	0.29
Time to conceive (3 categories)	0.55 (0.49;0.60)	0.010	0.20	0.57 (0.49;0.65)	0.017	0.13	0.58 (0.52;0.64)	0.036	0.0021
Final diagnosis (miscarriage, ectopic, other)	0.53 (0.47;0.58)	0.004	0.54	0.56 (0.48;0.64)	0.016	0.15	0.53 (0.47;0.58)	0.005	0.42
Final management (surgical, medical, conservative)	0.51 (0.45;0.57)	0.001	0.90	0.56 (0.48;0.64)	0.012	0.24	0.55 (0.49;0.60)	0.011	0.15
Fetal Heart (no=0; yes=1) (Miscarriage only)	0.52 (0.45;0.59)	0.002	0.76	0.55 (0.46;0.64)	0.010	0.37	0.53 (0.46;0.59)	0.007	0.40
Age (in years)	0.50 (0.44;0.56)	0.000	0.89	0.55 (0.46;0.63)	0.005	0.26	0.52 (0.46;0.58)	0.000	0.78
Education (5 categories)	0.54 (0.48;0.60)	0.013	0.39	0.55 (0.47;0.63)	0.033	0.09	0.53 (0.47;0.58)	0.004	0.85

Overnight admission (no=0;yes=1)	0.54 (0.48;0.60)	0.011	0.06	0.52 (0.44;0.60)	0.002	0.5	0.52 (0.46;0.57)	0.002	0.39
Previous termination (no=0;yes=1)	0.54 (0.48;0.60)	0.008	0.11	0.56 (0.48;0.64)	0.015	0.05	0.53 (0.47;0.59)	0.005	0.19
Previous children (no=0;yes=1)	0.51 (0.45;0.57)	0.000	0.68	0.52 (0.44;0.60)	0.002	0.53	0.54 (0.49;0.60)	0.009	0.09
Days to diagnosis (days)	0.50 (0.44;0.56)	0.001	0.67	0.54 (0.46;0.62)	0.001	0.57	0.50 (0.45;0.56)	0.001	0.56
IVF pregnancy (no=0;yes=1)	0.51 (0.45;0.57)	0.002	0.37	0.52 (0.44;0.60)	0.004	0.33	0.52 (0.46;0.57)	0.004	0.25
Gestational age (days)	0.53 (0.47;0.60)	0.005	0.25	0.54 (0.45;0.63)	0.005	0.31	0.51 (0.44;0.57)	0.000	0.91

Abbreviations: IVF – in vitro fertilisation

The REMARK checklist

	Item to be reported	Page no.
INTRODUCTION		
1	State the marker examined, the study objectives, and any pre-specified hypotheses.	Into, Page 6
MATERIALS AND METHODS		
Patients		
2	Describe the characteristics (e.g., disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.	Table 1&2
3	Describe treatments received and how chosen (e.g., randomized or rule-based).	Not applicable
Specimen characteristics		
4	Describe type of biological material used (including control samples) and methods of preservation and storage.	Not applicable
Assay methods		
5	Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.	Not applicable
Study design		
6	State the method of case selection, including whether prospective or retrospective and whether stratification or matching (e.g., by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.	Methods – p6
7	Precisely define all clinical endpoints examined.	Methods – p8
8	List all candidate variables initially examined or considered for inclusion in models.	Sup Table 1
9	Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.	Methods – p6
Statistical analysis methods		
10	Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.	Methods – p8
11	Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.	Sup Table 1
RESULTS		
Data		
12	Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the numbers of patients and the number of events.	Figure 1
13	Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including numbers of missing values.	Table 2
Analysis and presentation		
14	Show the relation of the marker to standard prognostic variables.	Not applicable
15	Present univariable analyses showing the relation between the marker and outcome, with the estimated effect (e.g., hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.	Table 3
16	For key multivariable analyses, report estimated effects (e.g., hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.	Not applicable
17	Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.	Table 2
18	If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.	Not applicable

Source: McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM: Reporting recommendations for tumor marker prognostic studies (REMARK). *J Natl Cancer Inst* 2005; 97: 1180-1184.

The REMARK checklist

DISCUSSION		
19	Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study.	Discussion – p11-12
20	Discuss implications for future research and clinical value.	Discussion – p12

Source: McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM: Reporting recommendations for tumor marker prognostic studies (REMARK). *J Natl Cancer Inst* 2005; 97: 1180-1184.

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Prognostic factors for post-traumatic stress, anxiety and depression in women after early pregnancy loss: a multi-centre prospective cohort study

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TITLE PAGE

Prognostic factors for post-traumatic stress, anxiety and depression in women after early pregnancy loss: a multi-centre prospective cohort study

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Abstract

Objectives: To investigate prognostic factors for anxiety, depression and post-traumatic stress symptoms one month after early pregnancy loss (EPL).

Design: A prospective cohort study. Consecutive women were recruited, and demographic and clinical data collected. Surveys containing the hospital anxiety and depression scale (HADS) and posttraumatic stress diagnostic scale (PDS) were emailed one month after a loss. Univariable logistic regression was performed to link factors with caseness of anxiety, depression or post-traumatic stress (PTS) according to screening measures.

Setting: Early pregnancy units of three central London hospitals.

Participants: 737/1116 eligible women with an EPL were recruited. 492 responded to HADS and 487 to PDS.

Primary and secondary outcome measures: Primary outcome is the area under the curve (AUC) to predict any psychological morbidity (defined as moderate/severe anxiety or depression, or meeting screening criteria for PTS) for each variable. Further outcomes are explained variation (R-squared) and p-value for any morbidity, and AUC, explained variation, and p-value for each morbidity separately.

Results: Women who had a current or past diagnosis of a psychiatric condition were more likely to meet criteria for anxiety, depression or PTS (75% for current versus 55% for past versus 30% for no diagnosis; AUC 0.61; R-squared 8.4%; p<0.0001), as were those with previous pregnancy loss (48% versus 30%; AUC 0.59; R-squared 4.3%; p<0.0001). Most of the assessed factors did not demonstrate potential utility in predicting psychological distress, including gestational age, overnight admission, time taken for diagnosis, pre-existing children, and the diagnosis itself (miscarriage versus ectopic versus other) (AUCs≤0.54; R-squared≤0.9%).

Conclusions: Women with a history of mental health problems, or those with previous losses, may be at higher risk of psychological illness one month after pregnancy loss. However, prognostic ability was poor overall. All women should be considered at risk.

Article Summary

Strengths and weaknesses

- We have involved a large cohort of women to explore a wide variety of prognostic factors for psychological morbidity after early pregnancy loss.
- We included women with miscarriage, ectopic pregnancy and resolved pregnancy of unknown location: few studies have included groups other than miscarriage
- We have assessed for a relationship with anxiety, depression and post-traumatic stress, both as a combined outcome and individually. Post-traumatic stress has been found to be the most common response after early pregnancy loss, but has been little studied.
- A weakness is in the use of screening questionnaires for psychological morbidity
- A further weakness is the drop out of participants: 67% of those recruited responded to the questionnaire

Introduction

Evidence to date has confirmed that early pregnancy losses (EPLs) may be associated with a high likelihood of anxiety, depression and post-traumatic stress (1-3). Given the high frequency of EPLs, and their impact at an important time in a woman's life (at work and at home), it is imperative that focus is given to ways to prevent or treat this psychological morbidity.

A Cochrane review, published in 2012, suggested that there was no evidence, from a total of 1001 participants across six studies, to support offering counselling in various formats to all women following early pregnancy loss (4). However, the predictive validity of those studies was deflated by a floor effect: they included all women with EPL rather than selecting women who were clinically distressed prior to the intervention and who therefore realistically could show improvement. It is probable that better results could be obtained by targeting treatment towards those who experience clinically significant symptoms of distress. Understanding what (if any) factors, in a woman's history or clinical encounter are be associated with an increased risk of psychological morbidity might enable treatment to be targeted at those at high risk, with better results.

A number of possible prognostic factors have been suggested by previous research, including childlessness (5, 6), previous losses (3, 6), previous subfertility (7), IVF pregnancy (8), past psychiatric history (2, 9-11) and longer gestation (3, 12). However, many of these have been identified on the basis of retrospective exploratory analyses for statistically significant differences between groups, and the degree to which they may actually be able to explain the variation in psychological morbidity between individuals remains obscure. Furthermore, limited research has been done linking potential factors to post-traumatic stress symptoms, which, according to this group's recent study is the most common psychological response (1).

This explorative study aimed to assess whether, in a large cohort, a prospectively chosen set of potential factors could be used to reliably and usefully predict those with psychiatric morbidity. It is a

study to assess for prognostic factors, and therefore without assessment of causation or analysis for confounders.

Methods

This is the third report from the Psychological Impact of Early Pregnancy Events (PIEPE) prospective cohort study. The first reported on anxiety, depression and post-traumatic stress (PTS) at one, three and nine months in women directly experiencing a loss and a control group in healthy pregnancy (1). The second reported on these symptoms in both women and their partners in a cohort of couples (13). This report focuses on exploring prognostic factors for morbidity reported at one month. Ethical approval was given by South-West Exeter National Research Ethics Service (reference 11/SW/0052).

Women with pregnancy losses before 20 weeks (miscarriage (including molar pregnancy), ectopic pregnancy, and resolved pregnancy of unknown location) were recruited from the Early Pregnancy Assessment Units (EPAUs) at three hospitals in central London (Queen Charlotte's and Chelsea, St Mary's, and Chelsea and Westminster Hospitals) between 13/11/13 and 15/3/16. Exclusion criteria were: age of participant <18 years, lack of proficiency in the English language (insufficient, based on the subjective assessment by the researcher, to complete the questionnaire without help or translation), inability to give informed consent, review following voluntary termination of a pregnancy, or if they were already a participant in the study following a previous loss.

Women were recruited consecutively, and could be recruited on the day of diagnosis of a loss or at follow-up within one month of diagnosis thereafter. Written consent was required. The target sample size of 721 women with EPL was based on data from our pilot study, with the aim to assess for a 20% difference in PTS prevalence in those with IVF and without, taking into account a predicted 60% response rate at one month (with the aim to include 440 responders) (14).

The clinical care of women was unaltered by participation in the study. Those with a diagnosis of incomplete or missed miscarriage were offered the clinically appropriate options out of expectant, medical (misoprostol administered by the patient at home) or surgical (under general anaesthesia) management. Women with ectopic pregnancy (EP) were offered expectant management, methotrexate or surgical intervention (usually laparoscopic salpingectomy) depending on symptoms and clinical markers. Women with resolving pregnancy of unknown location (rPUL) were asked to check for a negative urine pregnancy test after two weeks. Women with a confirmed diagnosis of a molar pregnancy were referred to the regional trophoblastic centre.

Details of the encounter were prospectively collected, including, for the purposes of this analysis, the woman's age at diagnosis, the date of last menstrual period (LMP), the final diagnosis (miscarriage, ectopic, other (PUL and molar)), the dates and outcomes of any scans (including whether a fetal heart had previously been visible in women who were subsequently diagnosed with miscarriage), and number of nights admission. The length of time from the first scan to a diagnosis of loss was calculated. Management was also recorded: if multiple interventions were required (most commonly medical or expectant management followed by surgical), then the final definitive management was used. Record was made as to whether the pregnancy was conceived via in vitro fertilisation (IVF).

Women were sent a link to a confidential online survey (in which they were identified by a study number) by email one, three and nine months after diagnosis of their loss. Only data from the one-month questionnaire was included in this analysis. Reminders that they were free to withdraw from the study were included in every communication. Without active withdrawal, two reminder emails at weekly intervals were sent to those who did not respond.

As part of the first questionnaire, respondents were asked their ethnicity, their past educational attainment, whether they had experienced past losses, past terminations of pregnancy (ToP), or had existing children. They were asked whether they had previously been diagnosed and/or received treatment for a psychiatric condition (currently, in the past, or no). They were also asked how long

they had been trying to conceive. The methods by which this data was obtained, and the groupings used in both data collection and analysis are summarised in Supplementary Table 1.

Surveys included two psychometric screening questionnaires: the Hospital Anxiety and Depression Scale (HADS)), and the Post-traumatic Diagnostic Scale (PDS). Both have previously been used in the pregnancy loss population, and have been shown in multiple contexts to have good psychometric properties (15). Further discussion of these measures is included in our primary analysis (1). A woman was considered to meet criteria for anxiety or depression if their score fell within the moderate or severe range (>=11/21 for each). For PTS, a PDS score >= 18/51, along with endorsement of the required number of symptoms within each cluster (re-experiencing, avoidance and hyper-arousal), was required (16).

Exploration of the potential prognostic value of each factor was performed by univariable logistic regression, initially for any morbidity (defined as moderate/severe anxiety or moderate/severe depression or PTS), and then for each morbidity individually. The primary outcome was the area under the receiver operating characteristic curve (AUC) for any morbidity. Further outcomes were the Nagelkerke R-squared to quantify the explained variation in the outcome and the likelihood ratio p-value for any morbidity, and the AUC, R-squared and p-value for each morbidity separately. Because missing values were limited among responders at one month, individuals with a missing value were excluded from the analyses involving that predictor only. The goal was to explore which prognostic factors could be subject to further research for developing a multivariable prediction model.

All statistical analyses were performed using R 3.6.1. The reporting was based on the REMARK and STROBE guidelines.

Results

A flowchart of women approached, eligible, recruited and who responded is shown in **Figure 1.** Of the 737 women with early pregnancy loss who were recruited, 492 responded to the HADS questionnaire and 487 to the PDS. The questionnaires were sent one month after diagnosis, and responses were a mean of 40 days after diagnosis (standard deviation, 12; interquartile range, 32-45). Of those responding to HADS, 366 cases were miscarriage, 75 were EP, and 51 were other diagnoses (including resolved and persistent pregnancy of unknown location and molar pregnancy). Demographic, background clinical, and response data on all respondents is shown in **Table 1.** There was a small proportion of missing data for all variables except gestational age, for which 84 cases were omitted where this was unknown.

The variable with the highest AUC was past or current diagnosis of a psychiatric disorder (AUC 0.61, R-squared 8.4%, p<0.0001) (Table 2). 75% (15/20) of those with a self-reported current diagnosis of a psychiatric disorder met criteria for anxiety, depression or PTS, compared to 55% (45/82) of those with a past diagnosis, and 30% (115/382) in those without a past psychiatric history (Figure 2, Table 3). AUCs for each morbidity separately were 0.60 (anxiety), 0.64 (depression), and 0.61 (PTS) (Supplementary Table 2).

Those with past losses also appear to be at higher risk of any morbidity (AUC 0.59, R-squared 4.3%, p<0.0001): 48% (86/180) women with any previous loss met criteria for any disorder, compared to 30% (92/307) in the group without previous losses. AUCs for each morbidity separately were 0.59 (anxiety), 0.64 (depression), and 0.57 (PTS).

There is a modest suggestion of prognostic value for time to conceive (AUC 0.56, R-squared 2.2%, p 0.02) and ethnicity (AUC 0.57, R-squared 2.4%, p 0.07). 49% (40/81) women who had taken more than one year to conceive met criteria for any disorder, compared to 35% (105/296) in those taking <1 year, and 30% (33/110) in those in whom the pregnancy was unplanned. 40% (72/182) women of White

British ethnicity, 35% (17/48) of Asian ethnicity, 34% (17/50) of Black ethnicity, 29% (46/156) of other White ethnicities, and 51% (26/51) of any other ethnicities met criteria for any morbidity.

Factors with little to no evidence of potential prognostic value (AUC≤0.54, R-squared≤0.9%, p≥0.14): include: the diagnosis itself (miscarriage versus ectopic versus other), having seen the fetal heart on previous US imaging (miscarriage only), the woman's age, educational attainment, overnight admission, previous termination of pregnancy, previous children, IVF conception, duration of the time to diagnosis from first scan, and gestation at time of diagnosis (in those for whom this is known).

AUC, Nagelkerke R-squared and p values for each morbidity separately (anxiety, depression and PTS) were generally similar for each predictor variable: there was no suggestion that predictors would be valuable for certain conditions (Supplementary table 2).

Overall, even those factors likely to be associated with any morbidity (based on p-values) do not seem to have strong prognostic ability (based on the AUC and R-squared).

Discussion

Our principal finding was that psychological morbidity (post-traumatic stress, anxiety or depression) appears to be more common in those with past or current psychiatric history, and in those with a history of previous pregnancy loss. There is a modest suggestion of potential prognostic ability according to time taken to conceive and ethnicity. Individually, however, all factors have modest AUCs and explain little of the variation in the outcomes (even taking into consideration that R-squared values for binary endpoints tend to be modest in general). The most promising factors could be considered for inclusion in a prediction model in future research, but our results indicate that such model may be of limited utility. A considerable proportion of women with psychological morbidity will probably have none of the potentially prognostic factors from our study.

The strength of this study is in its large size relative to other studies in this area, across a diverse population from three central London hospitals, and in the assessment of multiple, prospectively chosen potential prognostic factors. Another strength lies in its inclusion of women with ectopic pregnancy, which have not been the subject of any such analysis to date. Only one small study has previously assessed for prognostic factors for post-traumatic stress, which our group has found to be the most commonly endorsed condition (3).

A weakness is the considerable drop out between recruitment and response to the first questionnaire (though unavoidable in studies of this nature, and similar to other studies in this field). It was also necessary to use screening questionnaires rather than the gold-standard of individualised assessment by a trained professional.

A decision was made to assess for factors predictive of psychological morbidity at one month rather than at later time points because a) response rates were expected to be higher at one month, and b) this avoids the impact of further pregnancy (healthy or otherwise). However, arguably the most clinically important responses are those that persist over time, and therefore assessing for predictors of longer-term PTS could also be of value.

Previous studies have found higher anxiety and depression in women without children, and with reducing numbers of existing children (5-7). This study did not suggest that the absence of previous children was able to predict those with morbidity. This may be in part due to methodological reasons: for example, this study uses a categorical (presence of psychological morbidity) rather than a continuous outcome (scores from psychometric questionnaires), as a pathological level of symptoms was felt to be the important outcome to try and predict. It is also possible that there have been cultural shifts over the past three decades: modern day women may be more susceptible to distress relating to the loss itself than concern over childlessness. Previous studies have also found that gestation may be associated with increased anxiety, depression and post-traumatic stress scores (3, 12). In contrast to these studies, we did not include stillbirths. Moreover, the vast majority of included women experienced losses in the first 12 weeks of pregnancy (mean gestation 71 days for miscarriage (SD 17), and 46 days (SD 18) for ectopic pregnancies), limiting power to detect differences between the first and second trimester.

In this study, although delay to conception showed a suggestion of modest predictive potential, IVF conception did not. A previous study in Hong Kong suggested IVF pregnancies were associated with higher traumatic impact after loss (8), but excluded those with children or with a history of any psychiatric illness, and also used a continuous outcome measure, which may underlie the difference.

Neither gestation nor overnight admission (which is likely to indicate severe pain, heavy blood loss, or the need for emergency surgery) seem to be prognostic of psychological distress. This sends an important message to clinicians: even diagnoses at very early gestations (often referred to as 'biochemical pregnancies'), and with clinically mild symptoms, may provoke significant psychological sequelae, and must be treated with compassion.

In 2011, criteria for the diagnosis of miscarriage were changed in order to minimise the possibility of error and inadvertent termination (17). As a result, the scan outcome of a 'pregnancy of uncertain viability', which requires a repeat scan 7-14 days later for confirmation, has become more common.

It could be hypothesised that this longer delay to diagnosis (which might also increase the likelihood of unplanned passage of pregnancy tissue outside of hospital) could have psychological implications: it is reassuring that a longer delay to diagnosis does not seem to be prognostic of morbidity. It is possible that appropriate counselling about the likely outcome, or the increased opportunity for discussion with healthcare professionals during follow-up, might ameliorate any potential negative impact of a delay.

Going forward, it is possible that screening for psychological morbidity after a loss will be a more appropriate way of targeting treatment than a prediction model. The optimal methods and timing of such screening, and its reliability, requires further research.

Conclusions

It is unlikely that a useful model to predict psychological distress in the aftermath of EPL can be developed. Clinicians should be particularly alert to the risk of morbidity in those with a past or current psychiatric history, and those with previous losses. However, it is imperative that staff working in early pregnancy are vigilant to the risk of disabling mental health conditions in all women after pregnancy loss, irrespective of their gestation, the details of their clinical encounter, or their previous obstetric history.

Ethics approval Ethical approval of the study protocol was granted by the NRES committee of South-West Exeter, reference 11/SW/0052.

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Competing interests None declared.

Author Contributions TB and MJ devised the original study protocol, which was amended by JF. JF, NMJ, ST, SB and MA recruited participants for the study. NF and BVC were responsible for statistical analysis of the results. JF, TB and MJ wrote the first draft of the manuscript that was then critically reviewed and revised by the other co-authors. DT commented on the drafts of the paper. All authors approved the final version of the manuscript for submission. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. TB is the guarantor, and affirms that the manuscript is an honest, accurate and transparent account of the study being reported; and that any discrepancies from the study as planned have been explained.

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Disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Data sharing statement Data are available upon reasonable request

Patient and public involvement A pilot study was used to confirm the acceptability of the study methodology, especially the recruitment of women at an acutely upsetting time. Feedback from women was used to optimise the participant information .

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List of Tables

List of Figures

Supplementary Material

Supplementary tables

Supplementary Table 2 *AUC, Nagelkerke R2 and p value for each morbidity (anxiety, depression and post-traumatic stress) separately. Displayed in order of the obtained AUC for any morbidity*

Supplementary material

REMARK Checklist

STROBE Checklist

Tables

Table 1 *Prospectively chosen parameters chosen for inclusion, subdivided into data obtained prospectively from clinical records, and data obtained from questionnaire sent one month after diagnosis*

	All recruits		Respondents to questionnaire sent one month after diagnosis	
Variable	All (737)	Missings	All (492)	Missings
Data from clinical records				
Final diagnosis				
Miscarriage	537 (73%)	0 (0%)	366 (74%)	0 (0%)
Ectopic	116 (16%)	0 (0%)	75 (15%)	0 (0%)
Resolved PUL	84 (11%)	0 (0%)	51 (10%)	0 (0%)
Age (in years)	34 (5)	0 (0%)	35 (5)	0 (0%)
IVF this pregnancy	50 (7%)	0 (0%)	38 (8%)	0 (0%)
Gestation at diagnosis	65.4 (20.0)	130 (18%)	66.3 (19.5)	84 (17%)
Nights admission	0.3 (0.7)	12 (2%)	0.3 (0.7)	2 (0.4%)
Nights admission (yes vs. no)	163 (22%)	12 (2%)	100 (20%)	2 (0.4%)
Days from first scan to diagnosis	5.0 (7.7)	13 (2%)	5.1 (7.4)	6 (1%)
Final management				
Medical management	73 (10%)	12 (2%)	45 (9%)	2 (0.4%)
Surgical management	408 (56%)	12 (2%)	291 (59%)	2 (0.4%)
No treatment needed	244 (34%)	12 (2%)	154 (31%)	2 (0.4%)
Fetal heart (misc only)				
Yes	126 (23%)	4 (1%)	84 (23%)	3 (1%)
No	407 (76%)	4 (1%)	279 (77%)	3 (1%)
Data from first questionnaire				
Highest level of education				
No formal qualifications	6 (1%)	233 (32%)	6 (1%)	0 (0%)
GCSEs (or equivalent)	41 (8%)	233(32%)	41 (8%)	0 (0%)
A Levels (or equivalent)	52 (10%)	233(32%)	50 (10%)	0 (0%)
Uni degree/prof. qualif.	278 (55%)	233(32%)	271 (55%)	0 (0%)
Post graduate/PhD	127 (25%)	233 (32%)	124 (25%)	0 (0%)
Time taken to conceive				
Not planned	110 (22%)	240 (33%)	110 (22%)	0 (0%)
≤1 year	305 (61%)	240 (33%)	301 (61%)	0 (0%)
>1 year	82 (16%)	240 (33%)	81 (16%)	0 (0%)
Psych disorder				
Currently	21 (4%)	236 (32%)	20 (4%)	3 (1%)
In the past	86 (17%)	236 (32%)	83 (17%)	3 (1%)
No	394 (79%)	236 (32%)	386 (79%)	3 (1%)
Any previous pregnancy loss	264 (46%)	162 (22%)	182 (37%)	0 (0%)
Any previous termination	161 (23%)	25 (3%)	121 (25%)	0 (0%)
Any previous children	316 (44%)	24 (3%)	203 (41%)	0 (0%)
Ethnicity				
Asian	50	233 (32%)	48	0 (0%)
Black	53	233 (32%)	51	0 (0%)
Other	53	233 (32%)	52	0 (0%)
White British	187	233 (32%)	185	0 (0%)
White Other	161	233 (32%)	156	0 (0%)

Abbreviations: HADS – Hospital Anxiety and Depression Score; IVF – in vitro fertilization; PDS – posttraumatic stress diagnostic scale; PUL – pregnancy of unknown location

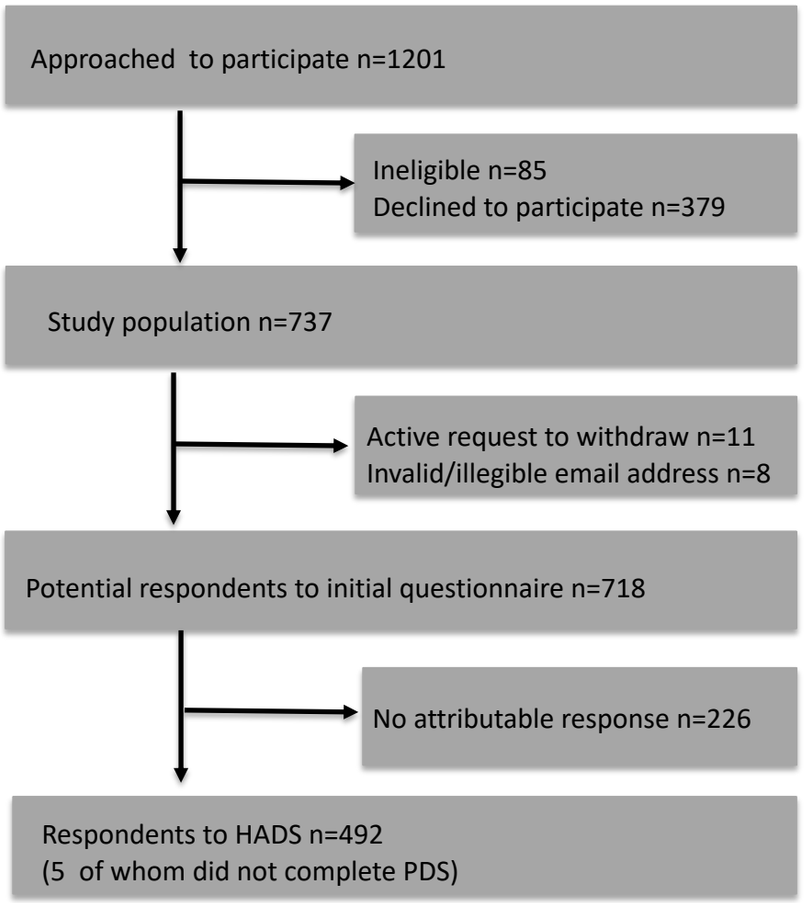
Table 2 *AUC, Nagelkerke R2 and p value in the prediction of any morbidity (anxiety, depression or post-traumatic stress) for each potential prognostic factor, displayed in order of decreasing AUC*

Predictor	AUC (95% CI)	R2	p value
Psychiatric disorder (no, in past, currently)	0.61 (0.55;0.66)	0.084	<0.0001
Any previous pregnancy loss (no=0;yes=1)	0.59 (0.54;0.64)	0.043	<0.0001
Ethnicity (White British/White other/Black/Asian/ Other)	0.57 (0.52;0.63)	0.024	0.07
Time to conceive (unknown/<1year/>1 year)	0.56 (0.51 0.61)	0.022	0.02
Final diagnosis (miscarriage, ectopic, other)	0.54 (0.48;0.59)	0.009	0.19
Final management (surgical, medical, conservative)	0.54 (0.49;0.59)	0.008	0.23
Fetal Heart (no=0; yes=1) (Miscarriage only)	0.53 (0.47;0.59)	0.008	0.34
Age (in years)	0.53 (0.47;0.58)	0.001	0.53
Educational attainment (none; GCSE; A-level; University; Post-graduate degree)	0.52 (0.47; 0.57)	0.003	0.89
Overnight admission (no=0;yes=1)	0.52 (0.47;0.57)	0.003	0.29
Previous termination (no=0;yes=1)	0.52 (0.47;0.57)	0.002	0.37
Previous children (no=0;yes=1)	0.52 (0.47;0.57)	0.002	0.39
Days to diagnosis from first scan (days)	0.51 (0.46; 0.57)	0.000	0.95
IVF (no=0;yes=1)	0.50 (0.45;0.56)	0.000	0.70
Gestational age (days)	0.50 (0.44;0.56)	0.000	0.89

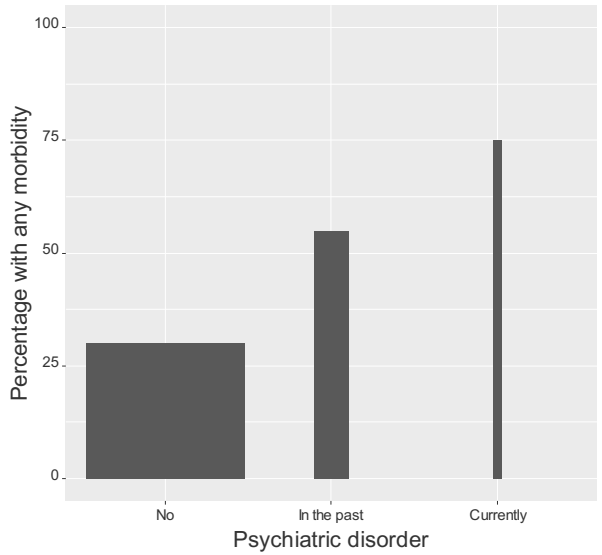
Abbreviations: AUC – Area Under Curve, CI – Confidence Interval

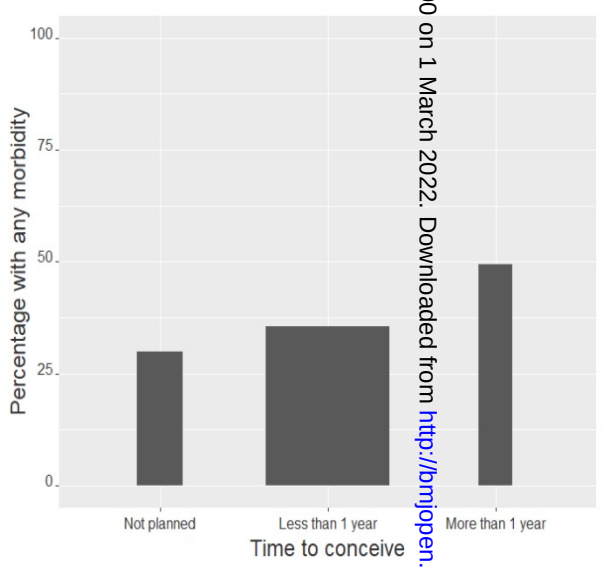
Table 3 *Descriptive statistics for the most important variables*

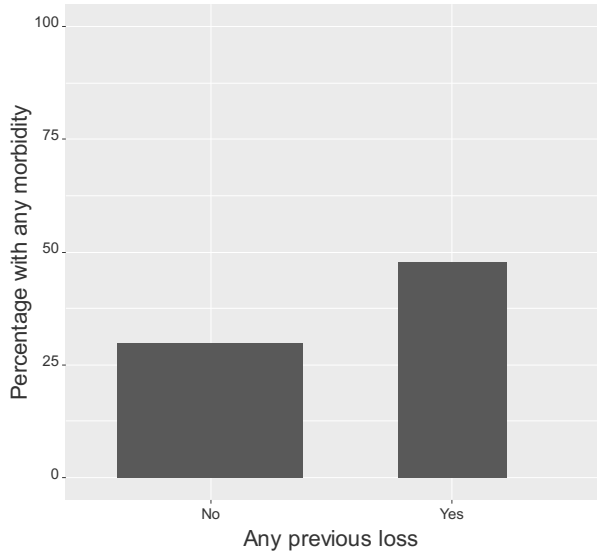
	Anxiety (%) (N=492)	Depression (%) (N=492)	PTS (%) (N=487)	Any (%) (N=487)
Psych Disorder				
No	76/386 (20%)	28/386 (7%)	86/382 (23%)	115/382 (30%)
Yes, in the past	29/83 (35%)	20/83 (24%)	39/82 (48%)	45/82 (55%)
Yes, currently	12/20 (60%)	4/20 (20%)	11/20 (55%)	15/20 (75%)
Missing	2/3 (67%)	1/3 (33%)	3/3 (100%)	3/3 (100%)
Any previous loss				
No	59/310 (19%)	20/310 (6%)	73/307 (24%)	92/307 (30%)
Yes	60/182 (33%)	33/182 (18%)	66/180 (37%)	86/180 (48%)
Ethnicity				
Asian	14/48 (29%)	5/48 (10%)	12/48 (25%)	17/48 (35%)
Black	15/51 (29%)	7/51 (14%)	13/50 (26%)	17/50 (34%)
Other	18/52 (35%)	14/52 (27%)	20/51 (39%)	26/51 (51%)
White British	49/185 (26%)	17/185 (9%)	56/182 (31%)	72/182 (40%)
White Other	23/156 (15%)	10/156 (6%)	38/156 (24%)	46/156 (29%)
Time to conceive				
Unknown/unplanned	20/110 (18%)	9/110 (8%)	24/110 (22%)	33/110 (30%)
>1 year	76/301 (25%)	30/301 (10%)	79/296 (27%)	105/296 (35%)
> 1 year	23/81 (28%)	14/81 (17%)	36/81 (44%)	40/81 (49%)

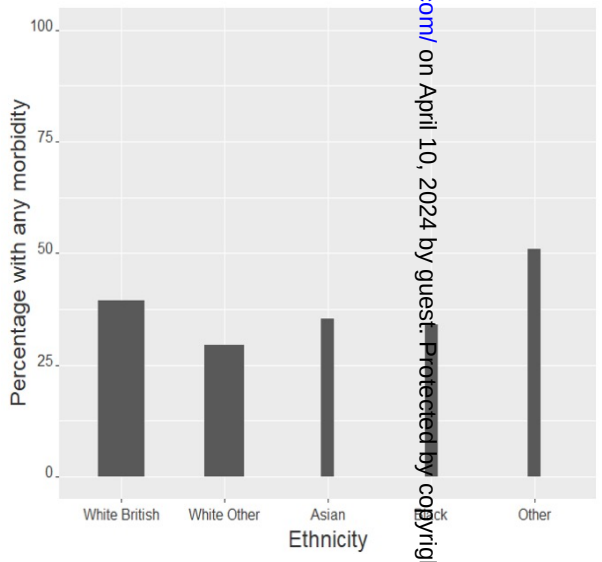


Abbreviations: HADS: Hospital Anxiety and Depression Scale, PDS: Post-traumatic Diagnostic Scale









Supplementary Data

Supplementary Table 1: *Table of predictor variables chosen, the method of data collection, the subgroups at measurement and the subgroups at analysis*

Potential predictor	Source of data	Subgroups when measured	Subgroups when analysed
Final diagnosis	Clinical records	Miscarriage (including molar)/ Ectopic pregnancy/ Resolved PUL	Miscarriage (including molar)/ Ectopic pregnancy/ Resolved PUL
Age (in years)	Clinical records *Date of birth to date of diagnosis*	Continuous	Continuous
IVF this pregnancy	Clinical records	Yes/No	Yes/No
Gestation at diagnosis	Clinical records *Date of LMP (if known) or embryo transfer to date of diagnosis**	Continuous/ Unknown	Continuous/ Unknown
Nights admission	Clinical records	Continuous	Continuous
Days from first scan to diagnosis	Clinical records *Date of first scan to date of diagnosis**	Continuous	Continuous
Final management	Clinical records *If more than one management, final management used*	Conservative/ Medical management of miscarriage/ Medical management of ectopic or PPUL with methotrexate Surgical management of miscarriage/ Salpingectomy for ectopic/ Salpingostomy for ectopic/ Other surgical management for ectopic	Conservative/ Medical management of miscarriage or ectopic/ Surgical management of miscarriage or ectopic
Fetal heart (miscarriage only)	Clinical records	Yes/ Yes with concerns/ No	Yes/No
Highest level of education	Questionnaire	No formal qualifications/ GCSEs(or equivalent)/ A-levels (or equivalent)/ University degree or professional qualification/ Post-graduate or PhD	No formal qualifications/ GCSEs(or equivalent)/ A-levels (or equivalent)/ University degree or professional qualification/ Post-graduate or PhD
Time taken to conceive	Questionnaire	Not planned/ 1-3 months/ 3-6 months/ 6-12 months/ 13-18 months/	Not planned/ <=1 year/ >1year

		19-24 months/ more than 2 years	
Psychiatric disorder	Questionnaire	Currently/ In the past/ No	Currently/ In the past/ No
Any previous pregnancy loss	Questionnaire	Types and numbers of losses previously encountered (stillbirth, miscarriage, ectopic, termination for fetal anomaly, PUL)	Yes/No
Any previous termination	Questionnaire	Yes/No	Yes/No
Any live children	Questionnaire	Yes – one/ Yes – two/ Yes- three/ Yes – four or more/ No	Yes/No
Ethnicity	Questionnaire	White British/ White Other/ South East Asian/ South Asian/ Asian Other/ Arab/ Black African/ Black Caribbean/ Black other/ Mixed	Asian/ Black/ Other/ White British/ White other

* Date of diagnosis as non-viable pregnancy: i.e. if diagnosed as molar on later histological diagnosis, date of scan confirming non-viability

Abbreviations: IVF – in vitro fertilisation

Supplementary Table 2 *AUC, Nagelkerke R2 and p value for each morbidity (anxiety, depression and post-traumatic stress) separately. Displayed in order of strength of the obtained AUC for any morbidity.*

Predictor	Anxiety			Depression			PTS		
	AUC	R2	P value	AUC	R2	P value	AUC	R2	P value
Psychiatric disorder (Ref = no)	0.60 (0.54;0.65)	0.062	<0.0001	0.64 (0.56;0.72)	0.077	<0.0001	0.61 (0.55;0.66)	0.076	<0.0001
Any previous losses (no=0;yes=1)	0.59 (0.53;0.65)	0.036	0.0006	0.64 (0.56;0.72)	0.063	<0.0001	0.57 (0.52;0.63)	0.027	0.0026
Ethnicity (5 categories)	0.60 (0.54;0.66)	0.039	0.01	0.64 (0.56;0.71)	0.061	0.005	0.56 (0.50;0.61)	0.015	0.29
Time to conceive (3 categories)	0.55 (0.49;0.60)	0.010	0.20	0.57 (0.49;0.65)	0.017	0.13	0.58 (0.52;0.64)	0.036	0.0021
Final diagnosis (miscarriage, ectopic, other)	0.53 (0.47;0.58)	0.004	0.54	0.56 (0.48;0.64)	0.016	0.15	0.53 (0.47;0.58)	0.005	0.42
Final management (surgical, medical, conservative)	0.51 (0.45;0.57)	0.001	0.90	0.56 (0.48;0.64)	0.012	0.24	0.55 (0.49;0.60)	0.011	0.15
Fetal Heart (no=0; yes=1) (Miscarriage only)	0.52 (0.45;0.59)	0.002	0.76	0.55 (0.46;0.64)	0.010	0.37	0.53 (0.46;0.59)	0.007	0.40
Age (in years)	0.50 (0.44;0.56)	0.000	0.89	0.55 (0.46;0.63)	0.005	0.26	0.52 (0.46;0.58)	0.000	0.78
Education (5 categories)	0.54 (0.48;0.60)	0.013	0.39	0.55 (0.47;0.63)	0.033	0.09	0.53 (0.47;0.58)	0.004	0.85
Overnight admission (no=0;yes=1)	0.54 (0.48;0.60)	0.011	0.06	0.52 (0.44;0.60)	0.002	0.5	0.52 (0.46;0.57)	0.002	0.39
Previous termination (no=0;yes=1)	0.54 (0.48;0.60)	0.008	0.11	0.56 (0.48;0.64)	0.015	0.05	0.53 (0.47;0.59)	0.005	0.19
Previous children (no=0;yes=1)	0.51 (0.45;0.57)	0.000	0.68	0.52 (0.44;0.60)	0.002	0.53	0.54 (0.49;0.60)	0.009	0.09
Days to diagnosis (days)	0.50 (0.44;0.56)	0.001	0.67	0.54 (0.46;0.62)	0.001	0.57	0.50 (0.45;0.56)	0.001	0.56
IVF pregnancy (no=0;yes=1)	0.51 (0.45;0.57)	0.002	0.37	0.52 (0.44;0.60)	0.004	0.33	0.52 (0.46;0.57)	0.004	0.25
Gestational age (days)	0.53 (0.47;0.60)	0.005	0.25	0.54 (0.45;0.63)	0.005	0.31	0.51 (0.44;0.57)	0.000	0.91

Abbreviations: IVF – in vitro fertilisation

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Table 1, p8, supp table 1
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

The REMARK checklist

	Item to be reported	Page no.
INTRODUCTION		
1	State the marker examined, the study objectives, and any pre-specified hypotheses.	Into, Page 6
MATERIALS AND METHODS		
Patients		
2	Describe the characteristics (e.g., disease stage or co-morbidities) of the study patients, including their source and inclusion and exclusion criteria.	Table 1&2
3	Describe treatments received and how chosen (e.g., randomized or rule-based).	Not applicable
Specimen characteristics		
4	Describe type of biological material used (including control samples) and methods of preservation and storage.	Not applicable
Assay methods		
5	Specify the assay method used and provide (or reference) a detailed protocol, including specific reagents or kits used, quality control procedures, reproducibility assessments, quantitation methods, and scoring and reporting protocols. Specify whether and how assays were performed blinded to the study endpoint.	Not applicable
Study design		
6	State the method of case selection, including whether prospective or retrospective and whether stratification or matching (e.g., by stage of disease or age) was used. Specify the time period from which cases were taken, the end of the follow-up period, and the median follow-up time.	Methods – p6
7	Precisely define all clinical endpoints examined.	Methods – p8
8	List all candidate variables initially examined or considered for inclusion in models.	Sup Table 1
9	Give rationale for sample size; if the study was designed to detect a specified effect size, give the target power and effect size.	Methods – p6
Statistical analysis methods		
10	Specify all statistical methods, including details of any variable selection procedures and other model-building issues, how model assumptions were verified, and how missing data were handled.	Methods – p8
11	Clarify how marker values were handled in the analyses; if relevant, describe methods used for cutpoint determination.	Sup Table 1
RESULTS		
Data		
12	Describe the flow of patients through the study, including the number of patients included in each stage of the analysis (a diagram may be helpful) and reasons for dropout. Specifically, both overall and for each subgroup extensively examined report the numbers of patients and the number of events.	Figure 1
13	Report distributions of basic demographic characteristics (at least age and sex), standard (disease-specific) prognostic variables, and tumor marker, including numbers of missing values.	Table 2
Analysis and presentation		
14	Show the relation of the marker to standard prognostic variables.	Not applicable
15	Present univariable analyses showing the relation between the marker and outcome, with the estimated effect (e.g., hazard ratio and survival probability). Preferably provide similar analyses for all other variables being analyzed. For the effect of a tumor marker on a time-to-event outcome, a Kaplan-Meier plot is recommended.	Table 3
16	For key multivariable analyses, report estimated effects (e.g., hazard ratio) with confidence intervals for the marker and, at least for the final model, all other variables in the model.	Not applicable
17	Among reported results, provide estimated effects with confidence intervals from an analysis in which the marker and standard prognostic variables are included, regardless of their statistical significance.	Table 2
18	If done, report results of further investigations, such as checking assumptions, sensitivity analyses, and internal validation.	Not applicable

Source: McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM: Reporting recommendations for tumor marker prognostic studies (REMARK). *J Natl Cancer Inst* 2005; 97: 1180-1184.

The REMARK checklist

DISCUSSION		
19	Interpret the results in the context of the pre-specified hypotheses and other relevant studies; include a discussion of limitations of the study.	Discussion – p11-12
20	Discuss implications for future research and clinical value.	Discussion – p12

Source: McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM: Reporting recommendations for tumor marker prognostic studies (REMARK). *J Natl Cancer Inst* 2005; 97: 1180-1184.