Imperial College London

"The psychological impact of early pregnancy events: its extent and determinants"

A thesis presented for the degree of PhD

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Abstract

Early pregnancy losses (EPLs) are ubiquitous, and a major part of healthcare provision in both primary and secondary care. However, their potential to precipitate psychological sequelae is not routinely acknowledged as part of the narrative of clinical care.

This thesis summarises historical evidence that consistently demonstrates an association with anxiety, depression and posttraumatic stress disorder (PTSD). That such evidence has not significantly changed practice to date may reflect the small size of the studies, their methodological limitations, and their publication in lower impact journals targeted at a diverse range of specialists (psychologists, gynaecologists and GPs). There is a clear gap in the literature regarding the impact on women with ectopic pregnancy, and evidence needs updating to reflect modern society and clinical practice.

Novel research, performed for the purposes of this PhD, involving web-based screening questionnaires, confirms a significant association with anxiety, depression and PTSD in a large group of women following EPL. The adjusted odds ratio of meeting criteria for anxiety and depression one month after loss compared to women in a healthy pregnancy was 2.14 and 3.88 respectively. Of particular note is the very high proportion of women with symptoms suggestive of PTSD (29% at 1 month, 21% at 3 months, and 18% at 9 months). Partners demonstrate significantly lower prevalence of all three disorders. Novel research also suggests that psychological morbidity in women after EPL cannot reliably be predicted by pre-existing or pregnancy-related factors, though appears more likely in women with a history of previous losses or psychiatric illness.

In conclusion, in view of the potential for EPL to precipitate severe psychological sequelae, known to be associated with huge personal and societal costs, an urgent priority must be to increase awareness and recognition of these conditions, and to facilitate prompt and efficiacious treatment.

Declaration of originality

I confirm that this represents my own work, conducted as a postgraduate PhD student at Imperial College London. All sources have been appropriately acknowledged and cited.

I have performed an extensive, systematic literature review on the subject, which I have published in Human Reproduction Update. In order to perform the research in question, I adapted a protocol that had previously been designed, submitted, and approved, and received approval for these amendments. Prior to my registration for this PhD, I performed a pilot study, which, during my registration, I wrote up and published. Once registered, over a period of two years, I managed recruitment of over 1000 women and partners attending three central London early pregnancy units to a study assessing the psychological impact of early pregnancy loss. I sent e-mail links to surveys, involving standardised psychometric instruments for depression, anxiety and post-traumatic stress disorder, at pre-determined time intervals. I compiled and cleaned the data from these surveys. I had extensive meetings and telephone discussions with a team of statisticians in Leuven, Belgium, who helped to determine the most appropriate statistical methods, and conducted complex modelling of the trajectory of mental health over time.

Copyright declaration

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Dedication

This work is dedicated to my daughter, Esme, born in the midst of writing and publishing.

Thesis-Related Publications and Presentations

Journal Publications

Farren J, Jalmbrant M, Ameye L*, et al*; Post-traumatic stress, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study, *BMJ Open* 2016;**6:**e011864. doi: 10.1136/bmjopen-2016-011864

Farren J, Mitchell-Jones N, Verbakel JY, Timmerman D, Jalmbrant M, Bourne T; The psychological impact of early pregnancy loss, *Human Reproduction Update*, dmy025, https://doi.org/10.1093/humupd/dmy025

Conference presentations

June 2016: RCOG International Congress: "A prospective, cohort study of post-traumatic stress disorder, anxiety and depression following early pregnancy loss"

Invited talks

November 2017: RCOG Annual Professional Development Conference, RCOG London; "The psychological impact of miscarriage and ectopic pregnancy on women and their partners"

November 2016: Association of Early Pregnancy Units Annual Scientific Meeting, Cardiff City Hall; "Psychological Outcomes following Early Pregnancy Events"

June 2016: Pre-congress Workshop, RCOG World Congress, Birmingham; "Managing expectations, breaking bad news and being compassionate - what should we say to women and what is the psychological outcome of early pregnancy loss?"

November 2015: Early Pregnancy and Acute Gynaecology Course, Hammersmith Hospital; "What are the psychological consequences of miscarriage and ectopic pregnancy?"

January 2015: Early pregnancy study day, Northwick Park Hospital – lecture entitled "Miscarriage diagnosis and management: current concepts and challenges"

Media appearances

BBC News, 2nd November 2016

Victoria Derbyshire, BBC 2, 2nd November 2016

Women's Hour, BBC Radio 4, 2nd November 2016

Also featured in multiple national and local newspapers including The Times, The Telegraph and The Sun, as well as in the international press.

Other related contributions

Tommy's Website, June 2017: "Responses after miscarriage or ectopic pregnancy" https://www.tommys.org/our-organisation/about-us/charity-news/responses-after-miscarriage-or-ectopic-pregnancy

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List of abbreviations

ANC Antenatal clinic

AOR Adjusted odds ratio

AUC Area under the curve

ASD Acute stress disorder

BDI Beck Depression Inventory

CES-D Centre for Epidemiologic Studies Depression scale

CI Confidence interval

CW Chelsea and Westminster Hospital

DIS Diagnostic Interview Schedule

DSM Diagnostic and Statistical Manual of Mental Disorders

(DSM IV published 1994, DSM 5 published 2013)

D-S Depression Scale

EMM Expectant management of miscarriage

EP Ectopic pregnancy

EPL Early pregnancy loss (i.e. miscarriage, ectopic, resolved PUL or molar pregnancy)

EPU Early Pregnancy Unit

GHQ General Health Questionnaire (-12: 12 item, -28: 28 item)

HADS Hospital Anxiety and Depression Scale (HADS-A – Anxiety, HADS-D – Depression)

hCG human Chorionic Gonadotrophin

HH Hammersmith Hospital

IES Impact of Events Scale (-R revised)

IQR Interquartile range

IVF *In vitro* fertilization

JF Jessica Farren

LMP Last menstural period

M1 Month 1 questionnaire

M3 Month 3 questionnaire

M9 Month 9 questionnaire

MMM Medical management of miscarriage

NICE National Institute of Clinical Excellence

NMJ Nicola Mitchell-Jones (second researcher for systematic review)

NOAS Newcastle-Ottawa Quality Assessment Scale

NSSQ Norbeck Social Support Questionnaire

OCD Obsessive compulsive disorder

OR Odds ratio

PDS Posttraumatic stress Diagnostic Scale

PHQ-9 Patient Health Questionnaire

PSE Present State Examination

PUL Pregnancy of unknown location

PUV Pregnancy of uncertain viability

PTSD Posttraumatic stress disorder

RCT Randomised controlled trial

RR Relative risk

RRS Rumination Response Scale

SASRQ Stanford Acute Stress Reaction Questionnaire

SCID Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders

SCL-90 Symptom Checklist 90

SCS Self-compassion Scale

SD Standard deviation

SMH St Mary's Hospital

SMM Surgical management of miscarriage

STAI State Trait Anxiety Inventory

ToP Termination of pregnancy

WHO World Health Organization

WHO-CIDI World Mental Health Composite International Diagnostic Interview

A miscarriage is a natural and common event. All told, probably more women have lost a child from this world than haven't. Most don't mention it, and they go on from day to day as if it hadn't happened, so people imagine a woman in this situation never really knew or loved what she had. But ask her sometime: how old would your child be now? And she'll know.

Barbara Kingsolver

Animal Dreams (New York: Harper Collins) 1990

Chapter 1: Introduction

Early pregnancy losses (EPLs) are common, with miscarriage affecting 25% of women who have been pregnant by 39 years of age (1). Ectopic pregnancy occurs at a rate of 11 per 1000 pregnancies (2). They represent a diverse clinical pathology, occurring at variable gestations, with a spectrum of clinical severity and intervention.

EPLs are unique in encompassing both bereavement and a personal clinical pathology. For this reason, an understanding of the emotional implications cannot easily be extrapolated from our understanding of other illness behaviour or grief reactions. It tends to be an event hidden from public view, with most women knowing little about miscarriage until they experience it themselves (3). Medical treatment is frequently perfunctory, reflecting only clinical need, and there is rarely provision for follow-up or support.

Grief and bereavement reactions, to different degrees, and depending on the circumstances of the loss, in response to the loss of a potential child and imminent parenthood, are perhaps inevitable. Some level of anxiety relating to one's future ability to procreate is also an anticipated response. For many, this will be a first encounter with matters beyond their perceived control, threatening their bodily integrity. It may lead to feelings of inadequacy, especially in society that values motherhood.

However, pregnancy losses are also recognized precipitants of longer-term psychological disorder, including anxiety, depression and posttraumatic stress disorder (PTSD). It is clear that these psychological responses are common, and that they occupy a spectrum of severity. However, the bulk of research on the topic published to date, particularly for PTSD, has been from small studies. They have often considered both early and late losses (i.e. stillbirth) together (4), and the emotional response to ectopic pregnancy, which may be different, has been largely uninvestigated.

Given its frequency, EPL may represent a significant contributor to psychological morbidity overall, with high associated societal cost. It is essential, therefore, to identify strategies to reduce it. Counselling in an unselected population has not yet proven effective(5). A better understanding of the type and timing of psychological responses may enable treatment to be more appropriately tailored, with better efficacy. Furthermore, an understanding of who is most at risk of these disorders may enable screening or treatment to be targeted, with improved results.

Partners may also be deeply affected by EPL. Their own emotions may relate to the personal loss, or to concern about the physical or psychological health of their partners, often compounded by a sense of helplessness. Limited research has been done in this field.

This thesis includes extensive literature review, and large-scale, multicentre, novel research. The central aim is to increase our understanding of the frequency and type of psychological morbidity that follows EPL, in both women and their partners. A further aim is to explore whether there are risk factors that may reliably predict those most likely to suffer from psychological illness.

1.1 Overview of early pregnancy loss

1.1.1 Miscarriage and molar pregnancy

Miscarriage is defined as the loss of an intrauterine pregnancy before a gestation at which it is able to survive (generally 23 weeks). The vast majority occur in the first trimester, with incidence estimates of 31% of all (including unrecognized) pregnancies, and 12-24% of recognized pregnancies (6, 7). The risk of miscarriage declines significantly after visualization of fetal heart activity, and with increasing gestation, with a risk of 1% after 16 weeks (8, 9).

The diagnosis of miscarriage is generally based on ultrasound findings, performed either to investigate symptoms (pain or bleeding), for reassurance, or as part of routine screening (currently between 11 and 14 weeks in the UK). Since a failing pregnancy that has arrested development can be indistinguishable from a healthy early pregnancy, a high proportion of initial scans may be inconclusive (termed a pregnancy of uncertain viability (PUV)). This is the case if the size of the fetus (crown-rump length) is less than 7mm, or the mean gestation sac diameter is less than 25mm. These cut-off values have recently been increased to ensure there is an appropriate margin of safety to avoid inadvertent termination of pregnancy (10). This increase will result in more women experiencing periods of diagnostic uncertainty, and may extend the duration of such uncertainty. Minimum repeat scan intervals have recently been clarified as one or two weeks, depending on the initial findings (11).

The physical experience of miscarriage varies widely. Some women will have minimal symptoms and either do not require treatment, or perhaps choose elective surgical management. At the other end of the spectrum will be women, often at a later gestation, experiencing severe pain and bleeding without warning, who may witness the passage of a clearly identifiable fetus. Some women will choose medical management (administering tablets to induce passage of the pregnancy tissue), the experience of which also varies widely.

A molar pregnancy is a complication usually resulting from fertilization of an empty ovum (complete mole), or dispermic fertilization of an ovum resulting in a triploid pregnancy (partial mole). The incidence is 1:714 live births (12). It may be strongly suspected from ultrasound appearances, but is generally confirmed by histological assessment. This has longer term implications, with prolonged follow-up, and advice not to conceive during this time.

1.1.2 Ectopic pregnancy

Ectopic pregnancy (EP) is defined as the development of a pregnancy outside the uterine cavity. The majority are tubal, developing in the fallopian tube, but they may also be cervical (in the cervical canal), scar (in a deficiency from previous uterine surgery), interstitial (between the fallopian tube and intrauterine cavity) or ovarian (within the ovary). They are usually diagnosed on ultrasound performed to investigate bleeding or pain in the first trimester, or incidentally in someone with known risk factors. EPs may resolve spontaneously, but more often require treatment. Overall, they pose higher clinical risk than miscarriage. Laparoscopic salpingectomy (removal of the affected fallopian tube) is the most common management. Some units offer methotrexate (a chemotherapy agent that targets rapidly dividing cells of early pregnancy) to selected cases. This requires rigorous surveillance until resolution. When EPs grow to the degree that they rupture the fallopian tube, presentation may be catastrophic, with life-threatening intra-abdominal haemorrhage. This universally requires immediate surgical management.

EP may commonly be associated with antecedent and future subfertility, due to its association with tubal blockage, and the potential for treatment to require removal of, or leave scarring within, the fallopian tube.

1.1.3 Pregnancy of unknown location

It may not be possible to confirm the location of a pregnancy on ultrasound scan. This is described as a pregnancy of unknown location (PUL) and follow-up with serum hormone levels (usually at 48 hour intervals) and repeat scans usually determines if it is:

1. an early intrauterine pregnancy, currently too small to see. This may be viable, or may ultimately miscarry
2. a pregnancy which has already miscarried, or is miscarrying at a small size without conclusive ultrasound evidence
3. an ectopic pregnancy that has not yet been identified

Often, pregnancy hormone levels decline spontaneously. In these situations, a miscarriage may be the presumed diagnosis, but a resolving ectopic cannot be excluded. These are referred to as a 'resolved PUL': a negative urine pregnancy test after two weeks confirms resolution. On occasion, the hormone level remains elevated but the pregnancy remains elusive on ultrasound scan. These are termed 'persistent PUL' and are usually managed conservatively until the site of the pregnancy becomes evident, or the hormone levels spontaneously decline.

1.2 Potential psychological sequelae

1.2.1 Grief

The grieving process is a 'natural' and expected response to the loss of a loved one. It can be a poorly defined clinical entity. In contrast to the other morbidities we discuss (anxiety, depression, PTSD), it does not have diagnostic criteria listed in the Diagnostic and Statistical Manual (DSM) (13, 14). Instead, listed are symptoms that would suggest reactions in excess of 'normal' grief.

Brier defines grief as "the affective, physiological, and psychological reactions to the loss of an emotionally important figure"(13). Yearning for the lost one has been found to be the most salient feature (15). Reactions also involve sadness and withdrawal, which decrease in intensity over days to weeks (16). Central to the understanding of 'normal' grief is that, while it may be extremely painful and consuming, it is usually self-limiting and it has less and shorter-lasting impact on psychological, social and health status than other psychological morbidity (17).

As the loss of a pregnancy, of a baby, and of motherhood, grief is described as a 'normal' or typical feature following a miscarriage. Beutel reported an incidence of 20% grief reactions, and 20% combined grief and depression(17). Scales of grief following miscarriage have shown similar values to that observed in people who suffer death of a close relative (13, 18). Grief is expected to decline over time, and to resolve within 6 months(13). There is evidence of a worsening of symptoms around the anniversary of the date of a miscarriage, or the estimated due date(19).

Purandare found similar levels of grief intensity after ectopic pregnancy as after miscarriage or molar pregnancy (20). Potvin found similar levels of grief following ectopic pregnancies to stillbirths and neonatal deaths, which have been found to be higher than in early losses (21).

There are, however, complexities in likening EPL to other bereavements. Following a miscarriage, there is no visible and publicly acknowledged child to mourn. There are also no memories or shared life experiences, no standardized rituals to acknowledge the loss, and it is often kept private.

There is considerable overlap between the symptoms of depression and those of grief, meaning one is at risk of both under-diagnosing (i.e. assuming a pathological response to be normal) and over-diagnosing (i.e. assuming a normal response to be pathological) depression in situations of loss. The two may co-exist, and grief may be more likely to be severe and prolonged when it co-exists with depression. Where grief persists, is more destructive or pervasive, or leads to major depressive disorder, it is often referred to as 'complicated' or 'pathological' grief(22, 23).

The possibility of including complicated grief as a separate psychiatric diagnosis is debated (24). In 1999, Prigerson and colleagues proposed a new diagnostic entity called 'traumatic grief' – considered distinct from PTSD or depression (25). Yearning for the lost attachment figure, and feeling stunned, are central components of this reaction. Later work, also by Prigerson, aimed to define 'prolonged grief disorder', again distinct from depression in the dominance of 'yearning' and 'feeling overwhelmed', rather than sadness, and of duration more than six months (26). It was not included in the Diagnostic and Statistical manual of Mental disorders version 5 (DSM-5)(14). It has, however, very recently been included in ICD-11 (released by WHO in June 2018) –with the description that the reaction must clearly exceed "expected social, cultural or religious norms for the individual's culture and context" and cause impairment in functioning.

In view of the absence of both strict diagnostic criteria and screening instruments for grief or traumatic grief, they have not been a focus of this thesis.

1.2.2 Depression

Depression is a condition in which there are symptoms of depressed mood, or loss of interest or pleasure most of the time over a period of at least two weeks, and in which such symptoms cause significant distress or impairment in functioning. Other criteria for major depressive disorder included in DSM-5 include weight loss or gain, insomnia or hypersomnia, feelings of worthlessness, decreased ability to think or concentrate, psychomotor agitation or retardation, and recurrent thoughts of death (14).

As discussed, it is well recognized that exaggerated or pathological grief and bereavement reactions may meet the criteria for major depressive disorder. In DSM-IV, there was a

'bereavement exclusion', which referred to advice to refrain from diagnosing major depressive disorder within two months following the death of a loved one. This was a contentious issue, considering under-diagnosis poses risks to affected individuals, and the illogical implication that bereavement was protective for depression. It was thus removed in DSM-5, and replaced by notes to help differentiate the two. Features that are suggested to exist in grief but not in depression are the preservation of self-esteem, and the intermittent nature of the painful feelings. Suicidal ideation or psychomotor retardation are more likely to indicate depression (27).

Depressive disorders have clear implications for psychosocial functioning and physical health. It has been found to account for 4.4% of total disability adjusted life years, making it the fourth leading cause of disease burden(28). Depressive symptoms may occupy a spectrum of severity before they reach the threshold to diagnose the disorder. Such 'subsyndromal' depression also has important clinical and functional implications, including increased use of health services, and reduced quality of life (29, 30).

The lifetime prevalence of a major depressive disorder in women is 21.3%, which is almost double that in men (12.7%) (31, 32). Traumatic personal life events in the past year have been found to be associated with a odds ratio of 6.4 for major depression (33). Bereavement is specifically recognized as one of the most prominent and consistent risk factors for depression (22).

1.2.3 Anxiety

Symptoms of 'generalized anxiety disorder' include uncontrollable worry, difficulty concentrating and irritability. It can be considered a normal response to the uncertainty and adversity of any medical illness(34). It is often co-morbid with other psychiatric conditions, most notably depression. In order to make a formal diagnosis of an anxiety disorder, there must be evidence of impairment in functioning (14).

According to Kessler's survey in the USA at the turn of the millennium, the 1-year prevalence of general anxiety disorder in community samples it is 3.1% (35). There are clear associations between anxiety and reduced quality of life measures(36).

Anxiety may also be focused on a particular set of worries, or manifest in a particular way (such as obsessive compulsive disorder). Brier's review discusses the fact that symptoms in pregnancy loss populations tend to be focused on related issues, such as the possibility of recurrence, or ones future ability to procreate (37). There may also be a high incidence of somatic complaints – such as fatigue or insomnia (38).

1.2.4 Acute stress disorder, posttraumatic stress disorder and adjustment disorder

Trauma can be considered an intensely distressing or disturbing experience – which can be emotional or physical. Research suggests that pregnancy loss is appropriately conceptualised as a 'traumatic stressor'(39). Emotionally, grief and uncertainty may prevail. Physically, trauma may result from considerable physical pain, loss of blood and tissue, emergency hospitalization or surgery.

In a large study involving 1581 women, Hamama and colleagues found that 32.6% of women who had experienced either an elective or spontaneous miscarriage appraised this event as "having been their worst or second worst" exposure to trauma in their lifetime (40). A further 13.9% appraised the elective or spontaneous miscarriage as having been "a hard time" and potentially traumatic.

Key to traumatic reactions are re-experiencing (or intrusion), avoidance and hyperarousal symptoms, and low mood. It is important to distinguish between initial trauma and its immediate response, and more long-term effects, but to recognize that they are closely interrelated.

<u>Acute stress disorder</u>

Acute stress disorder (ASD) refers to a stress reaction in the first month following the traumatic event. The diagnostic criteria are broadly similar to those of posttraumatic stress disorder (PTSD). ASD can be diagnosed from 3 days to one month after the event (PTSD requires at least 1 month). Minimum thresholds for diagnosis require symptoms to be reported from any symptom cluster (intrusion, negative mood, avoidance, arousal and dissociative symptoms), not all clusters (as for PTSD).

A diagnosis of ASD is strongly predictive for development of PTSD, including following miscarriage(41).

<u>Posttraumatic stress disorder</u>

PTSD is a type of anxiety disorder precipitated by a traumatic event, representing failed recovery. Such events challenge the person's existing knowledge of the world, and shatter their sense of control and predictability (42). There is a perceived ongoing threat, and this is interpreted to have widespread negative implications for the future.

Cognitive models suggested to explain the development of PTSD suggest a negative appraisal during and following an event, resulting in a fragmented and poorly integrated memory, which can be triggered by a wide range of cues, without a sense of it being in the past. This leads to a sense of current threat(43). Compounding these symptoms is their interpretation (e.g. 'I'm

going mad', or 'I should have got over this'). Challenging them, and recovery, may be prevented by thought suppression and avoidance strategies.

Diagnosis requires a number of criteria to be met. American criteria for diagnosis have recently changed in DSM-5 (14). These were updated from DSM-IV, which was published in 1994 with a text revision in 2004. The less frequently used WHO ICD-11 criteria, updated in June 2018, have not changed. Evidence suggests that DSM-IV symptoms can be used to closely approximate DSM-5 diagnoses(44). Among DSM-5 changes is the removal of a criterion stipulating the need for 'helplessness, fear or horror' as part of the initial response (as it has been shown to have no value in prediction of PTSD).

The first criterion involves a history of exposure to real or threatened death or serious injury to self, or directly witnessed. It can also include learning about the death or serious injury of a loved one – but now only if accidental or violent (and not from natural causes – as was included in DSM-IV). DSM-5 specifies that medical incidents may quality if they involve 'sudden, catastrophic events'. Those early pregnancy losses that result in emergency admission to hospital, surgery or blood transfusion may clearly fulfill this. In less acute situations, the interpretation of whether they fulfill the criterion of vicarious trauma by observing death or serious injury is subjective. Some women and couples start relating to their embryo as a child early in the pregnancy, and for them a loss may be equated with death of an infant. Indeed, in a recent survey study, 37% of those with miscarriage reported feeling like they had lost a child (45).

There are then criteria involving symptom clusters, each of which must be endorsed: intrusion or re-experiencing symptoms (such as nightmares or flashbacks), avoidance symptoms (of reminders of the event, or estrangement from others), arousal symptoms (e.g. sleeping problems, reckless or self-destructive behaviour) and, an addition in the new criteria, negative alterations in mood (which includes self-blame).

The duration of symptoms must be over one month, and cause impairment in social or occupational functioning. If the symptoms persist for more than three months, they are regarded as 'chronic'.

Again, many features overlap with other psychiatric conditions. At the heart of a diagnosis of PTSD are the involuntary re-experiences – which contrasts to the more 'ruminative' thoughts in depression(27).

The national co-morbidity survey estimated the 12-month prevalence of PTSD according to DSM-IV to be 3.5% (SE 0.3) (35)

PTSD is associated with significant morbidity, with increased utilization of medical resources (46) and social and occupational impairment. It is frequently co-morbid (80% cases) with other psychiatric conditions, and is associated with enhanced suicide risk (14). There is also evidence that sub-threshold symptoms, so-called 'partial PTSD', have implications: one study found no difference in terms of social functioning, work functioning, or suicide attempt, in those meeting criteria for full, as compared to partial, PTSD (47).

Adjustment disorder

Adjustment disorder can be considered a differential to PTSD or ASD. The stressor need not meet the criteria specified for a diagnosis of the other two disorders (14). The term is also used when the stressor meets criteria, but the response does not. It must occur within three months of the event (but not continue for more than six months after its termination), and the reaction must be 'clinically significant', i.e. either out of proportion to the stressor severity, or have a functional impact.

DSM-5 specifically refers to the diagnosis of adjustment disorder in circumstances of death of a loved one, specifying that the symptoms must not be those of 'normal bereavement', and that *"the intensity, quality, or persistence of grief reactions [must] exceed what normally might be expected, when cultural, religious, or age-appropriate norms are taken into account".*

It can be expected to manifest with temporary functional disturbance at work or within relationships. The overlap with normal adaptive stress, and also other psychiatric disorders, may result in low recognition of this disorder (48). There are, however, recognized associations with suicide and self-harm(48).

1.2.5 Relief

It is reasonable to assume that some women will be relieved that a miscarriage has occurred. Spontaneous miscarriage may mean that women do not have to consider a termination, or an unwanted child.

Nordal Broen's study comparing termination and miscarriage provides quantitative data: the miscarriage group had a mean score of 1.3 for relief (using a scoring system where "1 = not at all", "2= a little" and "5 = very much so" on a likert scale) – as compared to 2.8 in the termination group(49). Qualitative research reports those with an unwanted pregnancy may be relieved, but also shocked by the physical trauma (50).

1.2.6 Suicide

At its worst, the feelings of worthlessness or sadness following early pregnancy loss could cause a woman to consider taking her own life. While suicidal ideation is a commonly recognized symptom of depression, and suicide a recognized complication of puerperal psychosis, it has only rarely in the literature been associated with early losses.

A study utilizing the Swedish registry from 1987 to 1994 showed higher rates of suicide in women who had experienced pregnancy loss within the year before suicide (18.1 per 100 000) as compared to the mean annual suicide rate (11.3 per 100 000), and the rate in women who has given birth to a live infant within that year (5.9 per 100 000)(51). The risk of suicide was highest during the two months after the end of the pregnancy.

The UK maternal confidential enquiry, covering 2006-2008, reported that out of 13 indirect deaths from suicide, two occurred in the context of a severe grief reaction following the loss of early pregnancy(52).

Friedman's study of 67 women following miscarriage reported one women cutting her wrists, and two women taking overdoses, during the follow-up period(53). A recent publication assessing suicide attempts in pregnancy showed a significantly increased risk in those with a history of miscarriage (54).

In a letter published in the New England Journal of Medicine in 1994, a team from Israel identified that 6 out of 160 women treated surgically for ectopic pregnancy had attempted suicide within a year (one successfully)(55). None had a past psychiatric history. The authors comment that precipitating factors are *"an insult to self-image, together with the trauma of surgery, and the threat to future reproduction".*

1.3 The impact on partners

It has consistently been found that men suffer from grief and stress reactions, to a level that was reported to be higher than anticipated (56). Men may be traumatised by the loss of the pregnancy, or may be affected by seeing their partners in pain, or in what is perceived to be a life-threatening situation.

However, gender differences are clear. This may be due to underlying differences in physiological or psychological make-up of men and women, or relate to differences in attachment (which could be enhanced with experience of pregnancy). There may be societal pressures for the man not to grieve, or to support the woman(57).

Partners have been found to grieve less intensely and for shorter periods of time (58, 59), except in one study where higher scores on the perinatal grief scale were reported (60).

Other reported reactions include partners feeling burdened by their wives' grief or depressive reactions (59), or feeling inadequate and frustrated by their inability to influence the outcome(56). Support from healthcare professionals may be suboptimal(60). A qualitative study, using the results from nine questionnaires, revealed that men feel marginalized, and that more support should be available (61).

In recent years, same sex couples have sought to achieve pregnancy with gamete donation, assisted reproduction and/or surrogacy. This opens a new group for consideration: these partners may neither carry, nor be genetically related to, the pregnancy. Wojnar discusses that, for lesbian women, the emotions are likely to be particularly hard to navigate in the context of already 'marginalised maternal roles', with society questioning their entitlement to motherhood(62).

Pregnancy losses may affect a couple's relationship. A study has shown the risk of marriage dissolution hazard ratio to be 1.22 (95% CI 1.08-1.38) following miscarriage (mostly occurring 1.5 to 3 years later)(63). The stress on the relationship is likely to be more significant where reactions are incongruous or conflicting(59).

1.4 Psychological symptoms in future pregnancies

After one EPL, women would be expected to have heightened awareness of the possibility of further losses, which may affect their desire to conceive. Engelhard explains that miscarriage "*challenges a sense of safety and control and trust in procreative ability*"(4). Friedman and Gath published evidence that 18% women feared further miscarriage and as a result were uncertain as to whether they would try again(53). In one study, it was hypothesized that a delayed increase in anxiety was secondary to resumption of menses, and thus efforts to conceive(64).

A majority of couples do conceive again: in one study, 86% were pregnant again within 1 year (65). Bergner showed a higher incidence of pregnancy-specific anxieties in the first trimester of a subsequent pregnancy, especially if prior recurrent loss(66). Data from the Australian Longitudinal Study on Women's Health showed higher sadness and low mood (OR 1.75 (95% CI 1.11-2.76)) and excessive worry (OR 2.01 (95% CI 1.24-3.24)) during a subsequent pregnancy in women with a history of any pregnancy loss (67).

Engelhard found 3% late onset PTSD in subsequent pregnancy (68). Forray published data on pregnant women visiting a maternal-fetal medicine referral clinic (69). 12.5% of women who had experienced previous complications (73.5% of which were miscarriage, 5.9% ectopic) met criteria for PTSD, compared with 0% in the comparison group. In the context of losses >18 weeks, Turton found an incidence of PTSD of 21% in the third trimester of a subsequent pregnancy, but resolution by one year post-partum. They found a significant association with conception occurring soon after a loss, which led them to suggest consideration of delay to subsequent conception (70). Another study including women with both elective and spontaneous abortion found incidences in a subsequent pregnancy of 12.6% PTSD, and 16.8% depression (40).

Some studies have looked at a possible therapeutic effect of a successful pregnancy. In one study, those who were pregnant by time of follow-up displayed significant decrease in grief as compared to those who had not conceived(65). They estimated that a subsequent pregnancy is equivalent to 8 months passage of time in terms of improvement of grief symptoms.

1.5 Impact on future pregnancies

While there is a reasonable understanding of how psychiatric diagnoses (depression, anxiety PTSD) impact quality of life and productivity, the potential impact on future pregnancies and pre-existing or future children is particularly important in this group. This is the route by which these events and their reactions may have a persisting impact through generations.

1.5.1 Impact on future early pregnancy outcome

One small study in women with two previous miscarriages showed that higher depression scores were significantly associated with risk of subsequent miscarriage (71). However, a larger study in the recurrent miscarriage population contradicted this(72). A large study in a low risk population, looking at both depression and optimism scores, also did not find such an association(73).

One study assessed incidence of pregnancy complications in women with PTSD, using data collected from coding for insurance claims(74). After correcting for demographic and psychosocial factors, they reported a higher incidence of ectopic pregnancy (OR 1.7 (95% CI 1.1-2.8)) and spontaneous miscarriage (OR 1.9 (95% CI 1.3-2.9)) in those with PTSD. They hypothesized that high-risk behavior, and a change in 'stress axis function', were to blame. However, the methodology did not allow assessment of causation, and it is likely therefore

that losses (or other complications) themselves contributed to PTSD in at least some women. A recent paper originating from Germany, retrospectively analyzing a large database of more than 100 000 pregnant women, including over 3000 ectopic pregnancies, showed significantly higher risk of ectopic (OR 1.8 (95% CI 1.54 – 2.09)) in those with a previous diagnosis of psychiatric disorder(75). However, this did not control for antecedent delays to conception, which is a possible confounder.

Another study raising the possibility of increased EPL risk after stressful life events was that of Neugebauer, who compared miscarriages subsequently (thereby avoiding recall bias) found to be chromosomally normal to those that were chromosomally abnormal. The odds ratio of reporting one or more negative life events in the months before a miscarriage in those with chromosomally normal miscarriages was 2.6 (95% CI 1.3-5.2)(76). This was unaltered by smoking, alcohol and caffeine exposure.

Studies looking for a relationship between antidepressant use and pregnancy loss have generally been reassuring (77). A recent study found that those exposed to SSRIs during early pregnancy were at a similar increased risk to those that had discontinued them prior to pregnancy(78).

1.5.2 Impact on future late pregnancy outcome

High stress and anxiety levels during pregnancy have been linked to preterm labour and growth restriction (79-82). Other research has shown that women with anxiety and depression have babies with lower Apgar scores at 1 and 5 minutes (83). One proposed physiological mechanism is based on a link between anxiety and uterine artery resistance, thus affecting blood flow to the baby (84). Another involves placental glucocorticoid signaling(85). Other studies have suggested poor health behavior in pregnancy in those with psychological ill-health, though for some the anxiety may result in increased healthcare utilization(86). In a study with a low prevalence of PTSD, there was suggestion of association between PTSD (screened for in antenatal clinics) and low birth weight and preterm birth, and a significant association between minor depressive disorder and low birth weight (87).

Research has also related ‘pregnancy related fear’ caused specifically by prior pregnancy loss with complications during pregnancy and delivery (including an increased rate of operative delivery) – though a significantly older age and less previous children in the miscarriage group may underlie these differences (88).

1.5.3 Impact on the postpartum period

Symptoms that persist into the post-partum period of subsequent pregnancies pose risks to bonding. A study looking at depression in women having their first baby, comparing those with a history of miscarriage to those without, showed an increased risk of depression (OR 1.66 (95% CI 1.03-2.69)) at one month postpartum in the former group (but not during the third trimester, or at 6 or 12 months post-partum) (89). In contrast, the Australian Longitudinal Study did not find any evidence of effect in the postpartum period (67).

Maternal depression during pregnancy has also been linked to ratings of negative affect in offspring (90). Postnatal depression may negatively affect long-term socioemotional and cognitive development of the infant, and cause attachment problems (91).

1.6 Direction of causality

Evidence that psychological ill-health may cause early losses raises a question as to whether pre-loss psychopathology may be a confounder for the relationship between loss and post-loss psychopathology. Studies attempt to control for this by asking about other pre-loss traumatic events, psychiatric diagnoses, or medication – but symptoms may be undiagnosed. Ideally, there would be pre-loss assessment – but this is a labour-intensive study design.

The diagnosis of PTSD after loss is based on that specific trauma– but there is clear evidence that prior PTSD or other psychiatric diagnoses increase risk of this response.

1.7 Initial impact as a predictor of longer-term impact

There is clearly a wide variation in initial response to loss. Some may be immediately responsive, while others behave with numbness and shock immediately, or preoccupation with the clinical aspects (92). If immediate or short-term response is predictive, then it may be possible to screen for longer-term impact.

There is some evidence to support this. Psychological impact has been shown to be more enduring in women who are more distressed immediately following a miscarriage(93-95). This is important as it implies that early screening may be helpful to predict those who are going to have longer or more severe symptoms.

1.8 Conclusions

In this chapter, we have discussed some of the complexities involved in classifying psychiatric morbidity following EPL. There is no diagnosis specific to pregnancy loss, despite the fact that

it is unique in many regards. 'Grief' is poorly defined, whereas depression, anxiety and PTSD have set criteria. 'Subsyndromal' symptoms not meeting specified criteria for the diagnosis of these conditions may also be important.

We have discussed the burdens of anxiety, depression and PTSD not only on wellbeing and quality of life, but also in terms of impairment of functioning, future reproductive health, and healthcare utilization. Given the high frequency of losses, if these are common reactions to early pregnancy loss, this represents a major public health issue, that forms the basis for this thesis.

1.9 Hypotheses

The hypotheses tested in this thesis were:

1. Women have a higher prevalence of moderate and severe anxiety and depression following an early pregnancy loss than in a healthy early pregnancy
2. The prevalence of anxiety and depression declines over time in those who do not experience further losses
3. There is a high incidence of posttraumatic stress in women following a loss, and the prevalence declines over time
4. Women who have experienced an ectopic pregnancy will suffer psychological sequelae
5. Anxiety, depression and posttraumatic stress can be predicted by pre-existing and encounter-related factors
6. Partners suffer from anxiety, depression and posttraumatic stress, but to a lesser degree than women, and with quicker resolution

1.10 Overview of structure

A systematic review of quantitative studies investigating depression, anxiety and PTSD following EPL is presented in Chapter 2. A literature review of risk factors associated with psychological morbidity follows in Chapter 3. Novel research occupies the remainder of the thesis. Methods are discussed in Chapter 4, followed by results from a pilot study of 186 women in Chapter 5. The main study involving 737 women with losses compared to 171 controls is then described: results in women are discussed in chapter 6, followed by validation of the posttraumatic stress diagnostic scale (PDS) in the context of pregnancy loss in chapter 7. Chapter 8 describes an analysis for associated factors. Chapter 9 covers the results from 192 men recruited following early pregnancy loss, compared to their female partners. Finally,

a response to each hypothesis, the suggested direction of future research, and suggestions for practice concludes this thesis.

Chapter 2: The psychological impact of early pregnancy loss: a systematic review

[This systematic review was published under the title "The Psychological Impact of Early Pregnancy Loss" in Human Reproduction Update, September 2018 (Impact factor 11.9)]

2.1 Introduction

Historically, the potential for EPL to cause psychological morbidity has been overlooked. Until the 1990s, few publications discuss this, and thereafter, the focus of many early studies was grief (96). However, as discussed in Chapter 1, grief is not considered a psychiatric diagnosis and is variably defined. Studies were also limited by small or unrepresentative study populations, variable timings of assessment, and qualitative data (97-99).

Research in the field has since multiplied, with sizable studies screening for psychiatric diagnoses (anxiety, depression and PTSD) following pregnancy loss. However, hindering overall interpretation is the diverse nature and timings of assessments, and comparison groups. A decision was therefore taken to perform a systematic review, to comprehensively summarise and compare research performed to date, and enable any gaps in the literature to be identified.

Objectives

The aim of this systematic review was to analyse and synthesize existing literature on the psychological impact of EPLs, answering:

- What is the incidence of depression, anxiety and posttraumatic stress following an ectopic pregnancy or miscarriage?
- What is the intensity and duration of these reactions?

2.2. Methods

2.2.1 Information sources

The following databases were used:

- MEDLINE (Ovid interface, 1948 onwards),
- Embase classic + Embase (Ovid interface, 1947 onwards).
- PsychINFO (Ovid interface, 1806 onwards)

This search was limited to the English language, and last updated on 27 July 2017.

2.2.2 Search Strategy

Studies involving women and partners who had experienced EPL were included in this review.

The outcomes included were anxiety, depression and posttraumatic stress.

Based on this, literature search strategies were developed using medical subject headings (MeSH). The psychological outcomes (anxiety, depression or PTSD) and type of pregnancy loss (miscarriage or ectopic pregnancy) were first expanded with the Boolean operator 'or', then linked together using 'and'.

Details of the search strategies are included in Appendix 1. The reference lists of included studies were scanned to ensure complete literature saturation, and the authors own references were added.

2.2.3 Eligibility criteria

Table 2.1 *Study eligibility criteria for inclusion in systematic review*

Criterion	Features of eligible studies
Study design	Prospective cohort studies
Participants	Studies evaluating outcomes in both women and men following a miscarriage or an ectopic pregnancy. Studies were only included if >=90% participants had experienced loss within first 24 weeks of pregnancy
Setting	There were no restrictions by type of setting
Timing	Studies with follow-up at any time point following a loss, providing timing was specified, and standardized across all participants
Comparators	Studies both with and without a comparison group
Outcomes	Studies using standardized psychometric measures for anxiety, depression and posttraumatic stress Included studies reported the proportion of cases above a defined threshold, or compared scores or caseness to the comparison group Studies focusing solely on grief were excluded
Language	Abstracts in English

2.2.4 Study selection

Titles and abstracts were first screened against the eligibility criteria above by two researchers independently (Jessica Farren (JF) and Nicola Mitchell-Jones (NMJ)). If it was clear that the article was not eligible, it was discarded. In the remainder, criteria were applied after review of the full text. Disagreements were resolved by consensus.

2.2.5 Data Extraction

Data was extracted into prospectively designed spreadsheets (first piloted on five papers, and refined) as follows:

- Study: Authors details, year of publication and country where the study was conducted
- Sample:
    - population (type of loss, gestation, management (if specified))
    - numbers of respondents to first assessment
    - recruitment and drop-out rates
- Outcome assessed: depression (D), anxiety (A), posttraumatic stress disorder (or an alternative measure of trauma) (T)
- Assessment tool used (interview or psychometric screening questionnaire)
- Results (presented according to timing of assessment):
    - proportion of participants reaching pre-defined threshold ('caseness' (C)) for anxiety, depression, PTSD or Acute Stress Disorder (ASD)
    - comparison of measures in EPL group vs comparison group (or women vs partners) – either by absolute scores (S) or caseness (C) (and whether controlling for confounders had taken place)
    - outcomes of grief, or general psychopathology (including "general health questionnaire" results - except where broken down to cover specific pathologies) were not recorded
- Significant changes in results over time
- Associated factors identified (with statistical significance $p<0.05$), and whether these relationships were seen to persist in multivariable analysis

The primary researcher (JF) extracted data, which was then checked by the secondary researcher (NMJ). Disagreements were resolved during research meetings, with the involvement of senior researchers (Maria Jalmbrant & Tom Bourne).

To avoid multiple publication bias, where multiple papers reported on different time points or types of assessment for the same study group, these were combined as a single tabulated row of the systematic review. For example, Neugebauer's group published four eligible studies on the same group of participants. Data from these was combined and presented as one entry.

Two authors were contacted for additional information not included in the original manuscript – one was able to provide the original data for inclusion (100), the other was not (101).

A separate spreadsheet was developed to summarise psychometric instruments used.

2.2.6 Quality Assessment

Quality assessment was performed using the Newcastle-Ottowa Quality Assessment Scale (NOAS) for Cohort Studies (see Appendix 2), by JF and checked by NMJ. Disagreement was resolved by discussion. Where an unexposed cohort was not used, this was documented under the 'comparability' section. Where the comparison group was exposed partners, an assessment was made according to NOAS comparability criteria even though, in theory, this is for a non-exposed cohort. A star for comparability was awarded if cohorts were controlled for (1) parity and (2) any other factor. The requirement for outcome assessment to be blind was omitted given the ubiquitous use of self-report measures, and proportion of non-controlled studies. Follow-up duration of one month, and of >=75% of participants, were awarded stars. Where follow-up was <75%, a star was awarded if there was comparison of former psychological pathology in those who responded and those who did not.

2.3 Results

2.3.1 Study Selection

As shown in the PRISMA diagram (Figure 2,1), 109 articles underwent full-text review.

Figure 2.1 *PRISMA diagram(102)*

(Reproduced from (103), courtesy of Human Reproduction Update, © Oxford University Press 2018)

Database searched	Articles identified
Medline	788
Embase	1632
Psychinfo	138

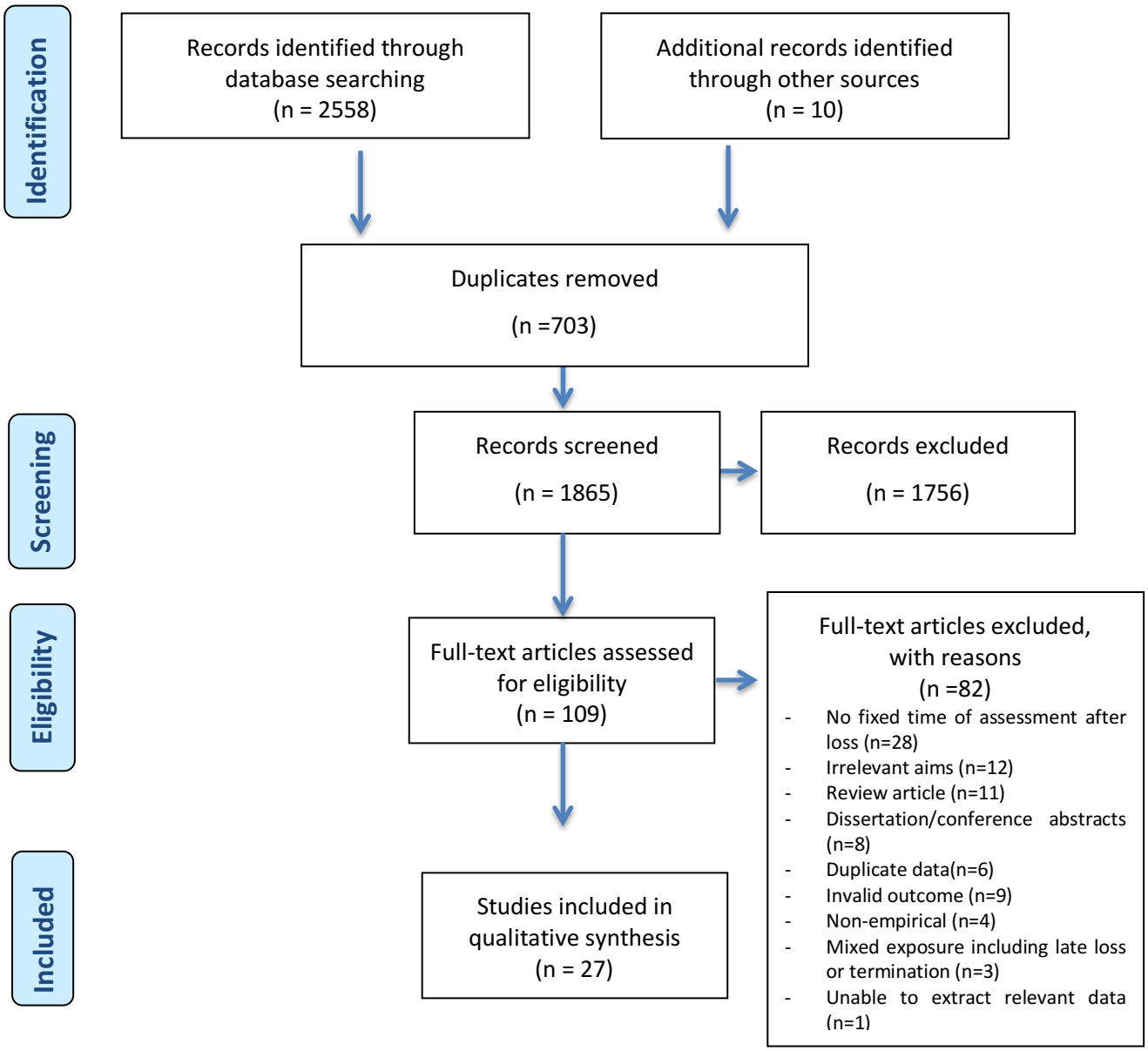


Table 2.2 *Baseline characteristics of studies included in systematic review (studies reporting on the same cohort (with multiple publications for different time points) combined as one entry)*

(reproduced from (103) courtesy of Human Reproduction Update, © Oxford University Press 2018)

First author, Year of publication & Study reference	**Years of recruitment; Country**	**Total N with EPL at first assessment Recruitment**	**Type of EPL & mean gestation** (weeks)	**Proportion with prior pregnancy loss** (%)	**Proportion with children** (%)	**Mean age** (years)	**Management**	**Exclusion criteria** (other than language barrier)	**Unexposed Comparison group**	**Outcome measures relating to anxiety, depression or traumatic impact**	**Total length of follow-up; % completing follow-up** (if >1 assessment)
Beutel 1995 (17)	Not specified; <1995 Germany	125 women Consecutive, from inpatient service	Miscarriage <20w Mean gestation 10.1w	22	42	31	N	-Diagnosis of psychosis	Pregnant women (mean gestations 10.6w) (80) Represenattive community sample (125)	D - D-S A - STAI	12m; 72%
Beutel 1996 (59)	Not specified; <1996 Germany	56 couples Consecutive patients	Miscarriage <500g Mean gestation 10w	18	48	W - 30 P - 33	N	-No stable partnership -Woman unwilling to have partner questioned	Representative community sample (56 women & 56 men(	D - D-S A - STAI	12m; 80%
Bowles 2006 (41)	Not specified; <2006 USA	25 women; From follow-up appointments	Miscarriage	N	N	26	N	N	None	T - SASRQ, PDS	30d; 76%
Cheung 2013 (104)	2008-2010 Hong Kong	150 women (75 Assisted Reproduction (AR) from AR unit, 75 after natural conception (NC) from EPU or gynae ward)	Miscarriage <12w Mean gestation in NC 10.4w Mean gestation in AR 9.6w	NC - 15 AR - 16	0	AR - 37 NC - 31	NC – 44% SMM, 21.3% MMM, 34.7% EMM AR – 12.0% SMM, 73.3% MMM, 14.7% EMM	-Non-Chinese -History of psychiatric illness -Living child(ren) ->=3 previous miscarriages	None	T - IES-R	12w; *9 non-completers excluded*
Prettyman 1993, Cordle 1994 (64, 105)	Not specified; <1993 UK	65 women Consecutive, from inpatient service	Miscarriage <16w 78% <13w	N	N	30	98% SMM	N	None	D&A - HADS	2yr; 77%

Cumming 2007 (100)	Not specified; < 2007 UK	400 women 226 partners Consecutive, from EPU	Miscarriage Mean gestation 9w	W-36 P-41	W-66 P-54	W - 31 P - 33	N	-Demise of one twin, with ongoing singleton pregnancy -Cerebral impediment	None	D&A - HADS	13m; 65%
Daly 1996 (106)	Not specified; <1996 Ireland	25 partners From miscarriage clinic	Miscarriage Mean gestation 11.9w	N	N	P -28	N	N	None	D&A- HADS	Within 6w
Engelhard 2001 (4)	Not specified; <2001 The Netherlands	110 women with miscarriage[a] Advertisements in magazines	Miscarriage <24w[a] Mean gestation 10.8w[a]	30	71	31	N	N	None	D - BDI T - PDS	3m; 89%
Farren 2016 (107)	2012-2013 UK	69 women (53 with miscarriage, 16 with ectopic) Consecutive from EPU	Miscarriage (M) <20w Mean gestation 9.1w Ectopic pregnancy (E) Mean gestation 7.1w	M - 42 E - 31	M - 42 E - 25	M - 33 E - 35	Of M: 45% SMM, 16% MMM, 37% EMM Of E: 88% laparoscopic	-<18 years	Pregnant women - mean 10.3w (30)	D&A - HADS T - PDS	3m; 63%
Friedman 1989 (53)	Not specified; <1989 UK	67 women Consecutive, from inpatient service	Miscarriage 91% 1st trimester	31	57	29	100% SMM	N	None	D - PSE & BDI	4w;
Garel 1996 (108)	1986-1987 France	144 women Consecutive, from inpatient service	Miscarriage 83% <14w	25	23	N	N	-Severe antecedent psychiatric morbidity -IVF pregnancy	None	D - interview based on DSM III	3m; 64% (those pregnant at follow-up excluded)
Janssen 1996 (109)	Not specified; <1996 The Netherlands and Dutch speaking Belgium	227 women Advertisements in magazines	Miscarriage and stillbirth Gestation – 90% <20w	42	67	29	N	N	Women at same intervals after live birth (213)	D&A - SCL-90 (depression and anxiety subscales)	18m; 94%
Johnson 2004 (110)	Not specified; <2004 UK	68 partners Pregnant women asked to pass leaflets to partner	Miscarriage <24w Mean gestation 11.9w	35[b]	59[b]	32[b]	N	N	Men after birth (210)	D - BDI A - STAI	1yr; 100%

Kong 2010 (111)	Not specified; <2010 Hong Kong	83 couples Women from inpatient service, and their male partners	Miscarriage <24w Mean gestation 9.8w	28	31	W - 32 P - N	45% SMM, 40% MMM, 14% EMM	-Follow-up likely to be problematic due to immigration regulations -History of psychiatric illness	None	D - BDI	1yr; 47%
Kulathilaka 2016 (112)	Not specified; <2016 Sri Lanka	118 women From outpatient service	Miscarriage <28w 72% <12w	N	58	30	All complete	N	Pregnant women with no history of miscarriage in past 12m (137)	D - PHQ-9	6-10w
Lee 1997 (113)	1995-1996 Hong Kong	209 women From inpatient service	Miscarriage Mean gestation 10.4w	22	63	31	N	-Non-Chinese women -Those without permanent residency rights in Hong Kong	None	D - SCID for DSM-III & BDI A - SCID for DSM-III	6w; 80%
Lok 2010 (93)	Not specified; <2010 Hong Kong	280 women From inpatient service	Miscarriage <24w Mean gestation 9.7w[b]	25	56	33[b]	N	-History of psychiatric illness	Non-pregnant/ not recently (<12m) pregnant women seeking contraceptive advice (150)	D - BDI	12m; 73%
Neugebauer 1992 (114a)	1984-1986 USA	382 women Attending medical centre	Miscarriage <28w 49% <12w	34	62	29	N	<18 years	Matched group of women registered for antenatal care from another study (283)	D- CES-D	6m; 70%
Neugebauer 1992 (115b)	1984-1986 USA	232 women Attending medical centre and completing assessment at 4 weeks	Miscarriage <28w 63% 1st trimester	36	63	29	N	<18 years	As above - plus non-pregnant/ not recently pregnant (<12m) group from random-digit phoning (318)	D- CES-D	4w
Neugebauer 1997 (116, 117)	1984-1986 USA	229 women Women completing 6m f/u (above) invited to participate in further assessment	Miscarriage <28w 68% 1st trimester	38	60	30	N	<18 years	Non-pregnant group from random-digit telephoning (who had not been pregnant < 12m) (230)	D - Diagnostic Interview Schedule	6m

Nordal Broen 2005, Nordal Broen 2006 (49, 118)	1998-1999 Norway	40 women From gynaecology department	Miscarriage Mean gestation 10.5w	*Mean number of previous miscarriages 0.4*	*Mean number of children 0.8*	30	N	-Mentally disabled -Suffering from serious psychiatric illness -Pregnancy following rape	Women undergoing ToP (80); Women aged 30-35 from general population	D&A - HADS T - IES	2yr; 98%
Sham 2010 (119)	2007-2008 Hong Kong	181 women Consecutive, from inpatient service	Miscarriage <24w Mean gestation 9.4w	30	57	34	72% SMM, 4% MMM, 24% already complete	Non-Hong Kong residents Not ethnically Chinese Serious psychiatric symptoms	None	D - GHQ-12 & SCID if GHQ >=4 (and in 1:10 with scores <4)	3m; 89%
Thapar 1992 (120)	1989 UK	60 women Consecutive, following SMM	Miscarriage 52% first trimester	23	57	45 <25yrs	100% SMM	N	Women registered at antenatal clinic (63)	D&A - HADS & GHQ-28	6-8w; 85%
Walker 2001 (121)	Not specified; <2001 UK	40 women From ultrasound or gynaecology department following scan	Miscarriage <24w 11.1w	8	43	31	100% SMM	N	None	D&A - HADS T - IES	3m; 83%

[a]using data provided by the author, three cases of stillbirth (>=24 weeks) were excluded. Mean age, prior loss and children reflect the whole group

Abbreviations: A – anxiety; AR – assisted reproduction; BDI - Beck Depression Inventory; CES-D - Centre for Epidemiological Study Depression Scale; D – depression; D-S - Depression Scale (Depressivitats-Skala); DIS – Diagnostic Interview Schedule; DSM - Diagnostic and Statistical Manual of Mental Disorders; EMM – expectant management of miscarriage; EPU – early pregnancy unit; GHQ-12/28 – 12 or 28 item general health questionnaire; HADS -Hospital Anxiety and Depression Scale; IES – Impact of Events Scale (-R – research version); IVF – in vitro fetilisation; MMM – medical management of miscarriage; m – months; N – not available; NC – natural conception; PDS – Posttraumatic stress Diagnostic Scale; PHQ-9 – Patient Health Questionnaire; PSE - Present State Examination; SCID - Structured Clinical Assessment for DSM; SMM – surgical management of miscarriage; SASRQ - Stanford Acute Stress Reaction; SCL-90 – Symptom Checklist 90; SCID - Structured Clinical Assessment for DSM; STAI – State Trait Anxiety Inventory; T – traumatic impact; ToP – termination of pregnancy; w – weeks; yr - yea

2.3.2 Study characteristics

Setting

The included studies were published between December 1989 and December 2016. They originated from the UK (seven study groups), Hong Kong (four), Germany (two), the USA (two), the Netherlands (two), Sri Lanka (one), Norway (one), France (one) and Ireland (one). All were published in English except for one study that was published in French (with an English abstract)(122).

Participants

Numbers of participants are shown in Table 2.2. Eight out of 21 study groups had results from less than 100 participants with EPL. The smallest study had 22 participants (106), and the largest 626(100).

Only one study included participants following an ectopic pregnancy(107). Two studies included stillbirth: for one, the authors provided raw data to allow extraction of those with losses <24 weeks (4). In the other, 90% were before 20 weeks)(109). The remaining studies included women with miscarriage alone, with mean gestation in the first trimester.

In three earlier published studies, included participants had almost all undergone a surgical procedure, reflecting a historic trend towards more active management of miscarriage(53, 64, 120). In one recent study, all participants had a complete spontaneous miscarriage (112). In two other recent studies, approximately half of women underwent surgical management (107, 111). Management was not discussed by the remaining 12 study groups.

Twelve out of 24 studies did not utilize a comparison group unaffected by loss, including one that investigated partners alone(106). Of eight studies using a control group that had not been affected by loss, four utilised women in normal early pregnancies (107, 112, 120), one utilised a group of women at equivalent time periods after live birth (109) (and another utilized men after live birth (110), three a group of non-pregnant women (59, 93, 119), and two compared to both non-pregnant and pregnant women (17, 114). One study group compared women following elective termination of pregnancy to those following miscarriage(49).

Two studies recruited pregnant women via advertisements in a magazine(4, 109), while the remainder recruited from an early pregnancy unit or ward. Response rates (in studies where participation was not defined by first response) in women varied between 61% (at one month(107)) and 94% (at one week(64)).

Outcomes

Depression was the most studied outcome, reported by all except two study groups.

Methods of assessment are detailed in Table 2.3. The majority of groups used self-report measures. One group used a structured interview (SCID), and then a self-report measure (the BDI) in those meeting criteria for major depression (113). Another used the SCID in those who met a threshold on the GHQ(119).

Table 2.3 *Methods of psychometric assessment, and cut-offs used to define caseness, in studies included in systematic review*

	Abbreviation	Full name	References using instrument	Details of scoring to ascribe 'caseness'
Self-administered instruments				
Anxiety	STAI	State Trait Anxiety Inventory	(17, 110)	n/a
Depression	BDI	Beck Depression Inventory	(4, 53, 93, 110, 111, 113)	(4, 53): score 15-19 'mild', >20 'moderate' ((4): removed question on weight) (93, 111): score >=12 'probable depressive disorder'
	CES-D	Centre for Epidemiological Study Depression Scale	(114-117)	Score >30 'highly symptomatic'
	D-S	Depression Scale (Depressivitats-Skala)	(17, 59)	n/a
	PHQ-9	Patient Health Questionnaire	(112)	Score >=10 'moderate/severe'
Depression and Anxiety	GHQ-28	General Health Questionnaire - 28 question	(120)	n/a
	HADS	Hospital Anxiety and Depression Scale	(49, 64, 100, 105-107, 120, 121)	Anxiety and Depression, each: Score 15-21 'severe' Score 11-14 'moderate' Score 8-10 'mild' (49): score >=8 (i.e. mild) considered 'case' All others: >=11 (i.e. moderate) considered 'case'
	SCL-90	Symptom Checklist 90	(109)	n/a
Traumatic impact	IES	Impact of Events Scale	(49, 110, 121)	n/a
	IES-R	Impact of Events Scale - Revised	(104)	n/a
PTSD	PDS	Posttraumatic stress Diagnostic Scale	(4, 41, 107)	Helpless or Terrified; at least 1 re-experiencing symptom, 3 avoidance and 2 hyperarousal symptoms; duration>1 month; and evidence of interference (4) score '2 or 3'considered positive (107) score '1, 2 or 3' considered 'positive'
ASD	SASRQ	Stanford Acute Stress Reaction Questionnaire	(41)	At least 3 dissociative symptoms, 1 re-experiencing symptom, 1 avoidance symptom, and 1 marked anxiety/increased arousal symptoms
Clinician-administered assessments				
Any specified disorder	DIS	Diagnostic Interview Schedule	(116, 117)	n/a
	SCID	Structured Clinical Assessment for DSM	(113, 119, 121)	n/a
	PSE	Present State Examination	(53)	n/a
	(not abbreviated)	Assessment using DSM-III criteria for major depressive episode	(108)	n/a

Abbreviations: ASD -Acute Stress Disorder; BDI - Beck Depression Inventory; CES-D - Centre for Epidemiological Study Depression Scale; D-S - Depression Scale (Depressivitats-Skala); DIS – Diagnostic Interview Schedule; DSM - Diagnostic and Statistical Manual of Mental Disorders; GHQ-28 – 28 item general health questionnaire; HADS -Hospital Anxiety and Depression Scale; IES – Impact of Events Scale (-R – research version); n/a – not applicable; PDS – Posttraumatic stress Diagnostic Scale; PTSD – Posttraumatic Stress Disorder; PHQ-9 – Patient Health Questionnaire; PSE - Present State Examination; RR – Relative Risk; SASRQ - Stanford Acute Stress Reaction; SCL-90 – Symptom Checklist 90; SCID - Structured Clinical Assessment for DSM;

Follow-up

Follow-up duration ranged from one month to five years, with only two studies reporting outcomes beyond 18 months. Response rates declined over time. In studies with assessment beyond three months, one excluded women who were pregnant again(108), one enquired about inter-current pregnancies(105), and two assessed for their impact on morbidity (49, 107).

Consideration of meta-analysis

After careful consideration, it was not felt that a meta-analysis would add value to this review. There was significant clinical diversity (see Table 2.2): for example, some studies excluded women with a psychiatric history, and there was wide variation in the presence of existing children (between 0 and 71% of participants). The majority of data was derived from Western Europe and the USA, with one fifth from Hong Kong. There has been discussion of significant cultural variation in responses to EPL, which would also threaten the value of any summary measure.

Moreover, there was methodological diversity in terms of timing of assessment, measures, and comparison groups used.

2.3.3 Risk of bias within and across studies

Table 2.4 shows the Newcastle-Ottawa quality assessment of each study (see Appendix 2). With respect to selection issues, three studies did not specify the derivation of their cohorts (104, 106, 112), and three studies used a self-selected population(4, 109, 110). Participants were generally reported to be representative of the EPL patient population, but in two studies at least 50% declined participation, without discussion of the representativeness of those who agreed (49, 100, 118). One group that were able to obtain information on those who declined showed that women were older, and both women and partners had a lower level of formal education, been married for longer, and a greater number of children, than those who had participated (93, 111). Beutel's study of couples found that partners who participated were more frequently married, and their female partners were less likely to believe that they had desired the pregnancy less than they had (59). Participation was lower in partners, for example 35% versus 50% (100), and thus the potential for bias higher.

Confirmation of EPL was by hospital records in all but two studies (4, 109).

In order to prove that psychopathology was not present prior to EPL, recruitment would need to occur prior to diagnosis: this was uncommon. One study involving partners (110) showed similar early pregnancy assessments in those whose partners went on to experience EPLs and healthy pregnancies.

No studies were designed to match exposed and non-exposed individuals (though in two studies, couples were recruited together, so matched in terms of exposure (59, 111)). Often the loss group

had more previous losses, or were older (17, 109). One study found a significantly higher rate of prior depression (42.4% vs. 18.8%) in the miscarriage group (17). Five study groups controlled for potential confounders (49, 93, 109, 112, 114, 115, 118).

Outcome assessment usually by self-assessment using standardized self-report measures, and was always performed exclusively for the purposes of the study. Follow-up duration was adequate (>=1 month) in all except two studies (53, 106). Drop out ranged from 61% over three months (in a study with consecutive recruitment from an early pregnancy unit (107)) to just 6% over 18 months (involving volunteers responding to an advert (109)). Some studies found no evidence of selective drop out according to baseline psychometric scores (17, 64, 93, 113, 120). One study reported that those with higher initial distress were more likely to take part in the three-month assessment (108). Other studies suggested that those most affected may be more likely to drop out (4, 107, 109).

Across studies, there may be concern of an unintended therapeutic effect of participation. Neugebauer's team found some evidence in support of this (114), but it was not considered in other studies.

A majority of studies excluded non-native language speakers or individuals with low literacy due to reliance on written assessments. The results of those studies using interview assessments may be affected by non-disclosure, due to embarrassment or fear of stigmatization (119).

2.4 Results: Psychological Morbidity

Table 2.5 summarises psychological morbidity according to time of assessment in studies without comparison groups; table 2.6 summarises studies with comparison groups.

2.4.1 Depression

Within a month after EPL, studies show significantly higher depression scores, and a higher proportion meeting a defined threshold, both than in women in healthy pregnancy and outside pregnancy(17, 93, 114, 120). Women following miscarriage and termination were found to have similar scores and caseness of depression (49). Significantly lower depression scores at one week, but no significant difference in caseness, have been found in partners (59, 111).

Table 2.4 *Newcastle-Ottawa Scale assessment of quality of studies*

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Study Fist author, year of publication and reference	**Selection**				**Comparability**	**Outcome**		
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration outcome of interest was not present at start of study	Comparability on basis of design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Beutel 1995 (17)	☆		☆			☆	☆	☆
Beutel 1996 (59)	☆	☆	☆			☆	☆	
Bowles 2006 (41)		n	☆		n	☆	☆	
Cheung 2013 (104)		☆	☆			☆	☆	☆
Cordle 1994, Prettyman 1993, (64, 105)	☆	n	☆		n	☆	☆	☆
Cumming 2007 (100)		☆	☆			☆	☆	
Daly 1996 (106)		n	☆		n	☆		
Engelhard 2001 (4)		n			n	☆	☆	☆
Farren 2016 (107)	☆	☆	☆			☆	☆	
Friedman 1989 (53)	☆	n	☆		n	☆		
Garel 1996 (108)	☆	n	☆		n	☆	☆	
Janssen 1996 (109)		☆		☆		☆	☆	
Johnson 2004 (110)		☆		☆		☆	☆	☆
Neugebauer 1992a, 1992b, 1997, Klier 2000 (114a, 115b, 116, 117)	☆[c]	☆[d]	☆		☆☆	☆	☆	☆
Kong 2010, Lok 2010 (93, 111)		☆[a]	☆		☆☆[b]	☆	☆	☆
Kulathilaka 2016 (112)		☆	☆		☆	☆	☆	
Lee 1997 (113)	☆	n	☆		n	☆	☆	☆
Nordal Broen 2005, 2006 (49, 118)		☆	☆		☆☆	☆	☆	☆
Sham 2010 (119)	☆	n	☆		n	☆	☆	
Thapar 1992 (120)	☆	☆	☆			☆	☆	☆
Walker 2001 (121)	☆	n	☆		n	☆	☆	

n - not applicable (no comparison group)

[a] Partners drawn from same community, female comparison group was non-pregnant women seeking contraceptive advice

[b] Controlled for age, employment status and parity in comparison between women and non-pregnant controls; differences between women and partners not controlled for

[c] Women who were white, had higher education and were married were over-represented at 6 month interview

[d] Pregnant women drawn from same community, community controls were not

Between 8% and 20% women with EPL meet the cut-off for moderate depressive symptoms between one and three months. One study in which 35% met this threshold assessed a self-selected group, in which 10% were more than 20 weeks gestation. More participants reached a cutoff of 'highly symptomatic' for depression than in community controls (114), but in a Sri Lankan study, after controlling for gestation and age, the comparison to pregnant women was no longer significant (112). Between 4 and 12% of partners meet a threshold for depression at this timepoint, with no significant difference in proportion of cases compared to women (100, 106).

Depression scores decline with time, with some studies suggesting resolution at one year(49, 100, 109). One study suggesting increased pathology at one year had a significantly higher incidence of psychiatric history in the exposed group as compared to the control group (17). Gender differences in depression scores were not significant after 12 months(59, 100, 111).

2.4.2 Anxiety

Studies using HADS (Hospital Anxiety and Depression Scale) show anxiety to be more frequent, severe and sustained than depression(64, 100, 105, 107, 118, 120). Up to 41% participants meet criteria at first assessment(64), with scores significantly higher than in an antenatal control group (120), and generally declining over time.

Scores were found to normalize compared to community controls at 6 months in two studies (17, 49, 118), but not until 12 months in Janssen's study when compared to women an equivalent time point after delivery(109). Partners showed less cases of anxiety than women at one-, six- and 13-month assessments (100).

2.4.3 PTSD

The most comprehensive study of posttraumatic stress following miscarriage showed a 25% incidence at 1 month, and 4% at 4 months(4). A later, smaller study (25 women) by Bowles found a 28% incidence of acute stress disorder (ASD, often seen as a precursor to PTSD) at seven days, and a 39% incidence of PTSD at one month (41). Out of 161 women three months after miscarriage in Hong Kong, only one patient was found to have PTSD (0.6%), and three with adjustment disorder (1.8%) on formal SCID assessment(119). The authors comment that this correlates with a lower incidence of psychiatric morbidity previously found in this population in other contexts and for other disorders.

Table 2.5 Cohort studies that have applied standardized psychometric questionnaires or diagnostic interviews at set time points after a miscarriage or ectopic pregnancy to assess proportion of participants reaching a threshold for psychological *morbidity (Depression (D), Anxiety (A) or measures of acute stress disorder (ASD), or posttraumatic stress disorder (PTSD)*

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First author, year of publication and study reference	Psychological Response			
	<One month	One-Two months	Three-Six months	One year +
Women only				
Friedman 1989 (53)		**One month:** 48% 'psychiatric cases'- all D category (PSE) 12% moderate D (BDI) 10% mild D (BDI)		
Garel 1996 (108)			**Three months:** 51% major D episode	
Prettyman 1993, Cordle 1994 (64, 105)	**One week:** 22% moderate/severe D 41% moderate/severe A	**Six weeks:** 8% moderate/severe D 18% moderate/severe A	**12 weeks:** 6% moderate/severe D 32% moderate/severe A	**Two years:** 0% moderate/severe D 16% moderate/severe A
Lee 1997 (113)		**Six weeks:** 12% major D (SCID) 8% moderate D (BDI) 2% mild D (BDI) 1.3% generalized A disorder (SCID)		
Engelhard 2001 (4)		**One month:**[a] 12% mild-severe D 25% PTSD	**Four months:** [a] 11% mild-severe D 6% PTSD	
Walker 2001 (121)	**Three weeks:**[b] 30% A 15% ASD		**Three months:** [b] 20% A	
Bowles 2006 (41)	**One week:** 28% ASD	**One month:** 39% PTSD		
Sham 2010 (119)			**Three months:** 10% Major D (SCID) 2.4% A disorders (SCID) - including. 0.6% PTSD	
Partners only				
Daly 1996 (106)		**Within six weeks:** 12% moderate/severe D 36% moderate/severe A		

[a]data allowing exclusion of three losses >=24 weeks gestation provided by author and presented here
[b]unable to extract all relevant data; unable to contact authors, or authors unable to provide raw data

Abbreviations: ASD -Acute Stress Disorder; A - anxiety; BDI - Beck Depression Inventory; D – Depression; PSE - Present State Examination; PTSD – posttraumatic stress disorder; SCID - Structured Clinical Assessment for DSM;

Table 2.6 Cohort studies that have applied standardized psychometric questionnaires or diagnostic interviews at set time points after a miscarriage or ectopic pregnancy to assess psychological morbidity *(Depression (D), Anxiety (A) or measures of acute stress, posttraumatic stress or traumatic impact (T)): caseness of disorders (given to 0 decimal places), and difference in caseness (C) or scores (S) compared to comparison group (with p value, if available)*

(A statistically significant (at p<0.05) increase in caseness or scores is displayed as an upward pointing arrow, no statistically significant difference as a horizontal arrow, and reduction as downward pointing arrow. Statistically significant results presented in bold) (reproduced from (103) courtesy of Human Reproduction Update, © Oxford University Press 2018)

First author, year of publication and study reference	Psychological Response			
	<One month	One-Two months	Three-Six months	One year +
Comparison to women in healthy pregnancy (PrC), or non-pregnant community comparison (CoC), or live-birth controls (LbC)				
Thapar 1992 (120)	**<24 hours:** D **↑ vs PrC (GHQ-D S) p<0.001** → vs PrC (HADS-D S) A **↑ vs PrC (GHQ-A S) p<0.05** **↑ vs PrC (HADS-A S) p<0.001**	**Six-Eight weeks:** D **↑ vs PrC (GHQ-D S) p<0.01** → vs PrC (HADS-D S) A **↑ vs PrC (GHQ-A S) p<0.01** **↑ vs PrC (HADS-A S)p<0.01**		
Neugebauer 1992a, 1992b, Neugebauer 1997, Klier 2000 (114-117)	**Two weeks:** 36% highly symptomatic D **↑ vs PrC (C) [b]** **RR x3.4 (95%CI 2-5)** ↑ vs CoC (C) [b] **RR x4.3 (95%CI 3-5.8)**	**Six weeks:** 20% at first interview highly symptomatic D **↑ vs CoC (C) [b]** **RRx2.6 (95%CI1.5-4.4)** 12% re-interviewed highly symptomatic D → vs CoC (C) [b] **RRx1.4 (95%CI0.8-2.4)**	**Six months:** 31% at first interview highly symptomatic D **↑ vs CoC (C) [b]** **RRx3.0 (95%CI1.2-5.9)** 12% re-interviewed highly symptomatic D → vs CoC (C) [b] RR 1.5 (CI 0.9-2.5) 11% major D (DIS) **↑ vs CoC (C)** **RRx2.5 (95%CI1.2-5.1)** 5% minor D (DIS) **↑ vs CoC (C)** **RRx5.2 (95%CI1.2-23.6)**	
Beutel 1995 (17)	**Immediately:** D[a] **↑ vs PrC (S) p<0.05** **↑ vs CoC (S) p<0.001** A[a] **↑ vs PrC (S) p<0.001** **↑ vs CoC (S)**		**Six months:** A[a] → vs CoC (S)	**12 months:** D[a] **↑vs CoC (S) p<0.05** A[a] → vs CoC (S)
Janssen 1996 (109)		**Mean 2.5 months:** 35% high/very high D **↑ vs LbC (S) p<0.0005** 22% high/very high A **↑ vs LbC (S) p<0.0005**	**Six months:** 26% high/very high D **↑ vs LbC (S) p<0.006** A[a] **↑ vs LbC (S)p<0.01**	**12 and 18 months:** D[a] → vs LbC (S) A[a] → vs LbC (S)
Kulathilaka 2016 (112)		**Six-ten weeks:** 19% D (interview) 17% moderate/severe D (PHQ-9) **↑ vs PrC (C)** **RR 1.96 (95%CI 1.04-3.73)** → vs PrC (C) [b]		

First author, year of publication and study reference	Psychological Response			
	<One month	One-Two months	Three-Six months	One year +
Farren 2016 (107)		**One month:** 16% moderate/severe D (miscarriage17%; ectopic13%) → vs PrC (C) 32% moderate/severe A (miscarriage 34%;ectopic25%) **↑ vs PrC (C)p=0.04** 28% moderate/severe PTSD (plus 13% not meeting duration criterion) (miscarriage 25%; ectopic 38%)	**Three months:** 5% moderate/severe D (miscarriage: 3%, ectopic: 9%) 20% moderate/severe A (miscarriage 24%; ectopic 9%) 39% moderate/severe PTSD(miscarriage 45%; ectopic 18%)	
Comparison to women undergoing termination of pregnancy (ToP)				
Nordal Broen 2005, 2006 (49, 118)	**Ten days:** 28% mild-severe D →vs ToP(S&C) [b] **↑ vs Popn. (S&C) p<0.001** 33% mild-severe A →vs ToP (S&C) [b] **↑ vs Popn. (S)p=0.005** **↑ vs Popn. (C)p=0.02** 48% intrusion **↑ vs ToP (S)[b] p<0.001** 8% avoidance → vs ToP (S) [b]		**Six months:** 10% mild-severe D →vs ToP (S&C) [b] → vs Popn. (S&C) 15% mild-severe A **↓vs ToP (C) [b] OR 5.1 p=0.001** → vs ToP (S)[b] → vs Popn. (S&C) 20% intrusion → vs ToP (S) [b] 7.5% avoidance → vs ToP (S) [b]	**Two years:** 8% mild-severe D →vs ToP (S&C) [b] → vs Popn. (S&C) 26% mild-severe A →vs ToP (S&C) [b] → vs Popn. (S&C) 0% intrusion → vs ToP (S) [b] 3% avoidance **↓ vs ToP (S) [b] p<0.01** **Five years**: 8% mild-severe D →vs ToP (S&C) [b] → vs Popn. (S&C) 21% mild-severe A →vs ToP (S&C) [b] → vs Popn. (S&C) 0% intrusion → vs ToP (S) [b] 2.6% avoidance **↓ vs ToP (S) [b] p<0.05**
Comparison of women and partners				
Beutel 1996 (59)	**One week:** D **↑W vs P (S) p<=0.001** **↑W vs CoC (S) p<=0.01** → P vs CoC (S) A **↑ W vs P (S) p <=0.05**		**Six months:** D **↑ W vs P (S) p<=0.05** → W vs CoC (S) → P vs CoC (S)	**12 months:** D → W vs P (S)
Cumming 2007 (100)		**One month:**[c] Women: 10% moderate/severe D 28% moderate/severe A Partners: 4% moderate/severe D 12% moderate/severe A D→W vs P (S) **A↑W vs P (S) p<=0.001**	**Six months:**[c] Women: 3% moderate/severe D 20% moderate/severe A Partners: 2% moderate/severe D 8% moderate/severe A D→W vs P (S) **A↑W vs P (S) p<=0.001**	**13 months:**[c] Women: 2% moderate/severe D 16% moderate/severe A Partners: 2% moderate/severe D 6% moderate/severe A D→W vs P (S) **A↑W vs P (S) p<=0.001**

First author, year of publication and study reference	Psychological Response			
	<One month	One-Two months	Three-Six months	One year +
Kong 2010, Lok 2010 (93, 111)	**Immediately:** Women: 27% probable D[d] **↑ vs controls (C)[b]** OR 3.96 p<0.001 **↑ vs controls (S)**p<0.001 Partners: 17% probable D[d] →W vs P (C) p=0.09 **↑W vs P (S) p=0.006**		**Three months:** Women: 19% probable D[d] **↑ vs controls (C)[b]** **OR 2.97 p=0.004** **↑ vs controls (S) p=0.04** Partners: 7% probable D[d] **↑ W vs P (C) p=0.017** **↑ W vs P (S) p<0.001** **Six months:** Women: 16% probable D[d] → vs controls (C)[b] OR 1.96 P=0.07 → vs controls (S) p=0.25 Partners: 4% probable D[d] **↑ W vs P (C) p=0.03** **↑ W vs P (S) p=0.006**	**1 year:** Women: 9% probable D[d] → vs controls (C)[b] OR 1.16 P=0.73 **↑ vs controls (S) p<0.001** Partners: 8% probable D[d] →W vs P (C) p=0.28 →W vs P (S) p=0.07
Comparison of partners following miscarriage to those after livebirth				
Johnson 2004 (110)		**< 3 weeks:** D → vs controls (S) A→ vs controls (S) **T ↑ vs controls (S)**		**1 year:** D↑ vs controls (S) A→ vs controls (S) **T ↑ vs controls (S)**

[a] unable to extract all relevant data; unable to contact authors, or authors unable to provide raw data
[b] results controlled for potential confounders
[c] raw data requested and presented here
[d] lower cut-off used to define caseness (using BDI) than elsewhere – Table 3.3

Abbreviations: A – anxiety; ASD - acute stress disorder; BDI - Beck Depression Inventory; C – caseness; CoC – community control; D – depression; DSM – Diagnostic and Statistical Manual of Mental Disorders; gest. – gestation; GHQ-28 – 28 item general health questionnaire (GHQ–D – depression score; GHQ-A – anxiety and insomnia score); HADS –Hospital Anxiety and Depression Scale; LbC – livebirth controls; n/a – not available; NOS – not otherwise specified; OR – odds ratio; P - partners; PrC – pregnant control; PDS – Posttraumatic stress Diagnostic Scale; P – partners; PSE – Present State Examination; RR – relative risk; S – scores; SASRQ - Stanford Acute Stress Reaction; SCID - Structured Clinical Assessment for DSM; T – traumatic impact (using the Impact of Events Scale); ToP – termination of pregnancy; vs – versus; W – women

2.4.4 Correlation between outcomes

Prettyman reported significant positive correlation between higher anxiety and depression scores (64). Engelhard found those meeting criteria for PTSD to be significantly more likely to meet criteria for depression (4). Johnson and Baker reported correlation between scores on depression, anxiety and trauma scales in partners (110). A minority of other studies reported on correlation between outcomes.

2.5 Discussion

An association between pregnancy loss and psychological morbidity has been demonstrated by a number of studies performed over the past three decades. Four to six weeks after loss, studies report between eight and 20% of women experiencing symptoms above a threshold for moderate depression,

and between 18 and 32% for anxiety. Resolution to background rates of both conditions seems complete within one year. Partners show less severe depressive and anxiety reactions initially.

Three studies reported between 25% and 39% of women reaching a threshold for the diagnosis of PTSD at one month. Recovery from posttraumatic stress has not been established.

The rates of the different disorders vary substantially across studies. For example, most markedly, the rates of PTSD at three months post loss varied from 0.6% (119) (using clinician-administered interviews in Hong Kong) to 39% in a UK pilot (using the posttraumatic diagnostic scale) (107). This may in part reflect different assessment methodologies (which may require validation in this context) and scoring. It may also indicate that research conducted in different locations, with different demographics and cultural norms, may not be usefully interpreted for other populations.

Given high non-participation and drop out, there may be bias across studies in terms of representativeness: either under-representation of those most affected (who may not wish to be reminded of the events) or least affected (who may be less motivated to take part). Elsewhere in the literature (in relation to industrial disasters, or termination of pregnancy) there is evidence of selective non-participation by those likely to be most affected (123, 124). Research of this nature necessarily relies on self-report measures, which exclude individuals with low literacy and those who do not speak the language in which the assessment is written. They also use cut-offs to define pathology that have not been comprehensively validated in EPL populations.

There are gaps in the literature. First, there has been little research into the impact of ectopic pregnancy: this was only reported in one study, making up <1% of the participants included in this review. Second, no studies have yet assessed for PTSD in partners. It is also important to note that studies are generally old, with only four study groups publishing in the last ten years. There has been a shift to earlier diagnosis and more conservative management recently. Expectations may also have changed, along with the perception of women's roles outside the household. For these reasons, psychological responses may have changed. By recruiting from hospitals, older studies may have selected more clinically severe cases (as uncomplicated cases would largely have been managed in the community).

Although the psychological response in these studies is ascribed to the loss itself, it is possible that it relates instead to the uncertain period of involuntary subfertility or prolonged childlessness that follows. There is some evidence that existing children are protective from depression after miscarriage (116, 120). One would also expect improvement with future successful procreation – though there is yet no evidence of this (118), and a plateau in symptoms in those without. The majority of studies performed to date have not assessed for further pregnancies (healthy or otherwise).

In order to prove causation, rather than association, between EPL and psychopathology, pre-loss psychological assessment would be necessary (in turn requiring much larger numbers of participants). The only study that was methodologically capable of this (109) found higher depression and anxiety scores in the group of women who subsequently lost the pregnancy (incompletely explained by the higher rate of past loss in this group). One possibility is that symptoms (e.g. bleeding or pain) led this group to expect a poor outcome prior to diagnosis. However, the possibility that psychological morbidity could itself directly or indirectly increase risk of EPL cannot be excluded (available literature both supports (71) and refutes (72, 73) this). Even if causation cannot be proven, the body of research identifies a group at high risk of psychological morbidity.

2.6 Conclusions

Women, and to a lesser extent, their partners, are at significant risk of psychological morbidity after miscarriage. Reactions are diverse: from those who are unaffected, to those who are completely debilitated. Research into the impact of ectopic pregnancies is lacking. Further assessment of PTSD symptoms is also warranted: results to date indicate concerningly high levels of pathology in two studies, but larger numbers, in an unselected population, and with validation of screening methods, is needed.

Chapter 3: Factors associated with psychological sequelae after early pregnancy loss: a literature review

3.1 Introduction

The prevalence of psychological morbidity, but lack of evidence for its treatment in an unselected population of women experiencing losses, suggests that better results may be obtained from targeting support to those that need it. It could therefore be beneficial to understand if any factors may be associated with psychological sequelae. These factors may be 1) pre-existing patient factors (such as demographic factors, or relating to past psychiatric and obstetric history), or 2) factors relating to the pregnancy itself (such as time taken to conceive), or 3) encounter related factors (involving diagnosis and treatment). An understanding of the impact of the clinical encounter could also enable management to be tailored to reduce psychological sequelae.

3.2 Methods

An extensive literature review was performed, building on information collected during the systematic review covered in Chapter 2, and including information from other texts screened in the process.

3.3 Pre-existing factors

The interpretation of associations with pre-existing factors requires caution. Some factors may be associated with increased background morbidity, rather than an increased vulnerability to the effect of miscarriage. For example, the finding that childless women after miscarriage are more depressed than women with children after miscarriage could be a) because childless women are generally more depressed, or b) because childlessness increases vulnerability to depression after miscarriage. To exclude the former, one either needs to control for pre-loss psychological morbidity (which is difficult, given the inherent inaccuracies of retrospective self-report, and labour intensive study design of recruitment before loss), or to assess the pattern in a control group (or by stratification in both groups). Without this, factors found to be associated may identify women more likely to experience psychopathology through an additive effect on risk, but do not necessarily denote particular vulnerability.

3.3.1 Age

Older women may be expected to be more anxious about future child-bearing potential than younger women, due to declining fertility and increasing miscarriage risk with age. Conversely, age may be

associated with resilience or a better support network. Possible confounders are existing children, or previous reproductive events.

Neugebauer's group did not find any effect of age (more or less than 35 years) on depression scores within four weeks, or risk of major depressive disorder at 6 months (115, 116). Those <25 years in both the miscarriage and the pregnant cohort had higher depression scores. However, at two months, in women <25 years, the adjusted odds ratio for depression in the miscarriage versus community cohort was 18.1 (95% CI 2.8-115.3), compared to 1.8 (0.8-4.0) in women>=25 years (125).

After multivariate analysis, Sham found that women with depressive disorders at three months post miscarriage in Hong Kong were significantly younger than those without (30.6 years compared to 34.0 years, (p=0.02))(119). Stirtzinger's Canadian study found almost identical mean depression scores in women regardless of whether they were more or less than 30 years. However, post-hoc analysis in those with multiple miscarriages showed that younger women (<30 years) had higher scores at 3 months (101).

There is no published evidence establishing a relationship between anxiety or PTSD and age.

3.3.2 Existing children

Existing children could be protective from psychological sequelae. It denotes at least partial fulfillment of one's reproductive potential, and precludes anxieties about involuntary childlessness. Children may also make the pregnancy less desired, or offer distraction. However, previous experience of motherhood may make a pregnancy more tangible and attachment higher.

Neugebauer showed the proportion of women 'highly symptomatic' for depression was 11 times higher (95% CI 5.6 – 16.7) in childless women four weeks after miscarriage than in childless community controls. This was compared to 2.3 times higher (95% CI 1.5– 3.3) when comparing both groups with children, evidencing the particular vulnerability of childless women(115). Work by the same group showed a similar pattern at 6 months: relative risk of major depressive disorder in women after loss versus non-pregnant community controls was higher for childless women (RR5.0) than for women with children (RR1.3)(116). These findings are echoed in smaller studies with univariate analysis (120, 126). In a post hoc analysis, a small study found that women who had multiple miscarriages but other living children were significantly less depressed at one year than women who were childless (p< 0.05)(101).

There has also been found to be a relationship to the number of living children: the impact on depression is less marked as the number of living children increases(115).

Thapar found anxiety scores within 24 hours of a loss to be significantly higher in those without children in a univariate analysis (120).

Studies that have not demonstrated an association between psychopathology and childlessness are small(53, 64), or have substantially lower levels of psychopathology overall(113, 119). These latter studies were performed in Hong Kong, and cultural differences have been postulated.

3.3.3 Prior pregnancy loss

Prior pregnancy loss may alter expectation in subsequent pregnancies, and thus could be protective. Alternatively, there could be a cumulative effect.

Using two large retrospective population based studies, Toffol demonstrated a correlation between the number of miscarriages, and the incidence of depressive disorder (127). One team studied only women with recurrent miscarriage (at variable timepoints after most recent loss), comparing those with two miscarriages (14 women) to those with three or more (40 women). They found no notable difference in anxiety or depression scores (128).

Neugebauer's team in fact found a very slightly lower incidence of depression in women after miscarriage with previous loss than those without (but higher in the community controls with past loss than those without) (116).

Friedman found significantly higher depression scores at four weeks in 21 women with prior miscarriage (compared to 46 without) on univariate analysis(53). Engelhard reported association between previous loss and depression, but not PTSD (4).

A small study with univariate analysis found a statistically significant increase in anxiety (but not depression) scores initially in those with previous miscarriage as compared to those with no previous loss (120).

3.3.4 Previous termination of pregnancy

One study in the recurrent miscarriage population found higher levels of anxiety in those with a previous elective termination on univariate analysis (128). This and other studies have not shown an association between previous elective termination and depression (53, 116, 117) – though not specifically powered to do so.

3.3.5 Social history

Lower education, lower social resources, high stress levels and the presence of other simultaneously occurring negative life events have been found to predict poorer mental health following miscarriage. These may of course represent independent risk factors for psychological morbidity, and have not yet been proven to increase vulnerability to the psychological effects of miscarriage(125).

Engelhard found that women with low educational attainment were significantly more likely to meet criteria for PTSD following a pregnancy loss(129), consistent with PTSD in other contexts. The paper discusses the fact that 'processing' of the traumatic event and integrating it into memory is a cognitive task, which can be supported by intelligence.

Women reporting past physical, emotional, or sexual abuse were more likely to experience acute stress disorder (ASD) following early pregnancy loss (41).

3.3.6 Social support and marital status

Friedman found that women who were unmarried were more likely to be defined as having 'psychiatric case status' four weeks after loss in univariate analysis (78% of unmarried women vs. 43% of married women, $p<0.05$)(53). There is also evidence of higher depression scores at 5 years in single (not married or cohabiting) women after miscarriage (49). Marital and family conflict has also been found to be associated with depressive symptomatology after loss (101).

Although these studies identify a group at higher risk of psychopathology overall, in controlled studies there is no evidence of an enhanced vulnerability in an unmarried group (115-117).

Lee found a measure of low marital satisfaction and perceived spousal support to be significantly associated with major depression in Chinese women in Hong Kong (assessed at interview 6 weeks following a loss)(113). Kong also found women with lower marital satisfaction were more likely to meet criteria for depression immediately after a loss(111). Psychological distress may affect the interpretation of, or, if detrimental to the relationship, absolute level of support from a spouse.

Lack of social support is widely recognized to increase the risk of PTSD in other contexts (130), but has not been assessed in relationship to pregnancy loss.

3.3.7 Past psychiatric and trauma history

Studies rely on report or documentation of past psychiatric diagnoses. Of course, this is less reliable than objective pre-loss assessment, as affected individuals may not have been formally diagnosed.

Past psychiatric history has consistently been found to be associated with depression after loss(17, 118). Among miscarrying women with a history of major depressive disorder, 54% experience a recurrence(116). Freidman found a higher likelihood of having seen a GP for psychiatric problems in those who were depressed (14/21 versus 18/46, $p<0.05$)(53). Sham found 4/15 women with depression after miscarriage to have a history of depression compared to 7/146 without (adjusted OR 8 ($p=0.007$))(119).

Past psychiatric contact, or self-reported poor psychiatric health, and a past history of anxiety, have also been associated with higher anxiety scores after miscarriage(100, 118, 121).

It is well recognized in other contexts that other previous trauma is predictive of PTSD (130).

Other recent life events have been associated with more anxiety symptoms, and a higher likelihood of a major depressive episode, after miscarriage (118, 122).

3.3.8 Religiosity

The role of religion in coping with stressful life events is complex. Religion can provide meaning, and encourage people to consider negative events as part of a greater purpose. In a qualitative study, religion was reported to provide positive meaning to the experience of EPL, such as learning about oneself, and the ability to empathise more (3). Religious groups may provide social support. However, religious pressure to start a family, or negative religious interpretation as punishment, may have a negative effect.

'Using prayer to cope with emotions' was not found to be predictive of PTSD or depression in a subsequent pregnancy following a spontaneous or elective termination (40).

3.3.9 Culture and ethnicity

The impact of culture and ethnicity on grief, depression or anxiety following pregnancy loss has not been established. Studies originating from Hong Kong have consistently shown lower rates of morbidity than in Western cohorts, raising the possibility of cultural variation(93, 119).

3.3.10 Individual cognitive factors

Certain cognitive traits may be protective from, or perpetuate, psychological distress following EPL.

Women who reported feeling personally responsible for the miscarriage were found to be more likely to suffer from ASD(41). The personality trait of neuroticism has also been found to be associated with PTSD (129).

In spite of increasing interest in the importance of traits of self-compassion and rumination, no studies have yet investigated them in relation to psychological adaptation to EPL.

3.3.11 Pre-existing knowledge about EPL

A recent study revealed that a majority of people believe miscarriage occurs in <5% of pregnancies(45), indicating expectations are unrealistic. There are, however, no studies that relate knowledge of miscarriage to psychological outcome.

There is a general consensus that 'breaking the silence' about miscarriage would have a positive impact, reducing feelings of guilt and personal failure (3). Bardos found that disclosures of miscarriage by public figures assuaged feelings of isolation(45).

3.4 Pregnancy related factors

3.4.1 Attitude towards pregnancy

One study showed an ambivalent attitude towards the pregnancy to be more common in those women with depressive reactions (as opposed to those with shorter term grief reactions, in which women had more positive attitudes)(17). In univariate analysis, Thapar demonstrated significantly higher depression scores in women who had not planned their pregnancy(120).

Neugebauer found little variation in depression scores within the miscarriage cohort regardless of how much the pregnancy was wanted(115). However, pregnant controls with unwanted pregnancies had higher depression scores, similar to those who miscarried, and those with wanted pregnancies, lower, suggesting increased vulnerability to the impact of miscarriage in the group who desired the pregnancy.

Unplanned pregnancy was associated with more anxiety 12 weeks after miscarriage in one study (64). Thapar also found higher depression scores immediately after loss of an unplanned pregnancy(120). Another study showed higher traumatic impact three weeks after loss of an unplanned pregnancy(121).

A sense of feeling bonded to the child was significantly associated with the risk of ASD in one small study (41).

3.4.2 Time taken to conceive, subfertility and assisted reproduction

Taking time to conceive may increase the amount the pregnancy is desired, or enhance anxiety about future reproductive potential.

One study found no evidence that increasing time taken to achieve a pregnancy is associated with psychological sequelae (131).

A study in Hong Kong comparing women with assisted reproduction to those with natural conception found significantly higher General Health Questionnaire (GHQ) scores, and higher traumatic impact (especially hyperarousal symptoms) in those with assisted reproduction (104). Another study from Hong Kong showed an adjusted odds ratio of 13 (95% CI 2.72-63.74) for depressive disorder in women with a history of infertility versus those without(119). A French team found the rate of depression to be higher in the group with treatment for subfertility immediately after miscarriage, but not at three months, in univariate analysis (122).

The background risk of psychopathology in women undergoing assisted reproduction is known to be higher(132).

3.4.3 Gestation, fetal movements and ultrasound appearances

One may expect an evolving relationship and attachment to the growing baby during pregnancy, which may be affected by perception of movements. Frost's article theorises that early ultrasound establishes a fetus as a person, thus contributing to the sense of loss (3). Lok discusses how recent technological advances may have changed the 'natural history of prenatal maternal attachment' (38). Seeing a 'child' may result in greater 'objective reality' and stronger parental attachment (86).

Janssen's study (which included stillbirth) showed anxiety and depression scores 2.5 months after loss to be higher in those with longer gestation at loss, as well as depression scores at one year(109).

Neugebauer's group found no difference in the relative risk of major depressive disorder according to trimester(116). Although later losses had a higher incidence of minor depressive disorder compared to first trimester losses (Incidence 8.5 per 100 losses, as compared to 4.0), these numbers did not reach significance(117).

Engelhard found a significant correlation between gestational length and both posttraumatic stress and depression severity at both one and four months(4).

There is evidence of higher immediate depression in women in whom there has been previous ultrasound evidence of a viable fetus (111). In her 2007 review article, Lok references her own thesis, reporting higher depressive symptoms at six months (38).

3.4.4 Diagnosis

There is minimal research on the psychological impact of ectopic pregnancy, and a difference between reactions to ectopic pregnancy and miscarriage has not been established.

A diagnosis of gestational trophoblastic disease (GTD) necessitates prolonged follow up (and, rarely, treatment), and delay to subsequent conception. Stafford found significant depression and anxiety symptomatology in women with GTD (133), though there is no published comparison to other miscarriages.

3.5 Encounter related factors

The clinical encounter during EPL can vary widely. Some women will be entirely asymptomatic and diagnosed on routine scan. Others will experience bleeding or pain, but conclusive diagnosis may take two weeks. A minority will present in extremis, needing emergency surgery.

3.5.1 Diagnostic uncertainty

The impact of any period of uncertainty (when a pregnancy is first of unknown location or viability) has not been assessed. Diagnostic delay may be psychologically challenging – or alternatively may gradually moderate expectations, and enable more contact with healthcare professionals.

3.5.2 Symptoms

Symptoms may provide warning and increase preparedness for loss. They may be physically traumatic.

Walker, in a study of 40 women, found that perceived warning signs of early pregnancy loss did not impact rates of acute stress disorder, posttraumatic stress symptoms, anxiety or depression(121). Brier, in a qualitative study, described higher distress in women with few warning signs (134).

No studies relate the clinical severity (e.g. degree of pain or bleeding, or emergency admission) to psychological outcome. A review of PTSD in the context of a variety of medical conditions found that the severity of the illness is not generally predictive (135).

3.5.3 Management

Miscarriage

Appropriate management of miscarriage may include: surgical evacuation, medical treatment, or expectant management.

The unpredictable timing of expectant management may prove difficult, lengthening the time to return to normal activities (136). Expectant or medical management may be associated with severe pain, bleeding, or the passage of an identifiable fetus. In surgical management, women may feel violated by a procedure during which they were unconscious, or find a procedure under local anaesthetic intensely painful.

A number of small, randomized controlled studies have attempted to analyse the emotional impact of different management strategies. The difficulty in performing these trials is two-fold. First, many women will have a preferred treatment, precluding randomization in a substantial (and potentially characteristically different) group. Indeed, Wieringa-de Ward's analysis of their substantial non-randomised group showed those who opted for expectant management had better mental health scores and less active grief at the outset. They hypothesise that this may be because of the attitude required to accept 'the uncertainties of expectant management'(131). Second, many of those randomized will deviate from their allocated management strategy, for clinical reasons or newly demonstrated preferences.

Overall, studies have not shown a consistent difference in anxiety or depression between management strategies. The largest randomized study, the MIST study, in which approximately 400

women were randomized to each of the three options, no differences in anxiety and depression scores 6-8 weeks after miscarriage were found (though 44% of medical/expectant groups ended up having surgery)(137). Nielson compared expectant and surgical management in 86 women, with no difference in the anxiety status at two weeks (though 26% allocated to expectant management had surgery)(138).

Two studies originating from Hong Kong showed no impact of management on anxiety and depression scores. Lee compared surgical and medical approaches in 218 women, and assessed at six weeks and six months (139). Kong compared all three management approaches in 180 women (140). Women with active intervention had greater posttraumatic symptoms immediately (using the Chinese version of the Impact of Events Scale), but not persisting at one month.

Wieringa-de Waard showed that, when Dutch women were randomized to either expectant (n=64) or surgical (n=58) management, the expectantly managed group had significantly higher general mental health scores, and lower anxiety scores (though the vast majority (305 women) declined randomisation)(131). Shelley randomized a total of 39 Australian patients, and showed, in contrast to the above, a tendency for more women randomized to medical or expectant management to be anxious or depressed than those in the surgical group (136).

More convincing is the ability to exert a preference, and success in achieving that preference, to have an impact. Nielsen found a trend towards higher distress in those randomized to expectant, but who ultimately had to undergo surgical, management(138). Wieringa-de Ward showed worse mental health scores in those randomized to, compared to exerted a preference for, surgery (131).

Qualitative studies have also highlighted the importance of being sensitive to patient choice, in the context of wide variation in beliefs and preferences(141). Lee comments that Chinese women see surgery as having a detrimental effect on the already 'devitalised' body, with medical management being more compatible with the 'Chinese ethnomedical belief system'. Such beliefs are culturally variable(139). A contrasting view may be that the immediate removal of non-viable tissue is necessary.

Ectopic pregnancy

A randomized study of methotrexate versus expectant management in 73 women with ectopic pregnancy or persistent PUL found no significant differences in health-related quality of life, including anxiety and depression(142). A randomized study of methotrexate versus laparoscopic surgery in 62 women also found no difference in psychological functioning(143).

An RCT of 100 women comparing laparoscopy followed by methotrexate administration, to laparoscopy plus salpingostomy, found that those who received methotrexate were significantly more

depressed at 2 days, but not at two weeks (144). Its interpretation in modern standard medical management, in which a laparoscopy is not performed for diagnosis, is unclear.

3.5.4 Hospital stay

Hospital stay may be a proxy for clinical severity, and correlate with the amount of support a woman receives from healthcare professionals.

Neugebauer did not find hospital stay to be predictive of depression levels(115): no other studies have commented on this.

3.5.5 Reason for miscarriage

Frost comments(3):

"…most women will never get a coherent explanation of why they miscarried. Thus miscarriage might be seen as an imperfectly scientised form of death. It is this…which makes miscarriage such a bewildering experience for many women and their partners. The lack of a cause/outcome framework can challenge their sense of living in a rational world"

Guilt and self-blame are promoted by the absence of medical explanation for miscarriage(145). Behavioural restrictions (such as avoiding alcohol) placed on pregnant women also imply responsibility for safeguarding the pregnancy's safety (146). The finding of a medical cause – such as a chromosomal abnormality – could be expected to alleviate this sense of responsibility for the poor outcome. Understanding of the cause may also help to rationalize hopes or anxieties about the future: it may be a relief that no potentially recurring cause is found.

One team investigated 143 consecutive miscarriages to ascertain their cause. The finding of a fetal chromosomal abnormality was found to reduce self-blame (147). The corollary is that those who do not find a cause (and investigation is not routine) may have enhanced self-blame. Tunaley found lower anxiety levels in those who accepted a medical explanation and believed there was a physical cause (148). In another study, those that felt personally responsible for a miscarriage were significantly more likely to develop ASD(41).

3.5.6 The impact of care received

There is evidence of dissatisfaction surrounding miscarriage care, including the lack of information, and disparity between the expected and actual sense of urgency in threatened miscarriage (53, 149). Qualitative papers, media articles and social media commonly discuss examples of insensitivity or dismissiveness from healthcare professionals, and the distress that this has caused. Many hospitals will have a cut-off of 20 or 24 weeks gestation, at which point women will have specialist care and support from a bereavement midwife: such a cut-off will not correspond exactly to distress levels.

Cuisinier found that those with a miscarriage were less satisfied with their overall medical care than those with a later loss (150).

Sensitivity to suboptimal or unkind treatment is likely to increase in those who are more distressed, so causality is difficult to establish. Satisfaction with a primary healthcare physician has been associated with better mental health trajectories in Australian women – though this may be due to recall bias (151).

3.6 Risk factors in partners

Generally, there has been less research in partners. Levels of distress have been found to correlate within couples(111). Johnson and Puddifoot found non-significantly lower IES intrusion and avoidance scores in partners of women miscarrying at a lower gestation, and who had not seen a scan(56). Another study found higher depression scores in those partners with a planned pregnancy(111).

3.7 Discussion

Childlessness is associated with more depression and anxiety after EPL, and increased vulnerability to the effect of loss. Younger women may have more depressive symptomatology, and be more vulnerable to depression after loss. Past trauma history, past psychiatric history, and poor social support appear to be associated with higher psychological morbidity, as they are in other contexts: this may not relate to the loss itself. Assisted reproduction may be associated with higher anxiety and depression levels before and after miscarriage, and a history of subfertility had been associated with depression. There is some evidence of increasing vulnerability to depression, anxiety and PTSD with advancing gestation in studies also involving late losses. Prior ultrasound evidence of a viable pregnancy may be associated with depression. There is not consistent evidence that past losses increase vulnerability to the impact of a further loss.

There is no evidence to guide the choice of management on emotional grounds, except in so far as ensuring patient choice is supported. There is no research on the impact of diagnostic delay. Symptoms themselves have not yet shown to correlate to distress levels.

All but one study (104) were not designed or powered to assess for risk factors: the results presented are generally the result of post-hoc analyses of multiple potential factors. In this context a focus on statistical significance (at 5% level) is fundamentally flawed: 1:20 would expect to show a significant result by chance. All the results should be interpreted in this context, especially those for which the impact appears small.

Many of the included studies have performed only univariate analysis: in exploratory evaluations for associated factors, univariate analysis is appropriate, but consideration must be given to potential confounders. Furthermore, as discussed at the outset, assessment for an impact in the control group may be important in establishing whether a factor imposes increased vulnerability to an EPL, or purely an additive effect. Looking only at a cohort with losses helps to gauge the emotional needs of the group (and therefore potentially allocation of general resources) – but it is not possible to attribute the symptoms to the loss alone(125). One could hypothesise that those who are not reacting to the loss itself may not respond to pregnancy-loss specific support and treatment.

Significant gaps in the literature include risk factors for PTSD and following ectopic pregnancy. More research is also needed to establish the impact of individual cognitive factors. This is of particular interest as a possible therapeutic target.

3.8 Conclusions

Clinicians should be especially alert to the risk of psychological distress in women with low social support, who have past psychiatric history, who are left childless by a loss, or who have experienced antecedent subfertility or assisted reproduction.

It remains to be seen how much of the variation in responses can be predicted by these factors, and whether therefore they are likely to form a useful tool in identifying those who would benefit from referral for assessment or support.

Chapter 4: Methods

4.1 Introduction

This chapter outlines methods used for novel research into the psychological impact of early pregnancy losses (both a pilot study, completing recruitment in 2013, and the main study, completing in 2016).

4.2 Aims of study

1. To establish the prevalence of moderate and severe anxiety and depression in women following an early pregnancy loss, compared to those in a healthy early pregnancy
2. To establish how this changes over time in those who do not experience further losses
3. To establish the incidence of posttraumatic stress disorder (PTSD) in women following a loss, and how this changes over time
4. To compare reactions following ectopic pregnancy and miscarriage
5. To assess for factors that predict the prevalence of anxiety, depression and PTSD (both pre-existing factors and encounter-related factors)
6. To establish the psychological morbidity in partners (anxiety, depression and PTSD) following a loss, and how this compares to women

4.3 Study design

A prospective cohort design was chosen. The aim to establish the incidence of psychological morbidity in our population made this the most appropriate observational study design. Compared to a case-control design, a cohort design also enabled multiple effects (i.e. anxiety, depression and PTSD) to be assessed, and for prospective recording of potential risk factors (thus minimizing recall bias).

4.4 Study population

The study was approved to take place in three central London hospitals:

- Hammersmith Hospital
- St Mary's Hospital
- Chelsea and Westminster Hospital

The study population consisted of 1) women with early pregnancy loss (EPL), 2) their partners and 3) a control group.

4.4.1 Women with EPL

Women with EPL were recruited from the Early Pregnancy Units (EPUs) of the hospitals.

Types of pregnancy losses included were:

- Miscarriage
- Pregnancy of unknown location (PUL):
    - spontaneously resolving or
    - persistent
- Ectopic pregnancy
- Molar pregnancy

Women who had already attempted to terminate their pregnancies (attending, for example, with retained tissue after a procedure) were not included. However, women were included if they were considering or planning a termination, but experienced EPL in the interim. Consideration was given whether to include women who had been advised to terminate their pregnancy due to an extremely poor prognosis for the baby, or significant risks to the woman (for example in cases of confirmed rupture of membranes <20 weeks). In this situation, the couple must take active steps to end the pregnancy: this may be expected to have different psychological response to a passive involvement in a miscarriage. Since the frequency of each diagnosis is low, and the nuances of the counseling and recommendation different in each case, it was not felt that a homogenous group of any significant size could be obtained, and thus a decision was made to exclude these.

Women with EPL were clinically managed according to local protocols, which were unaffected by the study. Those with miscarriage (unless complete) are offered the clinically appropriate options out of expectant management (with follow-up ultrasound scans to ensure completion), medical management (with misoprostol, and follow-up scan after two weeks) or surgical management (suction evacuation under general anaesthesia, usually without further follow-up). Women with ectopic pregnancies were offered expectant management (with repeat serum human chorionic gonadotrophin (hCG) testing), medical management (with a single dose of methotrexate, and hCG follow-up) or surgical management (usually laparoscopic salpingectomy): appropriate management depended on symptoms, ultrasound findings and hCG levels. Women with resolving PULs were requested to perform a urinary pregnancy test 2 weeks later to confirm that this was negative. Molar pregnancies were usually surgically managed if suspected on ultrasound, and referred to the regional trophoblastic centre for follow-up once the diagnosis was histologically confirmed.

4.4.2 Partners following EPL

If women with EPL were eligible and consented to recruitment, and their partner was present with them at the appointment, they were also approached to participate. Consideration was given to asking women presenting alone to pass on a request for their partners involvement, but it was deemed preferable to attempt consecutive recruitment of those present, where a full explanation could be given, and valid consent for participation gained.

4.4.3 Control group

A variety of potential control groups can be considered. Conceptually it is possible to argue that the comparison should be a) someone who has not had a pregnancy at all, or b) someone who has not had their pregnancy fail, and has a healthy ongoing pregnancy. Previous research in this area has used both non-pregnant community controls (17), women in healthy pregnancies (120), or both(115). One review article suggested that in view of the higher prevalence of psychological symptoms in pregnancy, a pregnant control group is desirable(152).

After extensive discussion, it was felt that women who were pregnant were likely to be matched in terms of relationship status and desire to have a family. Furthermore, it would have been challenging to access a non-pregnant control group, a source of which would not have been available within hospital clinics except in the presence of factors which could have been statistically suppressive (infertility clinic, or gynaecology clinic- in which a high proportion of women may be experiencing menstrual disturbance, or subfertility).

The control group was initially recruited from the early pregnancy unit (for the duration of the pilot study). However, there were two issues with this. First, a very high proportion of the women were attending for reassurance scans in view of previous losses. Ideally, we wanted a large group of control women with a low frequency of past loss (a similar, rather than inflated, rate to those experiencing their first loss). Second, recruiting women in healthy pregnancies was to the detriment of recruitment of losses (a larger group of which was needed), as only one researcher was available at any one time, and also to the detriment of other studies taking place in the unit, which aimed to recruit viable pregnancies. Thus, a decision was made to focus recruitment in the early pregnancy units to losses, and recruit controls from the routine antenatal clinic.

Women attending the antenatal clinic were doing so for their initial booking appointment or nuchal scan (performed between 11 and 14 weeks). Viability on the nuchal scan was confirmed before requesting active participation. These women continued routine antenatal care.

4.4.4 Inclusion and exclusion criteria

Inclusion required the participant to have capacity to give informed consent. Women and their partners over the age of 18 were included, so competence to consent could usually be assumed.

Our aim was to focus on early losses. A cut off of 20 weeks gestation at the diagnosis of loss was chosen. This represents the gestation that care is generally transferred from early pregnancy and gynaecology units to obstetric units.

It was vital for the reliability of the study that participants were able to fully understand detailed questions about their emotional state. Given appropriately validated questionnaires in other languages are very uncommon, a decision was made to only include those women who, on the subjective option of the person recruiting, understood written English to a sufficient degree to answer written questions without the need for an interpreter.

4.5 Recruitment methods

In order to minimise selection bias, recruitment was consecutive on the days on which the study investigators were available.

A poster (or powerpoint slide, on a screen) was displayed in the waiting area of the early pregnancy units and antenatal clinics to outline the rationale behind the trial, and its methods.

Treating clinicians introduced the study to prospective participants during their standard consultation. Women and their partners could be recruited at any point during their care in the unit. If they indicated that they were interested to hear more, one of the research team (if not the treating clinician) would join at the end of the consultation. After detailed explanation, and time to read the information leaflet, potential participants were then given the option to either:

a) sign the consent form on the day. If this option was chosen, a confirmation email was sent to them after 24-48 hours, requesting them to respond if they wished to withdraw

b) take the consent form away, and return it by post or at a later appointment if they consented

In order to evaluate the proportion of women and partners who were eligible, and consented to recruitment, record was kept of:

- Those excluded due to insufficient command of English, or other exclusion criteria
- Those who actively declined participation, and their reasons (if volunteered)
- Those who took the consent form, but never returned it (passively declined)
- Those women who volunteered to participate, who's partners were present but declined participation

After consent, each participant was given a unique study number which was used in every communication, and in the prospective recording of their clinical case.

4.6 Prospectively collected demographic and clinical information

At recruitment, background information was recorded. For women with EPL, this was updated with details of the complete clinical encounter after discharge.

Table 4.1 *Data prospectively collected from clinical records for women with early pregnancy loss and viable pregnancies*

Category	Data collected
Background	Date of Birth Age at diagnosis Parity* Previous miscarriage, ectopic, resolved PUL* Previous termination of pregnancy*
Index pregnancy	IVF in this pregnancy Last menstrual period Date of positive pregnancy test
Referral and diagnosis**	Date of first concerning symptom Reason for referral Date of first scan Initial diagnosis Final diagnosis Date of final diagnosis If intrauterine, presence of fetal heart activity on earlier scans
Management**	Initial planned management Any unplanned/emergency management Date of any first line management Any second or third-line management Dates of any management, and of discharge Any overnight admission Any blood transfusion Total number of scans
Future pregnancies**	Any future pregnancies on system Future pregnancies within 9-month follow-up

*prospectively recorded for main study only

** women with early preganancy loss only

4.7 Method and timing of follow-up

A decision was made that a web-based platform to fill in questionnaires would be the most convenient for the participants, and most efficient to consolidate and analyse. SurveyMonkey (www.surveymonkey.net) was found to be a suitable platform for this, which enabled the questionnaires to be presented as they would be on paper. Participants responded anonymously, identified only by their study number, which was emailed to them along with the link to the questionnaire.

It was also possible to send a paper version of the survey, or details of the webpage to be accessed, by post. This aimed to avoid exclusion of those without access to email or computers. However, no participants opted for this method.

Extensive consideration was given to the timing of the assessments. The justification behind leaving one month from diagnosis until the first assessment was to avoid a focus on an acute grief reaction, which could cloud assessment of psychopathology. Moreover, the diagnosis of PTSD requires symptoms to have been present for one month. From a practical perspective, a month's interval meant women could be recruited during follow-up (rather than on the day of diagnosis).

Three months was felt to be an appropriate point to re-assess. It would often be at a time of resumption of efforts to conceive, and less commonly in early pregnancy.

Nine months was chosen to assess long term symptoms, while avoiding time-points that could be especially sensitive – namely: a) the due date (which would be expected to be a maximum of eight months from diagnosis) and b) a year's anniversary from the diagnosis.

The control group was assessed after confirmation of viability on the nuchal scan between 11 and 13+6 weeks gestation.

Following analysis of the pilot study results, in which there was significant non-response, a decision was made that reminder emails should be written. Ethical approval was gained to send an email one and two weeks after the initial request to those who had not yet participated.

4.8 Background information asked at first questionnaire

The first questionnaire was an opportunity to ask further background information not routinely recorded as part of clinical records. With respect to past obstetric history, there was occasionally disparity between clinical records and patient responses. For this reason, where available, patient responses were used, with data from clinical records only used for analysis of non-response. Later questionnaires at three and nine months asked whether the participant was pregnant, and/or had experienced a further loss.

Table 4.2 *Questions included in one-month questionnaire, excluding psychiatric diagnostic rating scales*

Category	Questions asked
Demographic	Age Level of education Religion Ethnic origin Income Marital status Relationship status Length of time with current partner
Past medical history	Previous treatment in hospital Previous emergency surgery
Past obstetric history	Previous terminations of pregnancy Previous miscarriage Previous ectopic pregnancy Previous pregnancy of unknown location Previous stillbirth or neonatal complications Fertility treatment (including details) Time taken to conceive
Past psychiatric history	Past psychiatric diagnoses, detailed
Clinical experience	Severity of pain during this encounter* Severity of bleeding during this encounter*
Emotional, subjective experience	How much pregnancy desired How worried for own/for partners wellbeing* How distressed* How responsible they felt*
Views on treatment	Received clear information from healthcare professionals Emotionally supported by healthcare professionals Satisfaction with healthcare received

* Women with losses only

4.9 Psychological assessment

The gold standard for making a psychiatric diagnosis is an interview and mental state examination by a psychiatrist or psychologist. However, diagnostic rating scales provide an important adjunct to this process, and form the basis of research by making the large-scale screening for psychological impact

and mental disorders feasible. For this reason, it was clear from conception of this study that they would form an essential part of the methodology.

Diagnostic rating scales translate patient self-assessments into objective measures. Thresholds define levels likely to be consistent with a diagnosis, and scores provide a measure of severity on an ordinal scale (including 'subsyndromal' behaviour, which may still have important clinical implications).

Specific screening measures for psychological morbidity in the context of miscarriage have not been well established. This contrasts to postpartum depression(38). Instead, existing measures of anxiety, depression (sometimes appropriating the specific postnatal depression scale) and PTSD are used. These questionnaires may relate to one or multiple psychiatric diagnoses.

4.9.1 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was originally developed to identify psychopathy among physically ill (non-psychiatric) patients, and has since been found to perform well in assessing the presence and severity of anxiety and depression in a wide range of populations (153). It is widely acceptable to participants, and has good internal consistency (mean Cronbach's alpha for HADS-A 0.83, HADS-D 0.82)(154). It has been found to have at least as good screening properties as similar, but more labour intensive, instruments used for the identification of anxiety and depression, and thus selected for its brevity. It has been used extensively: a review article identified 747 papers using HADS by May 2000(154).

It has only been well validated in English speaking patients, due to difficulties in the translation and cross-cultural interpretation of some of the questions(155).

There are fourteen questions, seven measuring anxiety and seven measuring depression. Each item has four answer categories giving a score between 0 and 3 for each item, and a score between 0 and 21 in total. The higher the score, the greater the severity of anxiety or depression. A case is considered 'mild' with a score of 8-10, 'moderate' with a score of 11-14 and 'severe' with a score of >14.

In the context of miscarriage, HADS has been used in a number of papers(49, 64, 100, 105, 106, 118, 120, 121). Cumming validated the questionnaire, using a cut-off score of 11 to define caseness, against the clinician administered WHO CIDI (Composite International Diagnostic Interview), showing strong concordance for discrimination of cases from non-cases (100).

On the basis of its brevity, reliability, acceptability, and the precedent for use following miscarriage, HADS was chosen for the assessment of anxiety and depression in this study.

4.9.2 The Posttraumatic Diagnostic Scale

The Posttraumatic stress Diagnostic Scale (PDS) is a well-known diagnostic measure of posttraumatic

stress disorder (PTSD), according to the now outdated DSM IV criteria(156). The questionnaire has five sections:

1. Details/specification of a potentially traumatising event and when it occurred
2. Checking that the potentially event involved them/someone else being physically injured or danger to life, and that the event involved them feeling helpless or terrified.
3. Symptoms relating to the identified event:

    Re-experiencing – 5 questions

    Avoidance – 7 questions

    Arousal – 5 questions

4. Duration of symptoms; which must be more than one month.
5. Interference with functioning

Women with viable pregnancies completed a set of questions to screen for trauma, and were only directed to the PDS if qualifying trauma was idenitified. Women with EPL were specifically asked questions in relation to the loss – e.g. "having upsetting thoughts or images *about the pregnancy loss* that popped into your head when you didn't want them to" (where for the control group, the words 'pregnancy loss' were replaced with 'traumatic event').

There has been considerable discussion as to how best to score the PDS. In line with DSM-IV, the method suggested by the developer herself requires endorsement of at least 1 re-experiencing, 3 avoidance and 2 hyper-arousal symptoms (i.e. scores at least 1 (equivalent to 'once a week or less/once in a while') on the scale from 0-4). In addition, there must be evidence of impairment in functioning, evidence of helplessness, horror or terror, and a duration of more than one month . An overall severity score is also given. If used in this way, the scale shows satisfactory internal consistency, high test-retest reliability, and good concurrent validity(156). Research has also shown that the scale has satisfactory agreement (r=0.65) with the Structured Clinical Interview for DSM-IV in other contexts, with a sensitivity of 0.89 and a specificity of 0.75 (157).

Engelhard, in her work following assessing PTSD following miscarriage, found a different cut-off more appropriate(4). She required scores of at least 2 (equivalent to on the Likert scale to be '2-4 times a week/half the time') for a symptom to be considered endorsed. In direct personal communication with Professor Engelhard, for the purposes of this thesis, she confirmed that she had used a more conservative cut off as Foa's more liberal scoring had led to unbelievably high PTSD. She later investigated the trade-off between sensitivity and specificity using the two methods for scoring PDS, compared to a SCID interview, in a broad group of 65 PTSD sufferers (experiencing a wide variety of traumatic events), compared to 40 individuals with other anxiety disorders. The conservative

threshold showed a sensitivity of 0.48 and specificity of 0.8, compared to the original more lenient scoring which showed a sensitivity of 0.86 and specificity of 0.58 (158). It is worth noting that much better performance was obtained by comparison to a healthy control group. In a different context, she found that the liberal scoring over-estimated PTSD by a factor of 3.5 compared to the SCID (159).

Other severity cut-offs have been suggested and validated in other populations (160). A cut-off of 18, alongside the three symptom cluster criteria being met (as per Foa's original instructions), and interference of overall level of functioning (or >=2 areas of interference), has been found to optimize sensitivity and specificity in the diagnosis of PTSD in a large sample involved in motor vehicle accidents, sexual and physical assaults. The severity score alone (without a symptom cluster assessment) has been found to perform almost as well - also with a proposed cut-off of 18.

The pilot study considered PTSD diagnoses according to Foa's original scoring. However, the results of the SCID interview allowed us to compare a number of scoring methods used in the existing literature. From this a decision was made to use Ehring's criteria, as detailed in Chapter 8.

The new symptom cluster included in the DSM-5 diagnostic criteria for PTSD since 2013 relates to negative alterations in mood. Also, now included in the 'arousal' symptom cluster is reckless or self-destructive behaviour. These are not covered by PDS. However, there is evidence that DSM-IV symptoms can be used to closely approximate DSM-5 diagnoses(44). Over time, a new scale has been developed and validated to reflect these new criteria (PDS-5). A paper published in 2016 showed excellent internal consistency, test-retest reliability and concurrent validity with the PTSD symptom scale interview (PSS-I-5) (161).

At the time when the research protocol for this study was developed, the new criterion had not been added, and the PDS-5 had not been developed or validated. Thus, we used the original PDS.

4.10 Structured clinical interview for posttraumatic stress disorder

In view of the change in PTSD diagnostic criteria during the study, and the higher than expected levels of the disease according to the pilot study, a decision was made that the PDS, and the various potential scoring methods, needed to be validated by comparison to a clinician administered instrument.

The SCID (Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders) is the most commonly used clinician-administered instrument (162). It contains standardized questions, which parallel inclusion criteria, covering DSM-5 criteria for major psychiatric disorders. The subsection for PTSD was used: in accordance with instructions, if criteria for PTSD were not met, an assessment for adjustment disorder was undertaken. The SCID was chosen in preference to the World Health Organisation Composite International Diagnostic Interview (WHO-CIDI), which is longer,

and more complicated to administer and summate . Research has shown the SCID for PTSD to show consistent and positive results, and it is generally considered a 'gold standard' in the standardized assessment of PTSD for research purposes (163).

It was decided that comparative SCID assessment should be as close as possible to the one-month time point, which was associated with the greatest symptomatology in the pilot results.

Following an amendment, for the final few months of recruitment, consecutive women were asked at recruitment whether, as an optional additional aspect to their participation, they agreed to be contacted to arrange a semi-structured interview. If consent was gained, they were e-mailed following completion of the first online survey, asking whether a convenient time for the interview could be arranged. Although given the option of conducting the interview face-to-face, all women chose phone assessment for convenience.

The SCID was administered by a clinical psychologist or her trainee, who were blind to the results of the PDS. Where appropriate, questions related to the pregnancy loss, as they were for PDS. A summary of the assessment was, with the patient's permission, sent to the GP, highlighting whether they met screening criteria for PTSD.

4.11 Other diagnostic rating scales

Other self-report questionnaires completed by the participants were:

- State Trait Anxiety Inventory (STAI)
- Rumination Response Scale (RRS)
- Self-compassion scale – short form (SCS)
- Norbeck Social Support Questionnaire (NSSQ)

The STAI, RRS and SCS reflect some additional hypotheses that are not covered in this thesis, to assess for cognitive factors that may reduce or perpetuate levels of psychological distress. Clarifying the role of these factors could lead to a better understanding of how to best help these women using psychological treatments such as cognitive behavioural therapy (CBT). A further hypothesis of future interest is the impact of partner support, measured by the NSSQ.

4.12 Withdrawal

In every communication, the participant was reminded that their involvement was voluntary, and that they were free to withdraw. If volunteered, the reason behind withdrawal was recorded.

In addition, at the start of the online questionnaire, participants were asked to tick “yes” or “no” to the question “I consent to the use of my survey results in the assessment of the psychological impact of pregnancy complications in the context of this study and other related studies”.

4.13 Escalation of concerns

The information leaflets provided on enrolment to the study contained details of organisations providing support, and advised participants to consider reviewing their emotional symptoms with their GP.

If in any communication there was reason to be concerned that the participant may be at risk from the severity of their psychological symptoms (most frequently due to comments in free-text boxes at the end of the survey), they would be contacted by telephone (following an email to warn them to expect a call). We would discuss our concerns, their current emotional state, and advise them to seek further assessment (if not already receiving care). Permission would be gained to contact their GP. If we were not able to contact the participant directly, their GP would be contacted and asked to review them.

4.14 Ethical approval and revisions

Ethical approval of the study was granted by the National Research Ethics Service, South-West Exeter, reference 11/SW/0052. Approval was initially granted in June 2011, with a major amendment in 2015 to allow recruitment of women for SCID assessment.

4.15 Statistical analysis

All statistical analyses of results were performed using SPSS v24, R 3.4.3 and SAS v9.4.

Initial exploration of missingness (i.e. non-completion of questionnaires, or drop out over study duration) was performed, according to both background variables and psychological symptoms at first assessment

Methods are briefly described according to each aim. More detail regarding statistical methods can be found in Appendices 6 and 8.

1. *To establish the incidence of moderate and severe anxiety and depression in women following an early pregnancy loss, compared to those in a healthy early pregnancy*

   Based on dichotomous HADS scores (<11 mild, >=11 moderate to severe) the adjusted odds ratio of being depressed and anxious in the EPL group at M1 and the control group were

computed by conducting a logistic regression analysis, adjusting for age, IVF pregnancy, existing child(ren) and history of EPL.

2. *To establish how this changes over time in those who do not experience further losses*

   In order to investigate anxiety and depression over time, a longitudinal logistic regression was conducted. Random intercept and random slope logistic regression models were fitted including the covariates 'maternal age' (years), 'history of any EPL' (yes/no), 'IVF pregnancy' (yes/no), 'time' (months after EPL), 'previous children' (yes/no), and whether a further loss is experienced (yes/no, time-varying), and whether the patient is pregnant again when filling in the questionnaire (yes/no, time-varying).

3. *To establish the incidence of posttraumatic stress disorder (PTSD) in women following a loss, and how this changes over time*

   Sensitivity, specificity and concordance of caseness/non-caseness ratings for posttraumatic stress based on five potential scoring criteria on the PDS, and SCID-RV assessment for PTSD were calculated to determine the most reliable scoring method.

   According to the optimal scoring method, the caseness in women following an EPL was calculated, with additional exploration of the patterns of symptom clusters endorsed.

   Caseness in the control group reflects a diverse range of stressors, and was thus explored and described, but not used in a straightforward comparison to the group with EPL.

   Random intercept and random slope logistic regression models were used to assess the change in PTSD caseness over time.

4. *To compare reactions following an ectopic and miscarriage in women*

   Interaction between time and type of EPL were included in the random intercept and random slope logistic regression models described above.

5. *To assess for factors to predict the prevalence of anxiety, depression and PTSD (both factors antecedent to the pregnancy and encounter related factors)*

   To examine the relationship of proposed factors with HADS (subdivided into anxiety and depression) and PDS caseness, separate regression analysis was performed for each factor (initially for any outcome, and then for each outcome individually). 95% confidence intervals were used to quantify uncertainty.

6. *To establish the psychological morbidity in partners (anxiety, depression and PTSD) following a loss, and to compare this to morbidity in women*

   Proportions of partners meeting criteria for moderate-severe anxiety and depression, and PTSD, were calculated.

   Only those women whose partners were recruited were included in a comparative analysis. A random effects logistic regression model was fitted for each outcome, including an effect of time and of gender. Using this model, odds ratios for the risk of moderate-severe anxiety and depression, and PTSD, at one month were calculated.

4.16 Conclusions

We have discussed the methods for a prospective cohort study assessing the psychological impact of EPL. The results of the pilot study follow in Chapter 5, and of the main study in chapters 6-9.

Chapter 5: Anxiety, depression and posttraumatic stress in women one and three months after early pregnancy loss: a pilot, feasibility study

This study was published in BMJ open in November 2016 entitled "Posttraumatic stress, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study". This paper received widespread media coverage, with an overall Altmetric attention score of 561.

5.1 Introduction

This chapter outlines results of a pilot study into the psychological impact of miscarriage and ectopic pregnancy, for which recruitment took place between January 2012 and July 2013. 186 women, including a control group, were recruited from the early pregnancy unit of Hammersmith Hospital.

The primary aim was to demonstrate the feasibility, and determine the sample size, of a larger study.

5.2 Methods

Women were recruited from the early pregnancy unit of Hammersmith Hospital over a period of 18 months. Recruitment took place on the days on which the main researcher was available: women were approached consecutively.

Initially women with miscarriage or ectopic pregnancy were recruited. Following an amendment to the study protocol in December 2012, allowing a control group to be recruited, all women attending the unit were approached. Hospital records were checked to determine the outcome: if a viable pregnancy was confirmed, the participant formed part of the comparison group in early pregnancy.

Women were managed according to local protocols as detailed in section 4.4.1.

Background and clinical data was prospectively collected as detailed in section 4.6.

All women recruited to the study were sent an email link to a survey 1 month after the diagnosis of a loss, or after first visualisation of fetal heart activity in the control group. Women with a diagnosis of loss who completed the 1-month survey were also sent a survey at 3 and 9 months.

All questionnaires included the Hospital Anxiety and Depression Scale (HADS) and Posttraumatic stress Diagnostic Scale (PDS) as detailed in Section 4.9. Scoring for PDS was performed according to Foa's original instructions: at 1 month, results were broken down according to those that met the 'duration criterion' (i.e. reported symptoms lasting >= one month) and those that did not.

Sample size was determined in advance. To detect a 20% difference in the rate of moderate and severe anxiety cases between the loss group at M1 and controls, assuming 10% in controls and 30% in losses at 1 month, with significance level 0.05 and power 0.80, and assuming a 1:3 ratio of controls to cases, we needed 128 participants: 32 controls and 96 losses.

Statistical analyses were performed using SPSS V.20 and GraphPad Prism V.6. To compare differences in binary variables we used Fisher's exact test. We considered a statistically significant p value to be <0.05. 95% confidence intervals for rates of psychological morbidity were generated using the Wilson method.

5.3 Results

5.3.1 Participants

198 eligible women were approached.

12 women declined to take part. Of those who voluntarily provided a reason, the majority explained that they did not want to be reminded of the event. One woman explained that her faith led her to believe that the loss was 'in God's hands' – and that she felt that 'questioning' her feelings was wrong

186 women were recruited. 11 women subsequently actively withdrew their consent by email (none providing a reason for doing so), leaving a study group of 175 women.

Information relating to study recruits (excluding those who actively withdrew) is seen in table 5.1.

The groups (viable pregnancy, miscarriage and ectopic pregnancy) were similar in terms of age at presentation. Gestation at presentation was lower in the ectopic pregnancy group. Similar proportions of the control and miscarriage group had pregnancies conceived though in vitro fertilisation (IVF), but no women with an ectopic pregnancy had IVF.

Most ectopic pregnancies were diagnosed on the first ultrasound scan (18/24, 75%). Most miscarriages had an initially inconclusive ultrasound scan (57/95, 60%). Most ectopic pregnancies (21/24, 88%) were ultimately treated surgically. 50/95 (53%) of miscarriages were successfully managed expectantly or with outpatient medical management.

Figure 5.1 *Flowchart showing numbers invited to participate, reasons for withdrawal, and response rates to 1- and 3-month questionnaires*

(Reproduced, with permission, from (107))

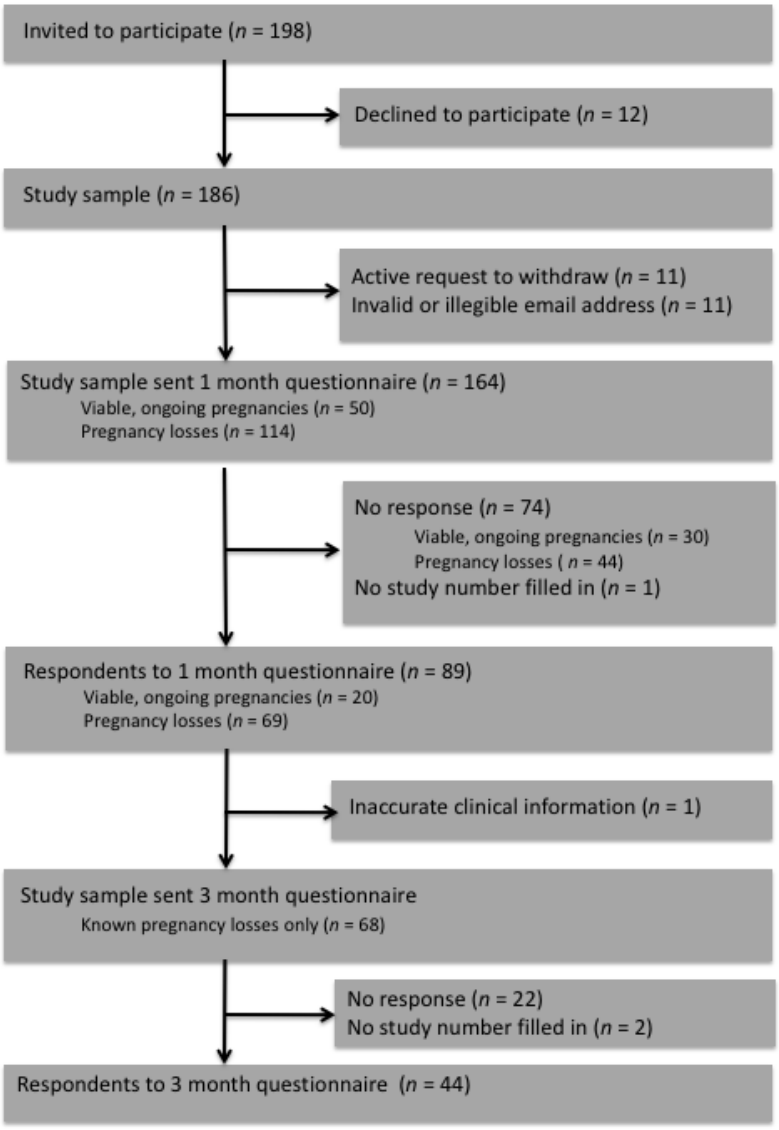


Table 5.1 *A comparison of response rates, demographic and background variables according to pregnancy outcome (viable pregnancy, miscarriage and ectopic)*

(Reproduced with permission from(107)

	Viable pregnancy	Miscarriage	Ectopic
Number recruited	58	104	24
Active withdrawal	2	9	0
Demographic and background characteristics			
Mean age *(years)*	34.1	33.0	34.9
Mean gestation at diagnosis *(weeks)*	10.3	9.1	7.1
IVF pregnancy (%)	4/56 (7%)	6/95 (6%)	0/24 (0%)
First ultrasound inconclusive (%)	13/56 (23%)	57/95 (60%)	6/24 (25%,)
Final Management (%)			
None required/Expectant		35 (37%)	1 (4%)
Medical management*	*n/a*	15 (16%,)	2 (8%)
Surgical management		43** (45%)	21*** (88%)
Lost to follow-up		2 (2%)	0 (0%)

* 'Medical management' describes use of misoprostol to treat miscarriage, or use of methotrexate to treat ectopic

** including: 1 molar pregnancy, 1 PPUL (investigated with laparoscopy and suction evacuation, ultimately diagnosed as failed intra-uterine pregnancy)

*** including 1 cervical ectopic (managed with suction evacuation)

IVF – In vitro fertilization; PPUL –Persistent Pregnancy of Unknown Location; n/a - not applicable

5.3.2 Responses to questionnaires

11 women provided illegible or invalid addresses, to which attempts to email bounced. Thus, a total of 164 women received questionnaires

At 1 month, 69/114 (61%) women with EPL responded. This includes one woman who, according to our latest medical records had been diagnosed with a viable pregnancy, but in her responses indicated that a miscarriage had taken place while abroad. This participant did not receive the subsequent questionnaires. In addition, one respondent (who self-reported a loss) did not comprehensively fill in her study number, and was excluded from the analysis.

The response rate for the control group was significantly lower: 20/50 (40%; p=0.02).

At 3 months, 44/68 (65%) of women responded. In addition, two respondents did not fill in their study number and were thus excluded.

Respondents were similar to non-respondents in terms of age, gestation, IVF pregnancy and management.

Table 5.2 *A comparison of response rates at one and three months in viable, miscarriage and ectopic pregnancy groups*

	Viable pregnancy	Miscarriage	Ectopic
Number recruited	58	104	24
Active withdrawal	2	9	0
Invalid email	6	5	0
Response rate at month 1	20/50 (40%)	53/90 (59%)	16/24 (67%)
Response rate at month 3	n/a	33/52 (63%)	11/16 (69%)
Proportion of respondents pregnant at 3 months	n/a	4/33 (12%)	2/11 (18%)

Only a minority of participants responded to the 9-month questionnaire (18/68 (26%) of those e-mailed). These results were therefore not analysed for the pilot study.

5.3.3 Anxiety and depression

At 1 month, 22/69 (32%) of women in the EPL group met criteria for moderate-to-severe anxiety, compared with 2/20 (10%) in the control group (p=0.04) (see Table 5.3). At three months, the proportion had declined to 9/44 (20%). The prevalence of moderate and severe depression symptoms was similar: 11/69 (16%) for women with EPL at 1 month, compared with 2/20 (10%) for controls, and 2/44 (5%) at 3 months.

The mean severity score was 7.8 for anxiety (SD 4.8) and 5.7 (SD 4.4) for depression in the EPL group at one month, compared to 6.6 (SD 3.0) for anxiety and 3.9 (SD 4.2) for depression in the control group. Mean scores declined at 3 months after losses: 6.8 (SD 4.2) for anxiety, and 4.2 for depression (SD 3.6).

The dropout between 1 and 3 months was non-significantly higher in those with moderate or severe anxiety and depression to those without: 11/22 (50%) dropout for those with moderate/ severe anxiety versus 13/46 (28%) with none/mild anxiety, 6/11 (55%) vs 18/57 (32%) respectively for depression.

5.3.4 Posttraumatic stress

At 1month, 28/69 (41%) women in the EPL group met PDS criteria for moderate or severe PTSD, excluding the criterion for the symptoms to have been present for 'more than one month'. At 3 months 17/44 (39%) met the criteria for probable moderate or severe PTSD. The mean severity score for all respondents with EPL was 15.3 (SD 9.9) at 1 month, and 11.6 (SD 9.5) at 3 months.

Re-experiencing was the most commonly endorsed symptom cluster at both 1 and 3 months. This was followed by avoidance and then hyperarousal at 1 month (reversed at 3 months). Of all questions asked, the most commonly endorsed statement was — 'feeling emotionally upset when you were reminded of the loss of your pregnancy' (40/69 (58%) women responding that this happened at least 2–4 times per week), followed by—'having upsetting thoughts or images about the loss of your pregnancy that came into your head when you did not want them' (30/69 (43%) women responding that this happened at least 2–4 times per week).

The reported impact of the symptoms on functioning is shown in table 5.4. The most commonly endorsed area was 'general satisfaction with life' and 'sex-life', both of which were affected in 70% of women.

The dropout rate between 1 and 3 months was non-significantly higher for those with probable moderate-to-severe PTSD at 1 month (8/19 (42%)), than for those without (16/49 (33%)).

In the control group, no women met the criteria for a diagnosis of probable PTSD for self-reported traumatic life events (not specifically probing for previous EPLs).

Table 5.3 *Proportion of respondents meeting criteria for anxiety and depression, according to HADS, and severity scores, in women with early pregnancy loss at 1- and 3- months, and a control group with viable pregnancy*

	Controls	**EPL - M1**	**EPL - M3**
Anxiety	2/20	22/69	9/44
(moderate & severe cases)	10%	32%	20%
(95% CI)	(3%-30%)	(22%-44%)	(11%-35%)
Mean anxiety score (/21)	6.6	7.8	6.8
(SD)	(3.0)	(4.8)	(4.2)
Depression	2/20	11/69	2/44
(moderate & severe cases)	10%	16%	5%
(95% CI)	(3%-30%)	(9%-26%)	(1%-15%)
Mean Depression score (/21)	3.9	5.7	4.2
(SD)	(4.2)	(4.4)	(3.5)

Abbreviations: HADS – Hospital Anxiety and Depression Scale; EPL – early pregnancy loss; CI Confidence Interval; M1 – month 1 questionnaire; M3 –month 3 questionnaire; SD - Standard Deviation

Table 5.4 *Proportion of respondents meeting criteria for posttraumatic stress disorder at 1 and 3 months (subdivided according to severity, including and excluding the duration criterion), individual symptom clusters within PDS endorsed, and areas of life symptoms reported to have impacted upon (Reproduced with permission from (107))*

	One month		Three months
	Including duration criterion**	Excluding duration criterion**	
Total proportion meeting PDS criteria (%, 95% CI)	22/69 (32%, 22%-44%)	31/69 (45%, 34%-57%)	19/44 (43%, 30%-58%)
Mild	3/69 (4%, 1%-12%)	3/69 (4%, 1%-12%)	2/44 (5%, 1%-15%)
Moderate	6/69 (9%, 4%-18%)	11/69 (16%, 9%-26%)	9/44 (20%, 11%-35%)
Moderate-Severe	10/69 (14%, 8%-25%)	14/69 (20%, 12%-31%)	7/44 (16%, 8%-29%)
Severe	3/69 (4%, 1%-12%)	3/69 (4%, 1%-12%)	1/44 (2%, 0.4%-12%)
Symptom clusters endorsed* (%, 95% CI)			
Re-experiencing	64/69 (93%, 84%-97%)		39/44 (89%, 76%-95%)
Avoidance	50/69 (72%, 61%-82%)		24/44 (55%, 40%-68%)
Hyper-arousal	39/69 (57%, 45%-68%)		27/44 (61%, 47%-74%)
Areas of life symptoms impacted on (%, 95% CI)			
Work	36/69 (52%, 41%-64%)		13/44 (30%, 18%-44%)
Household chores	22/69 (32%, 22%-44%)		9/44 (20%, 11%-35%)
Relationships with family	28/69 (41%, 30%-52%)		16/44 (36%, 24%-51%)
Relationships with friends	34/69 (49%, 38%-61%)		17/44 (39%, 26%-53%)
Fun and leisure activities	38/69 (55%, 43%-66%)		21/44 (48%, 34%-62%)
Sex life	48/69 (70%, 58%-79%)		21/44 (48%, 34%-62%)
General satisfaction with life	48/69 (70%, 58%-79%)		26/44 (59%, 44%-72%)
Overall level of functioning	35/69 (51%, 39%-62%)		20/44 (45%, 32%-60%)

*endorsed so as to meet criteria i.e. Re-experiencing – one or more positive responses to 5 questions, Avoidance – three or more positive responses to 7 questions, Hyper-arousal – two or more positive responses to 5 questions

** the duration criterion requires a respondent to verify that the symptoms they are reporting have been present for "more than one month". Where excluded, this requirement is disregarded

PTSD - post traumatic stress disorder; PDS – Posttraumatic diagnostic scale

5.4 Discussion

First and foremost, this pilot study demonstrated significant distress and psychological maladjustment in our cohort of women, with 39% of respondents meeting criteria for moderate or severe PTSD, and 20% for anxiety, after three months. Larger numbers of participants, as is the intention with the main study, to corroborate these findings, is justified.

We have demonstrated the feasibility of this study on a larger scale. Women were generally happy to be approached and take part. During recruitment, we received one complaint from a woman who felt it was inappropriate that she had been approached between receiving a diagnosis and discussing the onward management with a clinician. She felt that this had been insensitive timing, when she was acutely anxious and upset. As a study with the improvement in the emotional care of women as its central aim, we attached great significance to this feedback. As a result, from then on, we suggested that the clinician concluding the initial encounter would sensitively enquire as to whether they would be happy to talk to a member of the team conducting this research. All women who entered their study number at the start of the online questionnaire completed all remaining questions, providing reassurance that the required time commitment was appropriate.

There was a lower response rate than in other published studies: 61% for the first questionnaire. Our consecutive recruitment of women from the early pregnancy unit, and the high rate of consent to participate, is likely to explain this. Engelhard's study relied on advertisements placed in magazines, which will select a motivated group bound to be associated with a higher response rate (4). In Cumming's study, only 40% of those approached for the study returned their consent form, compared to 94% in our own(100). This reflects the fact that Cumming required women to sign and return a consent form by post after the initial approach, where as our participants could consent on the same day (and confirm later by email – which required a response in order to opt out). The default position of those disinterested or not wishing to be involved was thus to ignore the emails – both confirming their involvement, and then later containing the link to the questionnaire. Overall, the non-response rate is a reasonable reflection of the methodology, which will enable better categorization of non-respondents, and potentially secure better overall involvement.

The non-response rate raises a concern of a potential ascertainment bias, artificially inflating rates of psychopathology. However, although it is possible that women with a more significant emotional response were more likely to respond, it is also possible that these women avoid engagement with a process that makes them confront the event. The observed increased drop out of those with higher PTSD, anxiety and depression levels at the first assessment may support the hypothesis of an affected group of women who did not want to be reminded of their feelings.

In the main study, we will look at whether the non-respondents, and those who drop out after the first or second questionnaire, have different baseline characteristics e.g. in terms of parity. We will thus prospectively collect data on their past obstetric history. We will also send up to two reminder emails if the participant has not responded within one week, with the aim to improve response rates.

Respondents in our control group who did not suffer an EPL in the index pregnancy had a high rate of previous miscarriage (45% of respondents). This was due to the recruitment from the early pregnancy unit, where women with a history of EPL often attend for reassurance. It is also possible that women with a past pregnancy loss were more likely to invest time in the questionnaire. Thus, whilst our control group is a useful comparator, we are likely to be underestimating overall levels of distress related to early pregnancy loss if relying on it as a normative baseline. In the main study, the control group will be recruited from the antenatal clinics (where women are routinely reviewed), and, with larger numbers, we would aim to subanalyse the group of women without a previous loss.

We felt it appropriate to disregard the 'duration criterion' in the PDS, which stipulates that symptoms must be present for 'more than 1 month', at the 1-month assessment. On occasion this assessment was sent and completed at 28 or 29 days: even if PTSD symptoms had commenced at diagnosis, it is not clear how we could expect a participant to respond in this scenario. Additionally the 'traumatic event' as perceived by the respondent, may have preceded (e.g. at the onset of bleeding) or followed (e.g. at the time of management) the diagnosis by up to two weeks. The importance of the duration criterion in the accurate screening for PTSD, and thus appropriateness of this decision, will be assessed in Chapter 8.

The calculated prevalence of probable PTSD is higher than previously reported by Engelhard. This is likely to reflect the different way in which the PDS scale was scored. We scored according to Foa's original recommendation – where a symptom was considered endorsed if it occurs 'once a week or less/once in a while' – whereas Engelhard required a symptom to occur '2-4 times a week/half the time'. As part of the main study, we now intend to validate the results of the self-report surveys using a clinician administered instrument, which should indicate which scoring is more accurate in this population.

5.5 Conclusions

The pilot study has indicated high levels of psychopathology, particularly PTSD. It has also confirmed the feasibility and acceptability of the study.

Following this pilot, the following changes to the protocol were made, in advance of commencing recruitment for the main study:

1. Reminder emails were sent if the participant had not filled in the survey within a week of it being sent. This aimed to increase response rate
2. In the pilot study, the participant was only sent the 3- and 9-month questionnaires if they had filled in the initial questionnaire. For the main study, we sent every participant an invitation to every part, unless they requested to withdraw. Again, this aimed to increase response rate. It also aimed to include those who might have wished to avoid the initial surveys, but who wanted to participate later
3. In view of the low response rate, it was felt important to better categorise non-respondents. Thus data was prospectively collected on past obstetric history at enrollment
4. Based on higher than expected levels of PTSD, a decision was made that validation of the results of the PDS was required, by comparison to a clinician administered instrument
5. Due to high rates of previous EPL in the control group recruited from the early pregnancy unit, a decision was made to recruit the comparison group with viable early pregnancy from the antenatal clinic

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 PTSD between women with assisted reproduction and those without (chosen as an uncommon potential risk factor of interest) with power 0.80 and significance level 0.05, and assuming a frequency of 1:7 women having assisted reproduction.

Chapter 6: Anxiety, depression and posttraumatic stress disorder in women following early pregnancy loss: a prospective, multicentre, cohort study

6.1 Introduction

Systematic review reveals that the majority of studies relating to the psychological impact of EPL are outdated, and do not assess reactions after ectopic pregnancy. Research on posttraumatic stress disorder (PTSD) is also minimal.

Thus, the central aim of our novel research was to provide up to date, large-scale data on anxiety, depression and PTSD in women after all types of early pregnancy loss, and the resolution of these conditions over time.

This chapter presents results from 737 women after loss and 171 women in healthy pregnancy who were recruited between 2013 and 2016.

6.2 Methods

This was a prospective cohort study. Consecutive recruitment took place via the Early Pregnancy Units (EPUs) and antenatal clinics (ANCs) at three central London hospitals (Hammersmith, St Mary's, and Chelsea and Westminster Hospitals). The target sample size of 721 women with EPL was based on data from our pilot study, assuming a 61% response rate, as detailed in section 5.5.

Clinical information was prospectively collected as detailed in section 4.6.

All women experiencing losses were sent a link to a survey by email one (M1), three (M3) and nine months (M9) after diagnosis of EPL. Women in the control group with viable pregnancies were sent the questionnaire after confirmation of viability during routine dating scan (usually at 11-14 weeks). A lack of response to email requests for participation prompted up to two reminder emails at weekly intervals.

The surveys asked background information, and contained the HADS and PDS, as discussed in section 4.9.

6.3 Results: participants, response rates and timing

6.3.1 Participants

Overall, 1,396 women and controls were approached for participation between 13 November 2013 and 15 March 2016 (28 months).

Table 6.1 and Figure 6.1 demonstrate numbers approached, ineligible, and that declined (and their reasons for doing so, if volunteered).

Table 6.1 *Number of individuals approached, recruited, and reasons for non-recruitment (women with early pregnancy loss, and control women in healthy pregnancy, all sites)*

	Women with EPL	Controls
Approached	1201	195
Recruited % of all approached	737 (61%)	171 (87%)
Declined % of all eligible	361 (33%)	16 (9%)
Ineligible % of all approached	103 (9%)	8 (4%)
Reason (if volunteered) for declining participation:		
No reason given	177	8
Requested time to consider, but consent form not returned by post	107	5
Unplanned pregnancy	14	0
Doesn't want to be reminded/too upsetting	34	0
Time commitment	14	2
No access to email	15	0
Felt 'tempting fate'	n/a	1
Reason ineligible:		
Insufficient English	84	8
Already in study from previous loss	18	0
No mental capacity	1	0

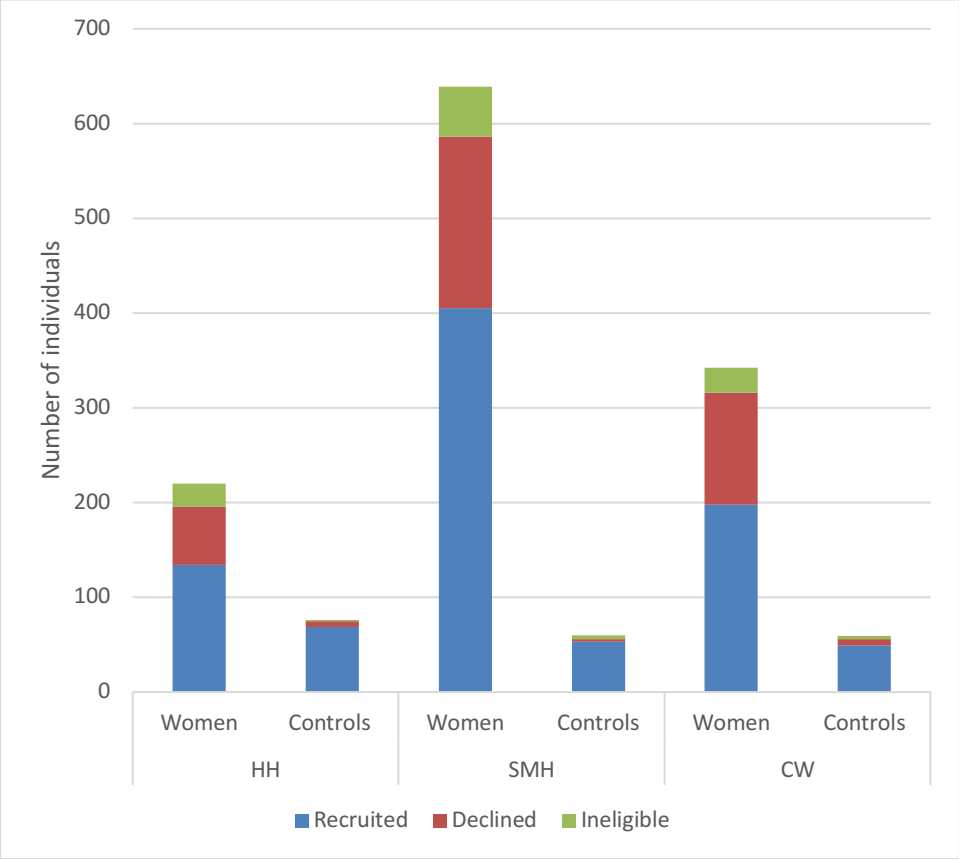
Abbreviations: EPL – early pregnancy loss; n/a – not applicable

8% of those approached were found to be ineligible, all but one of which was due to insufficient grasp of the English language. One patient was suffering from an acute exacerbation of bipolar disorder, was sectioned under the Mental Health Act, and deemed not to have capacity to consent.

47% of women who declined participation did not provide a reason for doing so. A further 28% requested time to consider, but never returned the consent form. The most common reason given, cited by 9% women, was to avoid being reminded of the loss by receipt of the questionnaire.

Overall, of those approached, 61% women with EPL, and 87% of women with viable pregnancies (control group) were recruited.

Figure 6.1 *Bar chart of numbers recruited, declined and ineligible according to group (women and controls) and hospital site*



Abbreviations: HH – Hammersmith Hospital; SMH – St Mary's Hospital; CW – Chelsea and Westminster Hospital

Significantly less controls than women with EPL declined participation: 9% versus 34% ($p<0.0001$).

The proportion of those approached who were ineligible, declined or recruited did not vary significantly between sites for women with EPL or controls (further detail can be found in Appendix 5, Tables A5.1 and A5.2).

Age and clinical details

Women with EPL were of mean age 2.3 years older than the control group, in keeping with increased susceptibility to miscarriage with age. The EPL and control groups were similar in terms of proportion with past losses, with psychiatric history, and with pregnancy conceived through IVF, as can be seen in Table 6.2. 47% of the control group had had a scan earlier in the pregnancy, prior to the routine dating scan.

Additional clinical information for those with EPL is recorded in Table 6.3. The mean gestation at diagnosis of loss was 65.4 days (SD 20.0, range 2-138). Gestation was calculated from the date of last menstrual period (LMP) if known (or, for IVF, the date of embryo transfer (assumed to be day 19)). In many cases the patient was already pregnant during their reported 'LMP', with bleeding representing

early pregnancy complications rather than menstruation, but did not identify themselves as such, thus explaining the lower end of the range of gestations (range from 2 days). 43 women (7%) were >13 week's gestation from LMP at time of loss. Women with miscarriage formed the biggest group of participants (73%), followed by ectopic pregnancies (16%). All women with molar pregnancies had intrauterine pregnancies. Most women with PUL were discharged after a second blood test, and asked to repeat a urine pregnancy test in two weeks ('resolved PUL'). Of five cases of persistent PUL (in which further investigation was required after two blood tests, but the location of the pregnancy was never confirmed), only one required active management with two doses of methotrexate.

Table 6.2 *Age and clinical details of women with early pregnancy loss and viable pregnancies (controls)*

	Women with EPL (n=737)	**Controls (n=171)**
Mean Age *(years)*	34.4 (SD 5.4) Range 19-54	32.1 (SD 4.9) Range 19-49
Past obstetric history:		
Miscarriage *Any* *More than one* *Unknown*	 231/737 (31%) 102/737 (14%) 29/737 (4%)	 42/171 (25%) 12/171 (8%)
Ectopic *Any* *More than one* *Unknown*	 31/737 (4%) 5/737 (1%) 31/737(4%)	 2/171 (1%) 1/171 (1%)
Live births *Any* *More than one* *Unknown*	 316/737 (43%) 106/737 (14%) 24/737 (3%)	 52/119 (30%) 9/117 (5%)
Index pregnancy:		
Mean gestation at recruitment *(days)* *(controls only)*	n/a	70.1 (SD 22.6) Range 30-161
IVF pregnancy	50/737 (7%)	12/171 (7%)
Any early pregnancy issues/scans *(controls only)*	n/a	81/171 (47%)
Month 1 questionnaire data:		
Past psychiatric disorder	12/88 (14%)	87/509 (17%)
Current psychiatric disorder	2/88 (2%)	22/509 (4%)
Desire for pregnancy (Likert scale - 1 = not at all, 4 = very much so)	3.5 (0.9)	3.7 (0.6)

Abbreviations: EPL – early pregnancy loss; IVF – in vitro fertilization; n/a - not applicable

Table 6.3 *Clinical details of all recruited women with early pregnancy losses*

		Mean (SD)/ Proportion (%)
Gestation at diagnosis of loss *(days)**		Mean 65.4 (SD 20.0) Range 2-138
Reason for referral	*Pain/bleeding* *Incidental finding on scan* *Clear passage of pregnancy* *Other *** *No clear reason documented*	522/737 (71%) 95/737 (13%) 6/737 (1%) 111/737 (15%) 3/737 (0%)
Final diagnosis	*Miscarriage* *Ectopic pregnancy* *Failed PUL* *Persistent PUL* *Molar pregnancy*	537/737 (73%) 116/737 (16%) 58/737 (8%) 5/737 (1%) 21/737 (3%)
Fetal heart pulsations previously seen on scan (miscarriage group only)	*Yes* *Yes with concerns* † *No* *Unknown*	125/558 (22%) 7/558 (1%) 422/558 (76%) 4/558 (1%)
Final management	*No active intervention necessary* *Medical management of miscarriage* *Surgical management of miscarriage* *Methotrexate* *Salpingectomy* *Salpingotomy* *Other surgical intervention* *Lost to follow-up*	244/737 (33%) 51/737 (7%) 330/737 (45%) 22/737 (3%) 66/737 (8%) 5/737 (1%) 7/737 (1%) 12/737 (2%)
Emergency surgical management‡		124/409 (30%)
Emergency admission		110/737 (14%)
Blood transfusion		18/737 (2%)

Abbreviations: IVF – in vitro fertilization; PUL – pregnancy of unknown location

* For molar pregnancies, date of diagnosis considered to be date of diagnosis of non-viability (as histopathological diagnosis of molar pregnancy often delayed).

** Including: A reduction in pregnancy symptoms, medical reasons (e.g. exposure to other illness or medication in early pregnancy), spontaneous rupture of membranes, or referral from termination clinic

† concerns include bradycardia, or a smaller than expected for gestation fetus. These concerns are routinely voiced to the patient to manage their expectations, and a repeat scan booked

‡ Surgical management considered 'emergency' rather than 'elective' if patient admitted as an inpatient for a procedure to be completed as soon as possible, due to preceding, or future risk of, significant haemorrhage

6.3.2 Responses

Data inconsistencies and duplicate responses

Pregnancy status

In part one, three respondents (CF152, CF195, SF254) stated that they were 'still pregnant' when, according to their free text responses, and according to our data, they had lost the pregnancy. Further analysis demonstrated that this reflected the way the question was worded: some women who were still undergoing follow-up (e.g. after medical management of ectopic), and thus still had a positive pregnancy test, classed themselves as 'still pregnant'. Most of their response data could still be analysed. However, as they were directed towards the PDS that was not specific to a loss, the PDS responses were removed. These respondents were also not asked whether they were worried for their own wellbeing, or how long before they returned to normal activities.

Duplicate responses

If there were duplicate responses attributed to a study number, often the first response was abandoned early in the questionnaire: the more complete response was thus used (23 cases over all questionnaires). Where two complete responses were received, the response closest to the time it was requested was kept (6 cases).

Consent

All respondents ticked 'yes' to the initial statement consenting to the use of the survey results in the study, and thus none were removed on this basis.

Response Rates

Table 6.4 demonstrates response rates for each of women with EPL and controls.

A minority of participants actively withdrew: passive non-response was overwhelmingly the cause for drop-out. Those that actively withdrew did not generally provide, and were not asked for, a reason for doing so. Five patients who volunteered a reason by email said that the reminders were upsetting. The control group were significantly less likely to respond than women after loss ($p = 0.001$ (Fisher's Exact test)).

Table 6.4 *Response, non-response and withdrawal in women with early pregnancy loss and controls in viable pregnancies*

	Women with EPL	Controls
Recruited	737	171
Subsequent miscarriage*		1 (1%)
Unable to confirm viability*		2 (1%)
E-mail address invalid	8 (1%)	4 (2%)
Active withdrawal before M1 completed	11 (1%)	5 (3%)
M1 respondents (%)	496 (67%)	88 (51%)
Passive non-response to M1	222 (30%)	71 (42%)
E-mail address invalid	8 (1%)	
Active withdrawal before M3 completed	19 (3%)	
M3 respondents (%)	426 (58%)	
Passive non-response to M3	284 (39%)	
E-mail address invalid	12 (2%)	
Active withdrawal before M9 completed	27 (4%)	
M9 respondents (%)	343 (47%)	
Passive non-response to M9	355 (48%)	

Abbreviations: M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire

*In the control group, the questionnaire was only sent after viability on the first routine scan (aimed to be performed between 11 and 13+6 weeks) was confirmed. In one case a miscarriage was confirmed after recruitment, and in two cases we could not identify the results of this scan.

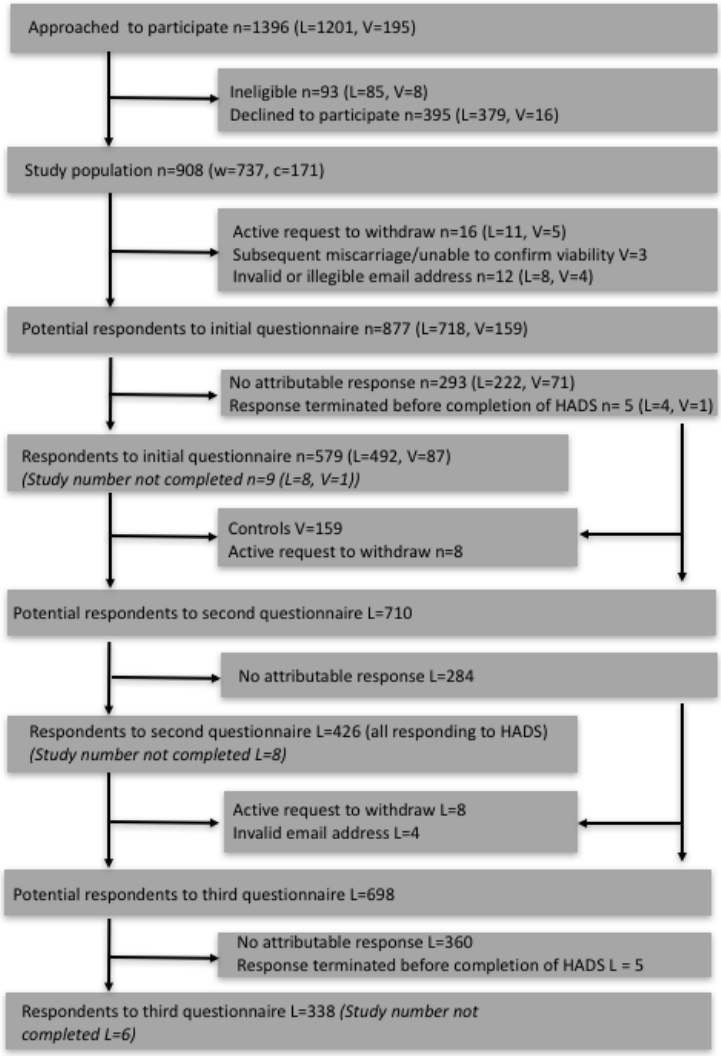
For subdivision by site of recruitment, see Appendix 5, Tables A5.3-4. Women with EPL recruited from CW were significantly more likely to respond at M1 than those from SMH (74% versus 65%, (p=0.04)), and at M3 than those from SMH or HH (66% versus 54% and 55% respectively). There was no significant difference between response rates according to site of recruitment at M9, or between HH and SMH at any time point. There were no statistically significant differences in response rates according to site of recruitment for controls.

6.3.3 Missing responses

In view of the high non-response and dropout rate, it was important to explore patterns of missingness. For this, we defined response as completion of the first psychometric questionnaire (HADS).

492/737 (67%) women responded to M1, 426/737 (58%) to M3 and 338/737 (46%) to M9. Overall, of women with EPL, 303/737 (41%) responded at all three time points, and 530/737 (72%) of the group responded at least once. The biggest drop out was between M3 and M9. Patterns of responses can be seen in Table 6.5.

Figure 6.2 *Flowchart of recruitment and response rates for women and controls*



Abbreviations: HADS – Hospital Anxiety and Depression Scale; n - total number; L – women with loss; V – women with viable pregnancy (control group)

Table 6.5 *Missing data pattern for women with early pregnancy loss*

Month 1	Month 3	Month 9	N	%
Completers (all parts)				
O	O	O	303	41%
Drop-out over study duration				
O	O	M	92	12%
O	M	M	79	11%
M	M	M	207	28%
Intermittent response				
O	M	O	18	2%
M	M	O	7	1%
M	O	O	10	1%
M	O	M	21	3%

Abbreviations: M – missing observation; O – available observation

Missing responses according to baseline data and pregnancy status at 3 months

We investigated thoroughly for any patterns of missingness based on background data and pregnancy status at M3 (see Tables 6.6 and 6.7). Of women with EPL, non-respondents, those who last responded at M1 or M3, and those who last responded at M9, were similar in terms of age and past obstetric history.

Women who ceased participation after the M1/M3 did not differ from those who completed M9 in responses to questions relating to desire for the pregnancy, distress about loss, satisfaction with the healthcare provided, and time taken to conceive. There was some difference between the proportion of women who continued responding to month nine, and who did not, in terms of education (proportion with post-graduate degree 18% of those with last response at M1/M3, and 29% of those with last response at month 9), and in terms of annual income (16% and 29% respectively earning more than £100 000 per year).

At M3, 38/313 (12%) of those who subsequently responded at M9 were pregnant, versus 20/112 (18%) of those who did not respond at nine months.

Table 6.6 *Baseline data, M1 responses, and M3 responses regarding pregnancy status, according to response status (non-responders, versus last information at M1/M3, versus last information at M9) in women with EPL*

	No response (n=207)		**Last info at M1/M3 (n=192)**		**Last info at M9 (n=338)**	
	Mean (SD) or n (%)	Missing	Mean (SD) or n (%)	Missing	Mean (SD) or n (%)	Missing
Background demographic and clinical data						
Type of loss:						
Miscarriage (inc molar)	147 (71%)	0	148 (77%)	0	263 (79%)	0
Ectopic	36 (17%)	0	27 (14%)	0	53 (16%)	0
Resolved PUL	24 (12%)	0	17 (9%)	0	22 (7%)	0
Age	33 (6)	0	34 (5)	0	35(5)	0
IVF pregnancy	8 (4%)	0	16 (8%)	1 (1%)	26 (8%)	0
Past miscarriage or ectopic (any/none)	62 (34%)	24 (12%)	71 (37%)	1 (1%)	120 (36%)	0
Proportion with children	92 (50%)	23 (11%)	85 (45%)	1 (1%)	139 (41%)	0
M1 responses						
Desire for pregnancy *Likert scale 1 – not at all, 4 – very much*	n/a		3.7 (0.6)	21 (11%)	3.7 (0.6)	13 (4%)

Distress about loss *Likert scale 1 – not at all, 5 – extremely*	n/a		4.1 (1.0)	21 (11%)	3.9 (1.0)	13 (4%)
Satisfaction with healthcare *Likert scale 1-not at all, 5 – very, excellent*	n/a		4.1 (0.9)	27 (14%)	4.2 (0.9)	17 (5%)
Highest level of education A-levels or lower University degree Post-graduate degree/doctorate	n/a		49 (28%) 93 (54%) 31 (18%)	19 (10%)	49 (15%) 182 (56%) 95 (29%)	12 (4%)
Annual income <£25000 £25-50 000 £50-100 000 >£100 000	n/a		49 (28%) 48 (28%) 48 (28%) 28 (16%)	19 (10%)	48 (15%) 64 (20%) 118 (36%) 96 (29%)	12 (4%)
Psychiatric disorder No Yes currently (< 6 months) Yes in past (> 6 months)	n/a		141 (82%) 8 (5%) 24 (14%)	19 (10%)	249 (77%) 13 (4%) 61 (19%)	15 (4%)
Time taken to conceive < 3 months/unplanned 3-12 months > 12 months	n/a		108 (63%) 32 (19%) 31 (18%)	21 (11%)	206 (63%) 68 (21%) 51 (16%)	13 (4%)
Previous termination of pregnancy	n/a*		59 (31%)	1 (1%)	72 (21%)	0 (0%)
M3 responses						
Trying to conceive at M3 Pregnant Further EPL Not trying to conceive Trying to conceive	n/a		20 (18%) 3 (3%) 57 (51%) 32 (29%)	80 (42%)	38 (12%) 7 (2%) 132 (42%) 136 (43%)	25 (7%)

Abbreviations: EPL – Early Pregnancy Loss; IVF – in vitro fertilization; M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire; PUL - pregnancy of unknown location

* prospectively collected data with respect to past terminations was found to differ significantly to that reported in anonymous questionnaires: prospectively collected data was thus discarded

Missing responses according to future pregnancies booked at the same hospital

We further investigated the impact of pregnancy during follow-up on response rates. For this, we could only analyse the subset of patients who had future pregnancy records at the time of analysis (August 2017). Those without records could not be assumed not to have been pregnant and have received treatment or booked elsewhere.

Of those with a healthy pregnancy by M9, 112/200 (56%) responded, compared to 56/102 (55%) who had not had a healthy pregnancy at M9. These very similar proportions go against a hypothesis of subsequent disinterest or avoidance when healthily pregnant.

Of those who had had a further EPL by M9, 44/70 (63%) responded, compared to 112/232 (48%) who had not had a further EPL. This may suggest a slightly higher involvement in those with subsequent losses, but these differences are not statistically significant (p=0.13, Fisher's Exact).

Missing responses according to psychopathology

One could hypothesise both that cases with high and low psychological morbidity would be more likely to drop out. The former due to lack of energy or active avoidance of reminders of the event, and the latter because of lack of interest.

Drop out according to anxiety, depression and PTSD scores and caseness at first assessment can be seen in Table 6.7.

Of those women with EPL with moderate/severe depression at M1, 55% (29/53) completed M9, compared to 67% (296/443) of those with no/mild depression (p = 0.09, Fisher's exact). Of those with moderate/severe anxiety at M1, 62% (74/120) completed M9, compared to 67% (251/376) of those with no/mild anxiety (p=0.3, Fisher's exact). Of those women with EPL meeting criteria for PTSD at M1, 66% (92/139) completed M9, compared to 65% (225/348) not meeting criteria (p=0.83, Fisher's exact).

Of those women with EPL with moderate/severe depression at M1, 81% (43/53) completed M3, compared to 80% (356/443) of those with no/mild depression (p=1, Fisher's exact). Of those with moderate/severe anxiety at M1, 86% (103/120) completed M3, compared to 80% (301/376) of those with no/mild anxiety (p=0.18, Fisher's exact). Of those with PTSD at M1, 82% (114/139) completed M3, compared to 78% (273/348) not meeting criteria (p=0.45, Fisher's exact.

Overall, there does not appear to be any evidence to suggest over-representation of those most affected at later time points with evidence, if anything, pointing towards those most affected by depression or anxiety being more likely to drop out by M9.

Table 6.7 *Depression, anxiety and posttraumatic stress scores and caseness at month 1 for EPL patients with last information at month 1, month 3, and month 9*

	Women with EPL		
M1 results	**Last info M1 (n=79)**	**Last info M3 (n=113)**	**Last info M9 (n=338)**
Missing data (n) - HADS	n/a	21 (19%)	17 (5%)
HADS depression score (mean (SD))	4.7 (4.5)	5.2 (4.8)	4.2 (4.2)
HADS depression score ≥ 11 (number (%))	10 (13%)	14 (15%)	29 (9%)
HADS anxiety score (mean (SD))	7.1 (4.4)	7.8 (4.7)	6.6 (4.5)
HADS anxiety score ≥ 11 (number (%))	17 (22%)	29 (32%)	73 (23%)
Missing data (n) - PDS	2 (3%)	22 (19%)	19 (6%)
PDS score (mean (SD))	12.2 (10.9)	14.4 (11.0)	12.9 (10.3)
PDS moderate/severe cases (number (%))	20 (26%)	27 (30%)	92 (29%)

Abbreviations: HADS – Hospital Anxiety and Depression Scale; M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire; PDS – Posttraumatic stress diagnostic scale

Missing responses in control group

Respondents in the control group with viable pregnancies were similar to non-respondents in terms of age, gestation at recruitment, IVF in the index pregnancy, past history of losses, and number of existing children (see Table 6.8)

Table 6.8 *Comparison of respondents versus non-respondents within control group*

	Non-Respondents (n=81)	**Respondents (n=87)**
Mean Age *(years)*	31.2	32.9
Miscarriage		
Any	23/81 (28%)	18/87 (21%)
More than one	6/81 (7%)	6/87 (7%)
Ectopic pregnancy	0/87	1/87 (1%)
Live births		
Any	27/81 (33%)	22/87 (25%)
More than one	4/81 (5%)	3/87 (3%)
Mean gestation at recruitment *(days)*	66.8	73.8
IVF pregnancy	4/81 (5%)	7/87 (8%)
Any early pregnancy issues/scans	44/81 (54%)	36/87 (41%)

Abbreviations: IVF – in vitro fertilization

6.3.4 Response timing

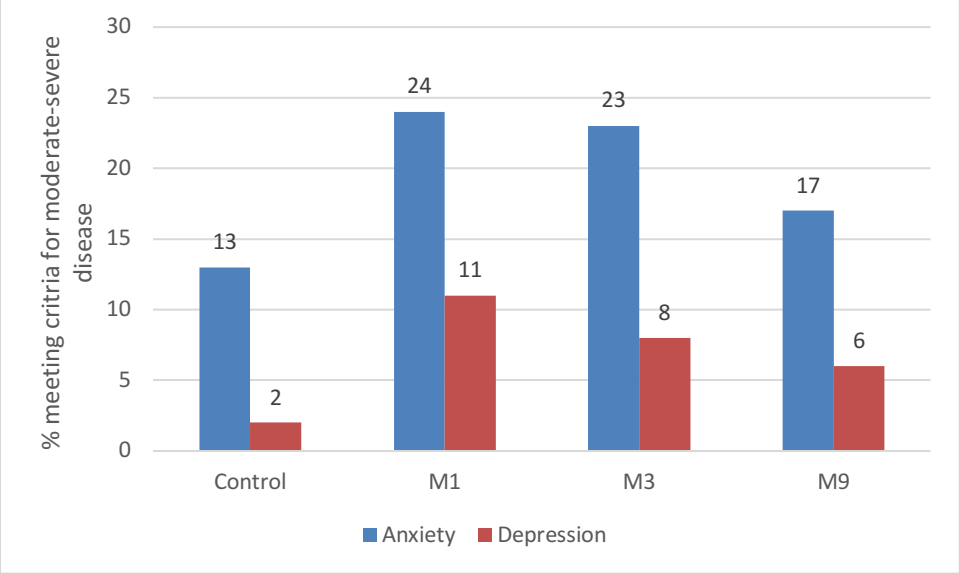
Responses to the first questionnaire (M1) (sent 30 days after diagnosis of loss) were a mean of 40 days after diagnosis (SD 12, IQR 32-45), to the second questionnaire (M3) (sent 90 days after loss) were a mean of 101 days after diagnosis (SD 19, IQR 91 - 105), and to the final questionnaire (M9) (sent 270 days after diagnosis of loss) were a mean of 277 days after diagnosis (SD 15, IQR 271-285).

6.4 Results: anxiety and depression

Histograms of the HADS anxiety and depression scores were made at each time point, and can be seen in Appendix 6, Figure A6.1. These show skewed distributions for both anxiety and depression: the frequencies of each score decreased as scores increased. By comparison, the control group also has a skewed distribution, but with less extreme scores.

Proportions of women meeting criteria for anxiety and depression are shown in Figure 6.3. Results broken down by type of loss (miscarriage and ectopic pregnancy) are shown in Table 6.9.

Figure 6.3 *Proportions of women meeting criteria for moderate or severe anxiety and depression (based on the Hospital Anxiety and Depression Scale) one, three and nine months after a loss, and in the control group in healthy pregnancy*



Abbreviations: M1 – month 1 questionnaire, M3 – month 3 questionnaire, M9 – month 9 questionnaire

Table 6.9 *The number of available observations in every group at each time point, the mean and standard deviation of anxiety and depression scores and the number and percentage of patients with moderate to severe anxiety and depression symptoms*

	Month 1		Month 3		Month 9	
	N	**Result**	**N**	**Result**	**N**	**Result**
Anxiety score (mean, SD)						
Controls	87	6.0 (3.4)	-	-	-	-
Miscarriage	366	7.1 (4.5)	315	6.9 (4.5)	249	6.3 (4.6)
Ectopic pregnancy	75	6.3 (4.5)	68	7.5 (4.7)	53	6.6 (4.1)
PUL	35	5.5 (4.2)	29	5.2 (4.1)	22	3.9 (2.9)
Molar pregnancy	16	7.1 (5.4)	14	6.5 (3.9)	14	7.2 (5.0)
Moderate/severe anxiety (n, %)						
Controls	87	11 (12.6%)	-	-	-	-
Miscarriage	366	93 (25.4%)	315	70 (22.2%)	249	43 (17.3%)
Ectopic pregnancy	75	16 (21.3%)	68	21 (30.9%)	53	12 (22.6%)
PUL	35	6 (17.1%)	29	3 (10.3%)	22	1 (4.5%)
Molar pregnancy	16	4 (25.0%)	14	2 (14.3%)	14	2 (14.3%)
Depression score (mean, SD)						
Controls	87	3.5 (2.6)	-	-	-	-
Miscarriage	366	4.7 (4.5)	315	4.1 (4.0)	249	3.6 (3.8)
Ectopic pregnancy	75	3.7 (4.2)	68	4.8 (4.2)	53	3.8 (4.2)
PUL	35	3.5 (3.6)	29	2.9 (3.4)	22	2.1 (2.5)
Molar pregnancy	16	4.2 (4.3)	14	3.1 (2.8)	14	3.6 (4.4)
Moderate/severe depression (n, %)						
Controls	87	2 (2.3%)	-	-	-	-
Miscarriage	366	45 (12.3%)	315	23 (7.3%)	249	13 (5.2%)
Ectopic pregnancy	75	5 (6.7%)	68	8 (11.8%)	53	6 (11.3%)
PUL	35	1 (2.9%)	29	1 (3.4%)	22	0 (0%)
Molar pregnancy	16	2 (12.5%)	14	0 (0%)	14	2 (14.3%)

Abbreviations: N – number; PUL- pregnancy of unknown location; SD – standard deviation

6.4.1 Anxiety

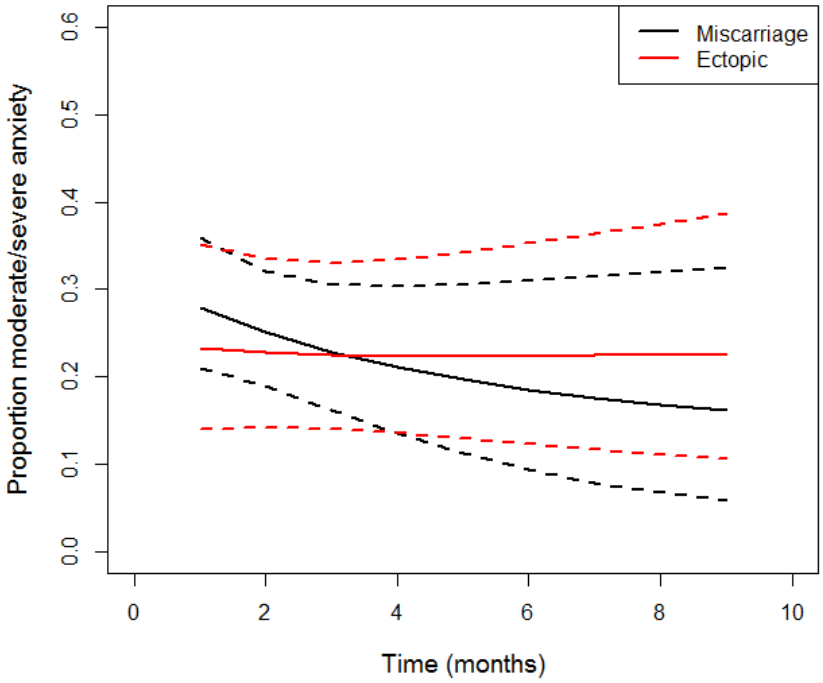
Of the EPL group as a whole, 24% (119/492) met criteria for moderate or severe anxiety (i.e. a score of >=11) from the first questionnaire, 23% (96/426) at the second questionnaire, and 17% (58/338) at the third questionnaire.

After fitting random intercept and random slope logistic regression models (with covariates: type of EPL, maternal age, history of EPL, IVF, time since loss, existing children, further loss, further pregnancy), we found that, for an average individual, there is a decrease in the probability of experiencing moderate to severe anxiety over time by 31% each month (OR 0.69, 95% CI 0.50-0.94). The decline is 35% each month (OR 0.65 (95% CI 0.44-0.94) after miscarriage and 20% each month (OR 0.80, 95% CI

0.59-1.10) after ectopic pregnancy. The decrease may be steeper after miscarriage than after ectopic pregnancy (p value for the interaction 0.14) (see Appendix 6 for more details of statistical methods).

A random intercept variance of 6.10 indicates that there are substantial differences between patients in terms of the odds of suffering from anxiety after taking into account the co-variates. However, the small random slope variance (0.09) indicates there are only slight differences in the evolution over time (after taking into account co-variates).

Figure 6.4 *Average evolution for anxiety over time for patients with miscarriage and ectopic pregnancy based on a mixed effects model containing an interaction effect between the type of EPL and time and 95% confidence intervals (dotted lines).*
We assume no further loss or pregnancy during follow-up, and average values for maternal age (35 years), history of any EPL (0.407), IVF pregnancy (0.082) and children (0.443).



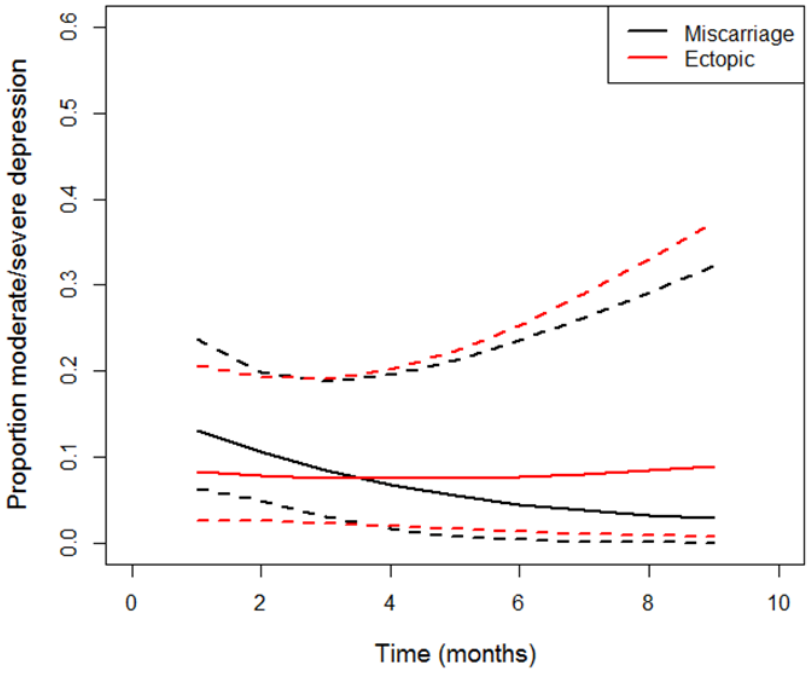
6.4.2 Depression

Prevalence of moderate or severe depression according to HADS was lower than that of anxiety at all three time points: 53/492 (11%) at M1, 32/426 (8%) at M3 and 21/338 (6%) at M9. This compared to 2/87 (2%) of the control group. Women following ectopic pregnancy had similar caseness and severity scores as those following miscarriage (see Table 6.10).

With respect to depression over time, in the average individual the odds of being depressed decreased by 13% each month (OR 0.87, 95% CI 0.53-1.44). The decline was 35% per month (OR=0.65, 95% CI 0.32-1.34) after miscarriage and 4% per month (OR=0.96, 95% CI 0.57-1.61) after ectopic. Again, the

decrease seems to be steeper in the miscarriage group (p value for interaction 0.06). As with anxiety, the random intercept variance is high (10.83), and the random slope variance is low (0.07).

Figure 6.5 *Average evolution for depression over time for patients with miscarriage and ectopic pregnancy based on a mixed effects model containing an interaction effect between the type of EPL and time and 95% confidence intervals (dotted lines).*
We assume no further loss or pregnancy during follow-up, and average values for maternal age (35 years), history of any EPL (0.407), IVF pregnancy (0.082) and children (0.443)



6.4.3 Comparison to control group in viable pregnancies

The mean anxiety score in the EPL group at one month was 6.88 (SD 4.54) versus 5.97 (SD 3.36) in the control group. The mean depression score in the EPL group was 4.45 (SD 4.39) versus 3.51 (SD 2.63).

12.6% (11/87) of the control group met criteria for moderate/severe anxiety, giving an unadjusted odds ratio (OR) for the presence of moderate/severe anxiety at M1 of 2.20. 2.3% (2/87) of the control group met criteria for moderate/severe depression, giving an unadjusted odds ratio for the presence of moderate/severe depression at M1 of 5.13.

A logistic regression using all available cases was fitted to obtain odds ratios for depression and anxiety between the EPL group and the control group. Age, IVF (yes/no), previous losses (none/any), previous children (none/any) were added to the model to correct for confounding influences. When adjusted for age, IVF pregnancy, existing children and any previous losses, the OR for anxiety was 2.14 (95% CI 1.14 - 4.36). For depression, the adjusted OR was 3.88 (95% CI 1.27-19.16) (See Appendix 6, Table A6.11)

***Table 6.10**: Mean HADS scores and % of patients that show moderate to severe depression and anxiety symptoms*

	Mean score (SD)		% Moderate/severe symptoms		OR	Adjusted OR with Firth bias correction (95% CI)
	EPL	Control	EPL	Control		
Depression	4.45 (4.39)	3.51 (2.63)	10.8% (53/492)	2.3% (2/87)	5.13	3.88 (1.27; 19.16)
Anxiety	6.88 (4.54)	5.97 (3.36)	24.2% (119/492)	12.6% (11/87)	2.20	2.14 (1.14; 4.36)

Abbreviations: CI – confidence interval; EPL – early pregnancy loss; OR – odds ratio

6.4.4 Normative population data

Normative population data for HADS from a UK study published in 2001 (involving 978 females, and 810 males, with a mean age of 41.5 years) showed that 24% of women showed scores within the mild range for anxiety, 11% moderate, and 3% severe(164). Proportions for depression scores were 8%, 3% and 1% respectively. Although age, education and social class were correlated with at least one scale, the overall effect size of each was small.

These proportions of 14% moderate/severe anxiety and 4% depression are thus similar to those found in our control group (13% and 2% respectively) in healthy pregnancy.

6.4.5 Correlation between anxiety and depression

Spearman correlations between anxiety and depression are high: around 0.7 for each time point in the EPL group.

6.4.6 Correlation between scores at different time points

Spearman correlations are high for anxiety and depression scores over time. The lowest correlation is found between M1 and M9.

This suggests that scores at one month are highly predictive of scores at later time points

***Table 6.11** Spearman correlation between HADS anxiety and depression scores at each time point for patients with early pregnancy loss (EPL)*

Assessment	Correlation co-efficient
EPL month 1 questionnaire	0.74
EPL month 3 questionnaire	0.73
EPL month 9 questionnaire	0.72
Controls	0.53

Table 6.12 *Spearman correlation between anxiety scores over time*

Time point	M1	M3	M9
Anxiety			
M1	1		
M3	0.72	1	
M9	0.62	0.71	1
Depression			
M1	1		
M3	0.68	1	
M9	0.56	0.72	1

Abbreviations: M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire;

6.5 Results: posttraumatic stress

6.5.1 Posttraumatic stress over time

Of respondents, 29% women with EPL at M1, 21% at M3 and 18% at M9 met criteria suggestive of PTSD according to Ehring's criteria (see justification for these criteria in Chapter 8). Results according to type of loss are shown in Table 6.13. The most commonly endorsed cluster at all three time points was the 're-experiencing' cluster. Similar proportions endorsed the avoidance and hyperarousal clusters at one and three months, with a slightly higher proportion of respondents endorsing the hyper-arousal cluster than the avoidance cluster at nine months. Overall, general satisfaction with life was most affected (sex life was affected by 6 more individuals at M1, but less at other time points).

Table 6.13 *The number of available observations in every group at each time point, the mean and standard deviation of posttraumatic stress diagnostic scale scores, and the number and percentage of patients with moderate and severe posttraumatic stress symptoms*

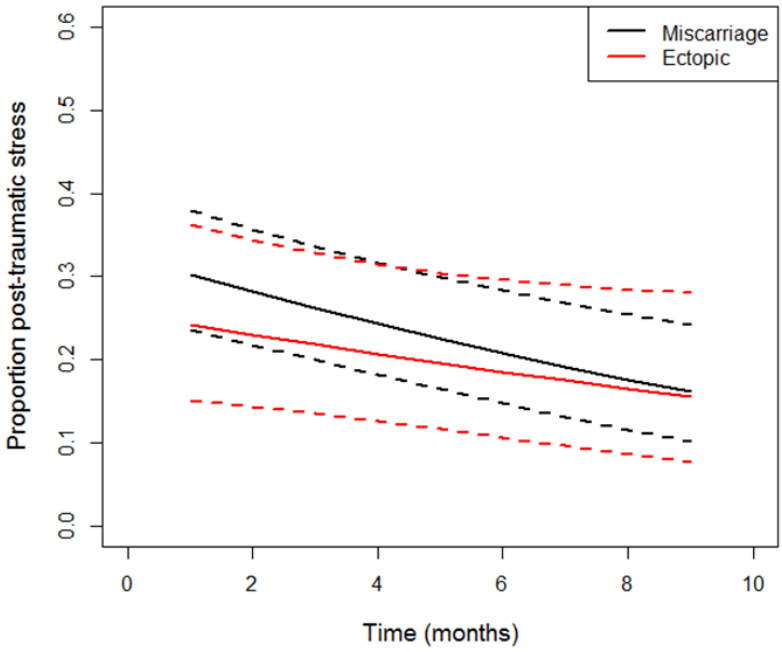
	Month 1		Month 3		Month 9	
	N	**Result**	**N**	**Result**	**N**	**Result**
PDS score (mean, SD)						
Miscarriage	363	13.7 (10.6)	308	10.6 (9.4)	249	9.0 (9.4)
Ectopic pregnancy	74	11.7 (10.1)	67	11.9 (8.9)	52	9.8 (8.6)
PUL	34	8.6 (7.8)	29	8.7 (7.7)	21	5.7 (7.1)
Molar	16	15.6 (12.6)	14	12.2 (8.6)	14	14.9 (13.0)
Moderate or severe posttraumatic stress (n, %)						
Miscarriage	363	109 (30.0%)	308	60 (19.5%)	249	41 (16.5%)
Ectopic pregnancy	74	17 (23.0%)	67	19 (28.4%)	52	11 (21.2%)
PUL	34	5 (14.7%)	29	3 (10.3%)	21	2 (9.5%)
Molar	16	8 (50.0%)	14	4 (28.6%)	14	5 (35.7%)

Abbreviations: PUL – pregnancy of unknown location

Based on the logistic regression model detailed in Appendix 6, there is a decrease in the odds of meeting criteria for PTSD by 20% each month (OR 0.80 (95% CI 0.72-0.89): for ectopic pregnancy this is 16% each month (OR 0.84 (0.69-1.03)) and for miscarriage 23% (OR 0.68 (95% CI 0.68-0.87)).

Figure 6.6 *Average evolution for PTSD over time for patients with miscarriage and ectopic pregnancy based on a mixed effects model containing an interaction effect between the type of EPL and time and 95% confidence intervals (dotted lines).*

We assume no further loss or pregnancy during follow-up, and average values for maternal age (35 years), history of any EPL (0.407), IVF pregnancy (0.082) and children (0.443).



6.5.2 Correlation of PDS scores over time

There was high correlation between scores over time: the highest correlation was between M1 and M3.

Table 6.14 *Spearman correlations between posttraumatic stress diagnostic scale symptom severity scores over time*

Time point	M1	M3	M9
M1	1		
M3	0.78	1	
M9	0.68	0.73	1

Abbreviations: M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire;

Table 6.15 *Mean score, and proportion of women meeting overall criteria, and criteria of each symptom cluster (subdivided by severity and method of scoring), according to the Posttraumatic Diagnostic Scale, in women with losses, at three time points following early pregnancy loss*

	M1 N=487	M3 N=418	M9 N=336
Helpless	361/484 (75%)	329/418 (79%)	264/336 (79%)
Terrified	246/484 (51%)	209/418 (50%)	181/336 (54%)
Helpless OR Terrified	384/484 (79%)	345/418 (83%)	275/336 (82%)
Proportion meeting each symptom cluster*:			
Re-experiencing	441/487 (91%)	349/418 (83%)	244/336 (73%)
Avoidance	290/487 (60%)	213/418 (51%)	138/336 (41%)
Hyper-arousal	290/487 (60%)	228/418 (55%)	173/336 (51%)
All three clusters	233/487 (48%)	162/418 (39%)	117/336 (35%)
Interruption of activities			
Work	189/487 (39%)	137/418 (33%)	93/336 (28%)
Household chores	151/487 (31%)	105/418 (25%)	72/336 (21%)
Relationships with family	154/487 (32%)	136/418 (33%)	84/336 (25%)
Relationships with friends	164/487 (34%)	151/418 (36%)	100/336 (30%)
Fun and leisure activities	191/487 (39%)	146/418 (35%)	96/336 (29%)
Sex life	240/487 (49%)	171/418 (41%)	107/336 (32%)
General satisfaction with life	234/487 (48%)	208/418 (50%)	134/336 (40%)
Overall level of functioning	175/487 (36%)	145/418 (35%)	93/336 (28%)
Any interruption of activities	340/487 (70%)	264/418 (63%)	174/336 (52%)
>= 2 activities interrupted, or of overall functioning	291/487 (60%)	223/418 (53%)	145/336 (43%)
Score			
Score >=11	241/487 (49%)	178/418 (43%)	109/336 (32%)
Score >= 18	146/487 (30%)	92/418 (22%)	63/336 (19%)
Duration > one month			
Of all respondents	173/487 (36%)	179/418 (43%)	52/336 (15%)
Total proportion meeting Ehring criteria (All clusters; Interruption >=2 activities; Score >=18)			
Posttraumatic stress	139/487 (29%)	86/418 (21%)	59/336 (18%)
Total proportion meeting Foa criteria (Helpless or terrified; All clusters; Any interruption, Duration >1 month; score >=11)			
Posttraumatic stress	94/486 (19%)	79/418 (19%)	22/336 (6%)

Abbreviations: M1 – month 1 questionnaire; M3 – month 3; M9 – month 9; PDS – Posttraumatic stress diagnostic scale

*endorsed so as to meet criteria i.e. Re-experiencing – one or more positive responses to 5 questions, Avoidance – three or more positive responses to 7 questions, Hyper-arousal – two or more positive responses to 5 questions

6.5.3 Description of posttraumatic stress in controls

The questionnaire sent to women experiencing a viable pregnancy screened for other trauma. 49/88 women who responded did not identify a traumatic event, and were therefore not directed to the rest of the questionnaire.

39 women identified a traumatic event (33 one event, 4 two events, and 2 three). Of these, 16 women reporting only one traumatic event, and 3 women reporting more than one traumatic event, had identified an EPL, and were thus not further analysed as part of the control group. Of those 20 remaining, four had only experienced relationship problems, three reported employment related issues, one a family argument, and one an unsuccessful round of IVF. These are not considered traumatic events in that they do not involve exposure to actual or threatened death, serious injury or sexual violence, and were thus excluded. In total, there were eleven control women reporting potentially traumatic events who had not experienced EPL: nine who had experienced bereavement, one a neonatal death at 23 weeks, and one who did not specify the nature of the trauma. Of these women with qualifying trauma, three met criteria. These were: a woman experiencing a neonatal death at 23 weeks (scoring 19, in the moderate range), a woman experiencing bereavement (scoring 20, also in the moderate range), and a woman who did not specify the nature of the trauma (scoring 22, in the moderate-severe range).

6.5.4 Population data on posttraumatic stress disorder

Kessler's 1995 study from a US population suggests a lifetime prevalence of PTSD according to DSM-III of 10.4% in women and 5.0% in men(165). Kilpatrick's more recent data, based on DSM-IV criteria (as used here), but also in a US population, suggests a lifetime prevalence of 14.4% in women, and 6.5% men, with six-month prevalence of 6.5% and 3.5% respectively. 94% of surveyed individuals reported at least one traumatic event (166).

6.6 Results: psychological morbidity following resolved pregnancies of unknown location and molar pregnancies

We have obtained a small amount of data on psychological outcomes from other types of pregnancy losses (PULs and molar pregnancies), as can be seen in Tables 6.9 and 6.13. Numbers of participants with these conditions are too small to comment on any differences between these and other types of pregnancy loss. Women do show symptoms of psychological morbidity, including PTSD, following these losses.

6.7 Discussion

We have found that, one month following a loss, up to one quarter of women experience moderate or severe anxiety, and one tenth experience moderate or severe depression. Using Ehring's criteria (as will be discussed in the Chapter 8), 29% women met criteria for PTSD at one month. At this time, women have approximately twice the odds of reaching a threshold for anxiety, and four times the odds of reaching the threshold for depression, as women in a healthy pregnancy (following a normal viability scan). Anxiety, depression and PTSD appear to decline over time in the average individual who does not experience further losses. Rates may be slightly lower initially, but decrease more slowly, following an ectopic pregnancy than a miscarriage. There was a high correlation between anxiety, depression and PDS scores at all time points, and little random slope variance when cases were modelled. This suggests that those who have high scores and meeting criteria initially are likely to continue to at later time points.

This is the largest study published to date performing psychological screening in women at set times after an EPL. It incorporates an up-to-date, demographically and ethnically diverse, sample of women experiencing EPL from three areas of London, and uses a comparison group of women in a healthy pregnancy.

Women were recruited consecutively, and details of the clinical encounter were prospectively collected from hospital records. It is the first study to assess PTSD in a sizable group, and to assess psychological morbidity following ectopic pregnancy outside the context of an interventional study.

The main unavoidable weakness of this study was the attrition rate: both those who did not respond to the initial questionnaire, and those who dropped out over study duration, introducing potential selection bias.

As discussed in the pilot study, our recruitment methodology in which participants usually consented immediately is likely to have been associated with a high recruitment rate (67% of eligible women with EPL and 91% controls). However, limited overall engagement in the study was instead reflected in high passive non-response.

Response rates were improved in comparison to the pilot study: 67% versus 61% at M1 for women, and 51% versus 40% for controls. This is likely to reflect the use of up to two reminder emails, sent at weekly intervals after the first request. Response rates at later time points were also much higher: 58% versus 38% overall at M3 for women. This also reflects the fact that all those recruited (unless they actively withdrew) were invited to participate at later timepoints, even if they had not responded at M1.

Extensive analysis of missing data reassuringly showed few differences in clinical or background variables in those who didn't respond at all, compared to those who responded to the earlier assessments, to those who responded throughout. It was noted that women recruited at Chelsea and Westminster, and also that women with higher annual income and higher education, were more likely to respond. Chelsea and Westminster is situated in a more affluent area of London, and it is thus likely that these two findings are interlinked. It may be that those who have higher degrees are more likely to have conducted research themselves, value it, and thus be more likely to invest time in it.

There was no compelling evidence of selective participation or drop out according to baseline psychological morbidity, or further pregnancy (healthy or otherwise). Non-responders may however have different psychological responses (either more or less effected), on which we are unable to comment: all studies are bound by this limitation. Our convenient, web-based design, may have maximized involvement of a disinterested group, but some passive non-response will always be expected in studies of this nature.

There could have been an unintended therapeutic benefit of taking part, as specifically assessed for and supported by one study in the past(114). This may result in underestimation of morbidity in the general (non-study) population.

It was not possible to exclude the presence of psychological morbidity prior to the diagnosis of a loss. Although psychiatric history was enquired about, this relied on the participant having been formally diagnosed, which may not be representative of actual morbidity. To reliably interpret the impact of the loss itself would require women to be recruited prior to the pregnancy loss (and ideally prior to conception, and thus any potential 'warning signs' that the outcome would not be positive, or pregnancy-related anxiety) – which is a labour intensive study design, severely limiting the size of the study group Without such an assessment, it is not possible to attribute depression or anxiety to the loss itself. As discussed in Chapter 2, some literature suggests psychiatric symptoms increase the risk of a poor outcome. However, the evident decline in symptomatology of all three conditions over time indicates that the loss itself is at least partly causative.

It was not possible to translate the psychometric questionnaires in a validated manner: and thus the exclusion of those who did not speak English to a sufficient standard was necessary. This is a common weakness of studies in this field, which is not easily overcome (validated translations of the questionnaires are only available in a small number of languages).

Screening questionnaires alone, rather than the gold standard of individualised assessment by a trained professional, were used in the majority of participants: the large size of the study was at the cost of reduced accuracy, as is usually the case in such research. The use of the PDS in particular is beset with complexity. First, it reflects now outdated PTSD criteria, without the inclusion of questions

relating to negative alterations of mood, or risk-taking behavior, added to DSM-5 into 2013. However, there is large-scale evidence to suggest that symptoms can be used to closely approximate DSM-5 diagnoses (44) – and thus no reason to doubt integrity of results on this basis. Second, as discussed within the methodology, there are multiple proposed definitions of caseness using the PDS. More stringent scoring is associated with higher specificity but lower sensitivity. At the outset, we assumed we would use the criteria originally proposed by Foa, as we had done in our pilot study. However, as explained in Chapter 8, another method proposed by Ehring (in later work with Foa) appeared to be more reliable at identifying cases, and has thus been used here. This retrospective decision, based on the 10% of women who were interviewed, is suboptimal, though we were left with little choice: with a variety of methods proposed and used in the EPL population, and no validation to date, there was no other appropriate basis on which to choose.

Proportions meeting criteria for PTSD were lower than in the pilot study when using Foa's original scoring for both: 19% versus 28% at M1 (non-significant), and 19% versus 39% at M3 (p=0.005). The higher drop out in the pilot study (which improved in the main study after the introduction of reminder emails) may be responsible for this. Proportions meeting criteria for PTSD were higher at later time points than in Engelhard's study, which reported 25% PTSD at one month and 6% at four months. This is secondary to the more stringent scoring she used, as previously discussed.

6.8 Conclusions

We have shown in a large, up-to-date cohort, that high proportions of women experience clinically significant anxiety, depression and posttraumatic stress symptoms following all types of EPL, which decline over time.

The annual incidence of miscarriage is approximately 250 000 each year in the UK – and may rise further in coming years if the trend towards later childbearing continues: in this context, 18% women in our cohort experiencing symptoms suggestive of PTSD nine months after a loss is a major public health issue. It suggests that re-evaluation of treatment is urgently required. This could be targeted at those found to have psychological distress or, possibly, those most likely to experience ongoing distress based on background or clinical factors. The possibility of predicting this group is evaluated in the next chapter.

Chapter 7: An exploratory analysis of factors that may be associated with psychological morbidity in women after early pregnancy loss

7.1 Introduction

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(5). It is possible that treatment aimed at symptoms we have described in Chapter 6, in particular PTSD, may be more efficacious. It is also possible that better results could be obtained by targeting treatment at those most likely to develop psychological sequelae.

A number of possible risk factors have been suggested by previous research, including childlessness, previous losses, previous subfertility, past psychiatric history and longer gestation, as discussed in Chapter 3. However, as discussed, many of these have been published on the basis of retrospective fishing exercises for statistical significance, and the degree to which they may actually be able to explain the variation in psychological morbidity between individuals, and hence potentially useful for a predictive model, remains obscure.

This explorative study aimed to assess whether, in a large cohort, a prospectively chosen set of potential predictive factors can reliably predict those with morbidity.

7.2 Methods

Methods for recruitment and assessment are detailed in chapter 4. This chapter uses data collected from 492 women who responded to the questionnaire sent one month after EPL.

Factors that were hypothesized to be most associated with increased psychological morbidity were prospectively established during a research meeting with clinicians with extensive experience of caring for women with EPL, and a psychologist with experience treating women with psychological morbidity after loss. These variables are shown in Table 7.1.

Exploration of the potential predictive value of each factor was performed by separate regression analysis, initially for any outcome (moderate/severe anxiety or depression, or PTSD – with cut-offs for as used previously), and then for each outcome individually. If there was missing data for a predictor variable, the individual was excluded from the analyses involving that predictor only. Due to the exploratory nature of this study, the issue of multiple testing is not addressed. The goal was to explore which risk factors could be subject to further research for developing a multivariable prediction model.

7.3 Results

Table 7.1 shows the area under the curve (AUC) statistic for each of the potential predictor variables. It describes the value of each variable in the prediction of any morbidity (anxiety, depression or PTSD). An AUC of 0.5 would suggest no value in the prediction of morbidity, where as an AUC of 1 would show perfect prediction.

Table 7.1 *AUC, Nagelkerke R2 and p value in the prediction of any morbidity (anxiety, depression or posttraumatic stress) for each potential predictor variable, displayed in order of decreasing predictive probabilities*

Predictor	R2	AUC	p value
Extent to which feel responsible (Likert 1-5)	0.114	0.66	<0.0001
Worry for own wellbeing (Likert 1-5)	0.084	0.64	<0.0001
Psychiatric disorder (no, in past, currently)	0.084	0.61	<0.0001
Any previous losses (no=0;yes=1)	0.043	0.59	<0.0001
Time to conceive (unknown/<1year/>1 year)	0.022	0.56	0.02
Final management (expectant/medical/surgical)	0.015	0.55	0.10
Desire for pregnancy (Likert 1-4)	0.010	0.54	0.06
Final diagnosis (miscarriage, ectopic, other)	0.009	0.54	0.19
Fetal Heart seen previously (no=0; yes=1)*	0.008	0.53	0.34
Age (in years)	0.001	0.53	0.53
Educational attainment (none; GCSE; A-level; University; Post-graduate degree)	0.003	0.52	0.89
Previous termination (no=0;yes=1)	0.002	0.52	0.37
Previous children (no=0;yes=1)	0.002	0.52	0.39
In Vitro fertilisation (no=0;yes=1)	0.000	0.51	0.70
Days to diagnosis (days)	0.000	0.51	0.95
Gestational age (days)	0.000	0.50	0.89
Nights admission (days)	0.000	0.50	0.90

* Miscarriage only

Those with a past or current diagnosis of a psychiatric disorder were at higher risk of depression, anxiety and/or posttraumatic stress. 55% of those with a current psychiatric diagnosis met criteria for PTSD, as did 48% of those with a past diagnosis of psychiatric disorder, as compared to 23% of those without any psychiatric history. This is visually represented in Figure 7.1.

Those with past losses were at higher risk of morbidity: those with any previous loss had a 48% chance of meeting criteria for any disorder, compared to 30% in the group without previous losses. The Area under the curve (AUC) for this interaction was 0.59, p<0.0001.

Asked at one month, a sense of responsibility for the loss, and having been worried for their own wellbeing, was associated with a higher probability of each outcome. The AUCs for these variables were 0.66 and 0.64 respectively (p values <0.0001).

Factors we found not to predict anxiety, depression or PTS include: the diagnosis itself (miscarriage versus ectopic), the duration of the delay to the diagnosis, the management chosen by the patient, having seen the fetal heart on previous US imaging, and increased gestation at time of diagnosis (in those for whom this is known).

Table 7.2 *Descriptive statistics of anxiety, depression and PTSD rates for the most important variables found to be associated with psychiatric morbidity*

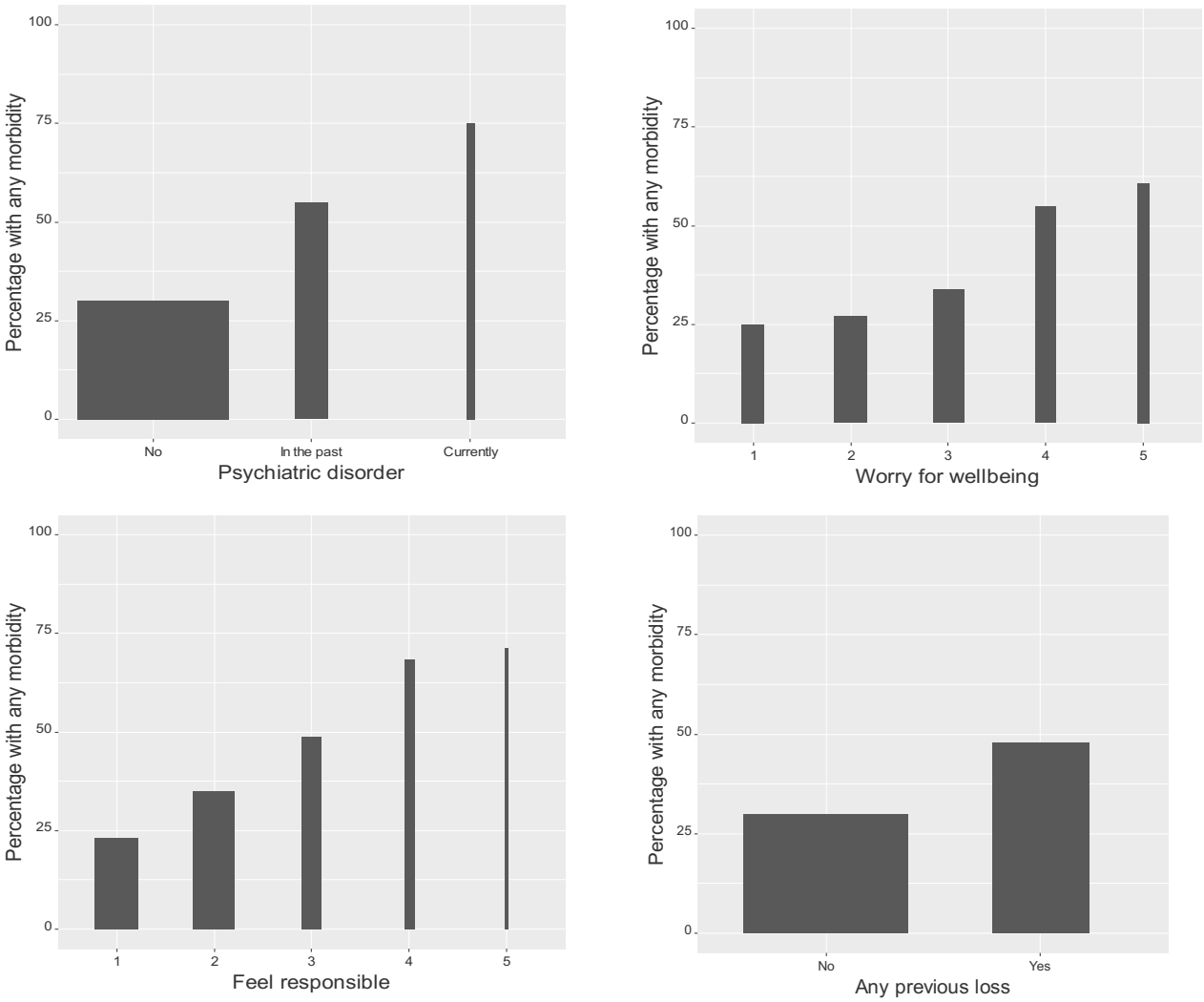
	Anxiety (%) (N=492)	**Depression (%) (N=492)**	**PTSD (%) (N=487)**	**Any (%) (N=487)**
Psychiatric Disorder				
No	76/386 (20%)	28/386 (7%)	86/382 (23%)	115/382 (30%)
Yes in the past	29/83 (35%)	20/83 (24%)	39/82 (48%)	45/82 (55%)
Yes currently	12/20 (60%)	4/20 (20%)	11/20 (55%)	15/20 (75%)
Any previous 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%)
Worry for own wellbeing				
1=”not at all worried”	11/93 (12%)	7/93 (8%)	19/92 (21%)	23/92 (25%)
2	21/133 (16%)	11/133 (8%)	31/133 (23%)	36/133 (27%)
3	28/131 (21%)	11/131 (8%)	31/130 (24%)	44/130 (34%)
4	34/84 (40%)	12/84 (14%)	33/84 (39%)	46/84 (55%)
5=” extremely worried”	24/46 (52%)	11/46 (24%)	24/46 (52%)	28/46 (61%)
Feel responsible for loss				
1=”not at all”	29/182 (16%)	14/182 (8%)	30/181 (17%)	42/181 (23%)
2	34/178 (19%)	15/178 (8%)	49/174 (28%)	61/174 (35%)
3	24/80 (30%)	9/80 (11%)	30/80 (37.5%)	39/80 (49%)
4	24/38 (63%)	8/38 (21%)	20/38 (53%)	26/38 (68%)
5=” extremely”	8/14 (57%)	7/14 (50%)	10/14 (71%)	10/14 (71%)

Overall, even those factors most likely to be associated with psychiatric morbidity are relatively poor at separating out cases from non-cases, and therefore overall unlikely to be usefully incorporated into a predictive model.

7.4 Discussion

We have found that psychological morbidity (posttraumatic stress, anxiety or depression) is more common in those with past or current psychiatric history, or in those with a history of other early pregnancy losses. Asked at one month, a woman’s sense of responsibility for the loss, and having been worried for their own wellbeing, are positively associated with a higher likelihood for all psychological morbidity. Factors that were not associated with increased morbidity were: whether the pregnancy loss was a miscarriage or ectopic pregnancy, the gestational age at diagnosis, having seen fetal heart

Figure 7.1: *Bar charts showing presence of any morbidity (anxiety, depression or PTSD) for the most important predictors. The width of the bars reflects the number of patients with that value for the predictor*



pulsations on ultrasound imaging prior to miscarriage, or admission to hospital overnight. The subjective desire for the pregnancy was also not predictive. We have found no grounds on which to recommend one management strategy over another, and can be reassured that recent increases in delays to diagnosis are unlikely to be causing increased morbidity overall.

It is important to note that those without the identified risk factors of psychiatric history and previous losses still have a high likelihood (30%) of meeting the threshold for at least one disorder. Thus, clinicians should be sensitive to the risk of disabling mental health conditions in all women after pregnancy loss.

The strength of this study is in its large size, 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 posttraumatic stress, which our group has found to be the most commonly endorsed condition(4).

As an exploratory analysis, the issue of multiple testing is not addressed. In this context, it is important not to place much emphasis on statistical significance. The analyses are also univariate, and the potential for confounders to obscure relationships must be considered. For example, age may be associated with a higher risk of morbidity, but also a higher chance of existing children (which may be protective): the impact of age alone may be cancelled out.

Questions covering the sense of responsibility for a loss, or being worried for their own wellbeing, were asked at the same time as the psychological assessment. It is thus plausible that they are predominantly reflective of psychological state, rather than predictive of it. A more appropriate assessment may be to see whether these questions (or others) asked closer to the time of the loss would be predictive of later morbidity. The feasibility of such an approach, and its acceptability to patients, would need to be evaluated. These sentiments may nonetheless represent important therapeutic targets: assuaging self-blame through thorough medical explanation, and reassurance regarding current and future physical wellbeing would seem appropriate in light of our findings.

It is important to recognize that factors found to be associated with higher psychological morbidity after loss may not imply increased vulnerability to the loss itself. This is particularly pertinent for psychiatric history. Although this still indicates a group at risk of more severe symptoms, they may not be attributable to the loss themselves, and thus may not respond to a pregnancy-loss specific intervention.

Previous studies have found higher anxiety and depression in women without children, and with reducing numbers of existing children (115, 119, 120). It is not clear why this study did not

demonstrate such an association, though worth noting that all except one study (Sham's) assessed this on the basis of severity scores rather than caseness. It is also possible that there have been cultural shifts over time. Some previous studies have also found that gestation may be associated with increased anxiety, depression and posttraumatic stress scores (4, 109). In contrast to these studies, we did not include late losses, and assessed for morbidity on a categorical (rather than continuous score) basis. Moreover, the vast majority of included women experienced losses in the first 12 weeks of pregnancy (mean gestation 71.1 days for miscarriage, and 46.1 days for ectopic pregnancies), limiting its power to detect differences between the first and second trimester.

In view of the overall AUCs, it seems unlikely that a predictive model will be appropriate or helpful in identifying those at risk of clinically significant morbidity, or who would benefit from intervention. Instead, it may be that screening for psychological morbidity after a loss is a more appropriate way of targeting treatment. The reliability of such screening, and its optimal timing, requires further research.

7.5 Conclusions

All women are at risk of experiencing significant levels of psychopathology at one month. We would suggest that clinicians should be particularly alert to the risk of morbidity in those with a past or current psychiatric history, and those with previous losses. Efforts to minimise self-blame, and to reassure about physical wellbeing, following loss, may be beneficial – and should be subject to further assessment.

On the basis of our results, we would suggest that screening women after loss for psychiatric morbidity, rather than modelling their risk of morbidity based on pre-existing and encounter related factors, is likely to result in better targeting of treatment to a greater proportion of those in need.

Chapter 8: Validation of the posttraumatic diagnostic scale in women following early pregnancy loss

8.1 Introduction

Diagnostic rating scales provide an important adjunct to psychological assessment in research projects, making screening for psychological impact cost-effective and feasible. They have been used in the majority of studies assessing the psychological impact of early pregnancy events published to date (see systematic review in Chapter 2).

At the beginning of 2015, concern was raised about the validity the posttraumatic diagnostic scale to screen for posttraumatic stress disorder for three reasons:

1. The number of women meeting criteria for PTSD in the pilot study was higher than expected
2. The change in PTSD criteria as detailed in section 1.2.4
3. Variation in scoring methods for PDS used in the literature, as discovered during systematic review

As a result, a decision was made that the PDS, scored according to a variety of methods proposed in existing literature, should be validated by comparing results from a clinician-administered instrument.

8.2 Methods

Four potential scoring methods for PDS were identified in the literature (see Table 8.1). One pertinent question in our work was the appropriateness of the duration criterion. The PDS questionnaire asks women to state whether symptoms have lasted 'less than one month', '1 to 3 months' or 'more than 3 months': according to the original manual, respondents would not meet criteria for PTSD if they responded 'less than one month'. This was unlikely to be appropriate at M1 – sent 28 days after EPL, and the way in which it was filled in was unlikely to be reflective of symptomatology. In the pilot paper, results 'with' and 'without' the duration criterion were presented separately for M1. For the main study, it was felt to be important to adopt a consistent

approach at all time points in order to perform the longitudinal analysis. Thus a further scoring method in which Foa's original scoring, but with this criterion abandoned, was assessed.

The structured clinical interview for DSM-5 was chosen as the gold standard screening instrument – as detailed in Section 4.10.

We took a pragmatic approach, aiming for 50 interviews (based on the limited of capacity of research team): this represented just over 10% those who completed M1. Women were approached consecutively at the end of the recruitment period (once ethics approval for this major amendment had been received) from August 2015.

The SCID was performed by telephone by a psychologist (Maria Jalmbrant (MJ)) or her trained assistant (Sophie Tapp (ST)), as soon as a mutually convenient time could be arranged after completion of the first questionnaire. The initial four interviews were used as training interviews, with MJ listening in on ST's assessment, and were later discarded. Notes were taken contemporaneously, and scoring was completed on the paper SCID questionnaires during the interview. Scores were then transferred onto an excel spreadsheet, and subsequently checked by the other assessor.

A comparison of the sensitivity, specificity, accuracy, and concordance for diagnosis of PTSD was performed according to the five potential scoring methods.

Table 8.1 *Scoring methods for PDS identified in existing literature: their origin, diagnostic criteria and proposed cut-offs for cases. A score of 1 corresponds to "once a week or less/once in a while", and a score of 2 to "2 to 4 times a week/half the time"*

Origin of scoring method	Criteria	Definition of cases
Foa's original scoring – with duration criterion (157)	Helpless or terrified AND At least one re-experiencing symptom (score 1+) AND At least three avoidance symptoms (each scoring 1+) AND At least two hyper-arousal symptoms (each scoring 1+) AND Interruption of at least one activity AND Duration >1 month	Moderate and severe scores – total score >=11

Foa – without duration criterion (as per pilot study at month 1)	As above – without duration > 1 month	Moderate and severe scores – total score >=11
Engelhard (4)	Helpless or terrified or horrified AND At least one re-experiencing symptom (each scoring 2+) AND At least three avoidance symptoms (each scoring 2+) AND At least two hyper-arousal symptoms (each scoring 2+)	All meeting criteria
Ehring criteria (160)	At least one re-experiencing symptom (each scoring 1+) AND At least three avoidance symptoms (each scoring 1+) AND At least two hyper-arousal symptoms (each scoring 1+) AND Interruption of overall level of functioning, or >=two other activities AND Total PDS severity score >=18	All meeting criteria
Cut-off score alone (160)	Total PDS severity score >=18	Severity score >=18

8.3 Results

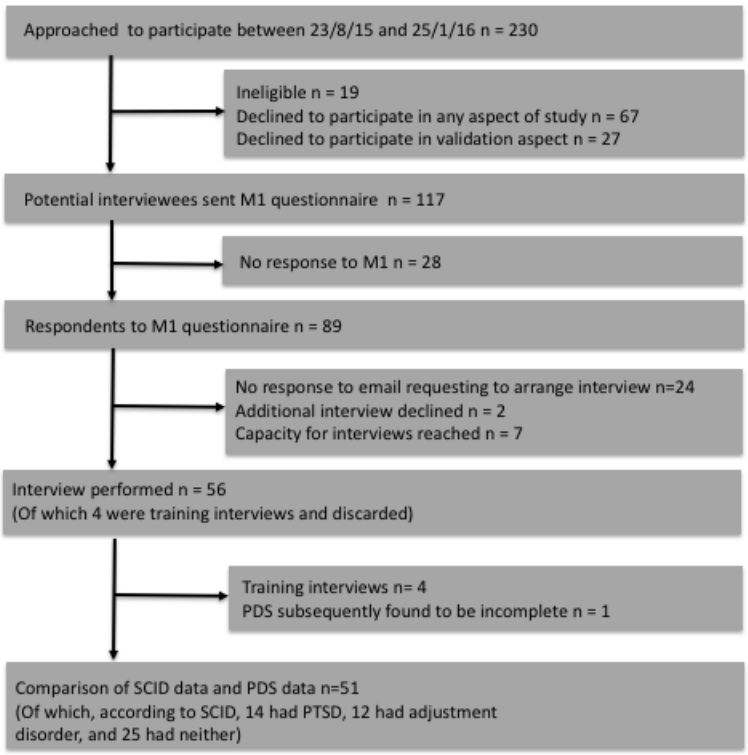
117/144 of those approached for SCID interview agreed. As demonstrated in figure 8.1, 28 did not respond to part 1, 24 did not respond to the email request to arrange an interview, 2 later declined, and 7 women were not contacted again (as our capacity to perform these interviews had been reached). SCID for PTSD was thus performed on 56 participants, with the first four interviews used for training and not included within the analysis. A further interview was discarded from the comparison as it was later realized that the patient had not completed the PDS. This left 51 interviews for analysis.

Interviews took place a mean of 23.9 (range 3-59) days after completion of the first questionnaire.

The PDS severity scores were compared in those approached for this aspect of the study, according to their participation with the SCID (see Table 8.2). There is a slight suggestion that those who did not respond to the email approach for interview had higher scores, and those who declined involvement in the interview at the outset had lower scores. However, overall, the mean

PDS score of those who took part in the validation, and those who were approached but did not, was the same (14.4).

Figure 8.1 Flowchart of approach for validation interviews



Abbreviations: M1 – month 1 questionnaire; n – number; PDS – Posttraumatic stress diagnostic scale; SCID – Structured clinical interview for the Diagnostic and Statistical Manual for Mental Disorders

***Table 8.2** Comparison of mean PDS severity scores according to participation in SCID*

	N	Mean PDS score (SD)
Declined SCID at recruitment (and completed M1)	12	8.83 (9.09)
No response to email approach for SCID after completion of M1	24	17.25 (10.85)
Actively declined SCID after completion of M1	2	7.00 (1.14)
Capacity for interview reached	7	16.29 (8.59)
Participants	55	14.45 (10.24)

Abbreviations: M1 – month 1 questionnaire, SCID – Structured clinical interview for the Diagnostic and Statistical Manual for Mental Disorders

According to the SCID, 14/51 (27%) met criteria for PTSD. Those who did not meet full criteria for PTSD were scored for adjustment disorder: a further 12/51 (24%) women met diagnostic criteria for this. Tables showing the individual PDS results for women with and without PTSD according to SCID are shown in Appendix 7.

Sensitivities, specificities, overall accuracy, and the kappa coefficients for concordance were calculated for each of the five potential scoring methods for the detection of PTSD , and can be seen in Table 8.3.

Table 8.3 *Sensitivities, specificities, accuracies and concordance (kappa co-efficient) in diagnosis of PTSD according to SCID, for each of the proposed PDS scoring methods*

Criteria	Sensitivity	Specificity	Accuracy	Kappa co-efficient (95% CI)
Foa	4/14 (29%)	33/37 (89%)	37/51 (72%)	0.21 (0.08-0.49)
Foa – without duration criterion	10/14 (71%)	24/37 (64%)	34/51 (67%)	0.30 (0.05-0.55)
Ehring – symptom clusters and score >=18	10/14 (71%)	31/37 (84%)	41/51 (80%)	**0.53 (0.27–0.79)**
Symptom severity score >=18	10/14 (71%)	30/37 (81%)	40/51 (78%)	0.49 (0.24–0.75)
Engelhard	5/14 (36%)	33/37 (89%)	38/51 (74%)	0.28 (-0.01-0.57)

There was the highest, and moderate, concordance for case/non-case discrimination for PTSD when using criteria proposed by Ehring (with requirement for symptoms in each cluster, plus score >=18) (kappa co-efficient 0.53 (95% CI 0.27 – 0.79)). Four women with PTSD according to SCID were not found to meet these criteria: two because they did not meet the required level for the avoidance cluster (3 symptoms) (these participants also had severity scores of <18), and two as the severity scores were <18 (scores were 10 and 17). Using a symptom severity score of 18 alone performed almost as well, but with very slightly lower specificity (one more false-positive). Foa's originally proposed method showed the least concordance: the low sensitivity reflects 8/14 participants with PTSD at SCID reporting a symptom duration of less than one month at the one-month questionnaire. Sensitivity for the diagnosis of PTSD was not increased by lowering the severity score to 11 as per Foa's method without duration, but specificity was reduced, reflecting more false positives.

There was no relationship between severity score and response to duration criterion in those meeting criteria on SCID for PTSD (those who reported duration of less than one month at the

first questionnaire had a mean severity score of 22, and more than one month a severity score of 21).

8.4 Discussion

By using the SCID in a representative sample of our study population, we have confirmed that a high proportion (14/51, 27%) of women meet criteria for PTSD following EPL. A further 12/51 (24%) meet criteria for adjustment disorder.

We have found varied results in the performance of the PDS in identifying those with PTSD, depending on the scoring method chosen, albeit with limited statistical power due to a small sample size. Ehring's method performed best, and was thus retrospectively chosen for our study. Overall, the agreement with SCID is considered moderate, with kappa coefficient of 0.53.

This method suggests a prevalence of 16/51 (31%) according to PDS at one month in this subgroup (and 139/487 (29%) in all women). Crudely, this offers reassurance that, while there is not absolute concordance between identified cases, the screening method does not appear to substantially over-estimate prevalence of PTSD (which was our primary concern). This is important for our aim to assess overall prevalence, though the suboptimal concordance may have detracted from our ability to detect true associated factors in the analysis in Chapter 7.

We have not found the duration criterion to be a useful predictor of PTSD at one month, and thus have retrospectively justified dropping this requirement for the first assessment in the pilot study.

Validation of the PDS has not been done in context of pregnancy losses before, and this data thus forms an important adjunct to the work on PTSD presented in this thesis, both in terms of confirming the presence of PTSD following EPL using a clinician-administered instrument in a substantial proportion of women, and in terms of verifying PDS as a satisfactory measure of PTSD according to DSM-5. This is especially important in view of the change in PTSD criteria during this study, presented in Chapter 2.

It is of course possible that more accurate instruments to screen for PTSD, or more accurate ways to score the existing PDS, could be developed de novo for use in this specific context. To do so would require much larger numbers of participants. This would more appropriately be performed on the new PCL-5 PTSD screening questionnaire that has been developed since the start of this study (in line with DSM-5). Evaluation might include a search for any redundant questions that are not specific to a diagnosis of PTSD. For example, one re-experiencing statement reads "Feeling

emotionally upset when you were reminded of the pregnancy loss": it seems unlikely that many women following miscarriage would respond "not at all or only one time", and removing it may yield higher specificity.

A weakness of this study is the delay between appraisal of symptoms using PDS and SCID (a mean of 24 days). Ideally, the questionnaires would have been administered on the same day, though this was not logistically feasible. Evidence presented elsewhere suggests that the odds of the average individual meeting criteria for PTSD drops by almost 20% each month. This would account for some apparent 'false positives' generated by PDS.

There was also significant non-participation and drop out. However, the PDS severity scores in those who took part in SCID and those who did not are similar. Although, , high (though unavoidable) non-participation raises concern about extrapolation to the general population, this at least suggests SCID was performed in a representative sample of those who agreed to participate in the study as a whole.

Ideally, the scoring method to be used would have been specified in advance in the study protocol, rather than relying on small numbers to pick the method that maximized concordant diagnoses (in spite of large confidence intervals). However, given the very limited literature to guide use or confirm validity of the PDS in this context, we felt this the most appropriate course of action. Even after optimising the criteria used, the sensitivity of the PDS was lower than in other contexts: Ehring reported sensitivity 0.82 and specificity 0.89 in those following motor vehicle accident and sexual or physical assault. However, our numbers were too small to imply any significant deviation from this performance.

8.5 Conclusions

Overall, there is evidence from a clinician administered instrument to support a hypothesis of high levels of PTSD in the three months following EPL. On the basis of these results, we used Ehring criteria (in which all three symptom clusters must be endorsed, there must be interruption to overall level of functioning, and a severity score of >=18) to determine cases of PTSD in our main study population.

Chapter 9: Anxiety, depression and posttraumatic stress in partners following early pregnancy loss

9.1 Introduction

The response of partners to early pregnancy loss is rarely given much consideration. Personal accounts by partners often focus on the lack of regard for their own bereavement, and frustration at their powerlessness. The systematic review in Chapter 2 has shown there is little information about posttraumatic stress in partners, and data relating to anxiety and depression are over a decade old. This chapter aims to assess a hypothesis that partners do suffer from these conditions, but at a lower rate than women.

9.2 Methods

If women with early pregnancy loss agreed to participate, and their partners were present at the consultation when consent to participate was given, and were eligible, they too were approached to participate.

Eligibility criteria were the same as for women: the diagnosis of loss before 20 week's gestation, age >=18 years, sufficient grasp of English and capacity to consent.

Partners were sent almost identical questionnaires to women (questions on the amount of pain and bleeding experienced were omitted), at the same time intervals (one, three and nine months after a loss).

The comparative analysis of women included only the subset of women whose partners agreed to participate.

9.3 Results

9.3.1 Participants

Just over half of women (386/737, 52%) who consented had their partners present. Of these, 192/386 (50%) were eligible and agreed to participate. Most did not volunteer a reason for not participating, but of 13 who did, 9 reported time constraints.

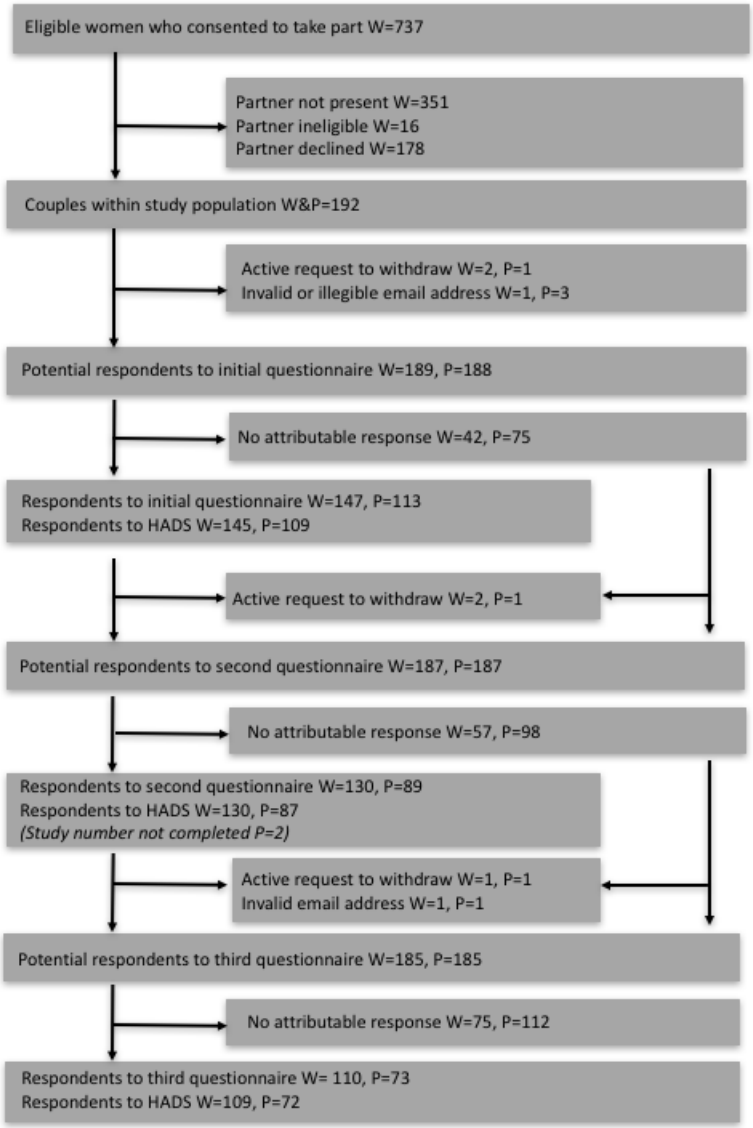
Table 9.1 *Partners with early pregnancy loss: A summary of number of individuals approached, recruited, and reasons for non-recruitment*

	Number (%)
Approached	386
Not present at consultation % of all women recruited	351 (48%)
Recruited % of all approached	192 (50%)
Declined % of all eligible	176 (48%)
Ineligible % of all approached	18 (5%)
Reason (if volunteered) for declining participation:	
No reason given % of all who declined	117 (66%)
Requested time to consider, but consent form not returned by post % of all who declined	46 (1%)
Unplanned pregnancy % of all who declined	2 (1%)
Doesn't want to be reminded/too upsetting % of all who declined	2 (1%)
Time commitment % of all who declined	9 (5%)
Reason ineligible:	
Insufficient English	16
Already in study from previous loss	2

Details of the clinical encounter in the subgroup of women whose partners were recruited were generally similar to those who's partners were not (see Appendix 5,Table A5.6). A higher proportion of the subgroup had no concerning symptoms, with diagnosis made incidentally on scan (29% versus 7%). Women may be more likely to bring their partners to a pre-arranged (rather than emergency) scan. Gestation was not, however, significantly different.

Overall, of those approached, 192/368 (50%) eligible partners agreed to participate. This is significantly lower than the participation rate in women (737/1098 (67%)) and controls (171/187 (91%)) (p value <0.0001 for both, Fisher's exact test).

Figure 9.1 *Flowchart of recruitment and response rates for couples*



Abbreviations: HADS – Hospital Anxiety and Depression Scale; n- total number; P –Partners; W – women

9.3.2 Response Rates

Table 9.2 demonstrates response rates of women and partners (subdivided by site in Appendix 5, Table A5.1). Partners were significantly less likely to respond than women after loss at every time point ($p < 0.001$ (Fisher's Exact test)).

Table 9.2 *Response, non-response and withdrawal in the subgroup of women with early pregnancy loss whose partners were recruited, and their partners*

	Women with EPL	Partners
Recruited	192	
E-mail address invalid	1 (1%)	3 (2%)
Active withdrawal before M1 completed	2 (1%)	1 (1%)
M1 respondents (%)	147 (77%)	113 (59%)
Passive non-response to M1	42(22%)	75 (39%)
E-mail address invalid	1 (1%)	3 (2%)
Active withdrawal before M3 completed	4 (2%)	2 (1%)
M3 respondents (%)	130 (68%)	89 (46%)
Passive non-response to M3	57 (30%)	98 (51%)
E-mail address invalid	2 (1%)	4 (3%)
Active withdrawal before M9 completed	5 (3%)	3 (2%)
M9 respondents (%)	110 (57%)	73 (38%)
Passive non-response to M9	75 (39%)	112 (58%)

Abbreviations: M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire

9.3.3 Missing responses

Response rates to each questionnaire can be seen in Table 9.3, with breakdown according to pattern of response in women in Table 9.4. Overall, of women with EPL, 152/192 (79%) responded at least once, compared to 125/192 (65%) partners at least once.

Table 9.3 *The number of observations at each time point, in women with EPL and partners*

Time point	Women with early pregnancy loss	Partners
Month 1 questionnaire	145 (76%)	110 (57%)
Month 3 questionnaire	130 (68%)	87 (45%)
Month 9 questionnaire	109 (57%)	72 (38%)

Partners who ceased participation after the M1 or M2 did not differ from those who completed M3 in responses to questions relating to desire for the pregnancy, distress about loss, satisfaction with the healthcare provided, and time taken to conceive. As in women, those with a post-graduate degree constituted a slightly higher proportion of those who responded throughout,

Table 9.4 *Missing data pattern for women and partners with EPL*

			Women with EPL		Partners	
M1	**M3**	**M9**	**n**	**%**	**n**	**%**
Completers (all parts)						
O	O	O	102	53%	60	31%
Drop-out over study duration						
O	O	M	24	13%	16	8%
O	M	M	16	8%	28	15%
M	M	M	40	21%	67	35%
Intermittent response						
O	M	O	3	2%	5	3%
M	M	O	3	2%	5	3%
M	O	O	1	1%	2	1%
M	O	M	3	3%	9	5%

Abbreviations: EPL – early pregnancy loss; M – missing observation; M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire; O – available observation

Table 9.5 *Depression, anxiety and posttraumatic stress scores and caseness at month 1 for partners with last information at month 1, month 3, and month 9.*

M1 results	**Last info M1 (n=28)**	**Last info M3 (n=25)**	**Last info M9 (n=72)**
Missing data (n) – HADS at M1	n/a	9 (36%)	7 (10%)
HADS depression score (mean (SD))	2.5 (2.5)	2.8 (4.1)	2.1 (2.4)
HADS depression score ≥ 11 (number (%))	0 (0%)	2 (13%)	0 (0%)
HADS anxiety score (mean (SD))	4.9 (4.0)	5.1 (5.0)	4.7 (3.1)
HADS anxiety score ≥ 11 (number (%))	3 (11%)	1 (6%)	3 (5%)
Missing data (n) – PDS at M1	1 (4%)	9 (36%)	8 (11%)
PDS score (mean (SD))	7.3 (8.9)	8.25 (8.3)	6.7 (5.9)
PDS moderate/severe cases (number (%))	3 (11%)	1 (6%)	3 (5%)

Abbreviations: HADS – Hospital Anxiety and Depression Scale; M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire; PDS – Posttraumatic stress diagnostic scale

than those who ceased participation at M1/M3 (30% versus 20%), as did those with higher annual income (see Appendix 5, Table A5.8). As can be seen in Table 9.5, HADS and PDS scores and proportion of cases were similar irrespective of timing of last response.

9.3.4 Response timing

Responses to M1 were a mean of 42 days after diagnosis (SD 12, IQR 33-47), to M2 a mean of 102 days after diagnosis (SD 14, IQR 92-108), and to M9 283 days after diagnosis (SD 16, IQR 273-287).

9.4 Anxiety and depression in partners

Histograms of anxiety and depression scores can be seen in Appendix 8. As with women, the distribution at all time points is skewed, with the majority of partners having low scores.

Table 9.6 *Severity scores, and proportion of respondents meeting criteria for anxiety and depression, according to the HADS, in partners, according to type of loss*

	Month 1		Month 3		Month 9	
	N	**Result**	**N**	**Result**	**N**	**Result**
Anxiety score (mean, SD)						
Miscarriage	81	4.7 (3.7)	62	4.8 (3.7)	49	4.4 (3.1)
Ectopic pregnancy	17	6.1 (3.7)	16	4.3 (3.8)	13	6.5 (4.9)
Failed PUL	9	4.0 (1.9)	6	6.0 (2.5)	6	4.3 (3.4)
Molar	2	2.5 (3.5)	3	6.0 (7.8)	4	7.0 (9.0)
Moderate/severe anxiety (n, %)						
Miscarriage	81	5 (6%)	62	5 (8%)	49	1 (2%)
Ectopic pregnancy	17	2 (12%)	16	2 (13%)	13	2 (15%)
Failed PUL	9	0 (0%)	6	0 (0%)	6	0 (0%)
Molar	2	0 (0%)	3	1 (33%)	4	1 (25%)
Depression score (mean, SD)						
Miscarriage	81	2.4 (2.9)	62	2.8 (3.4)	49	2.4 (2.4)
Ectopic pregnancy	17	1.9 (2.1)	16	2.3 (3.2)	13	2.9 (3.5)
Failed PUL	9	2.4 (2.5)	6	3.2 (2.9)	6	2.0 (1.7)
Molar	2	0.5 (0.7)	3	5.7 (9.0)	4	5.5 (9.0)
Moderate/severe depression (n, %)						
Miscarriage	81	2 (2%)	62	3 (5%)	49	0 (0%)
Ectopic pregnancy	17	0 (0%)	16	0 (0%)	13	0 (0%)
Failed PUL	9	0 (0%)	6	0 (0%)	6	0 (0%)
Molar	2	0 (0%)	3	1 (33%)	4	1 (25%)

Abbreviations: CI – confidence interval; HADS – Hospital anxiety and depression scale; PUL – pregnancy of unknown location; SD - Standard Deviation

Overall, there are were only 2(2%) partners with scores suggestive of depression at M1, and 7(6%) suggestive of anxiety. Scores and caseness was similar irrespective of type of loss, as can be seen in Table 9.6 (though numbers of losses other than miscarriage were very small).

In men normative population data from a study published in 2001, 17% meet criteria for mild anxiety according to HADS, 7% for moderate and 1% for severe. Rates are 6%, 1% and 1% for depression (164). Our study sample after pregnancy loss thus does not appear to have higher levels of moderate or severe anxiety or depression than this.

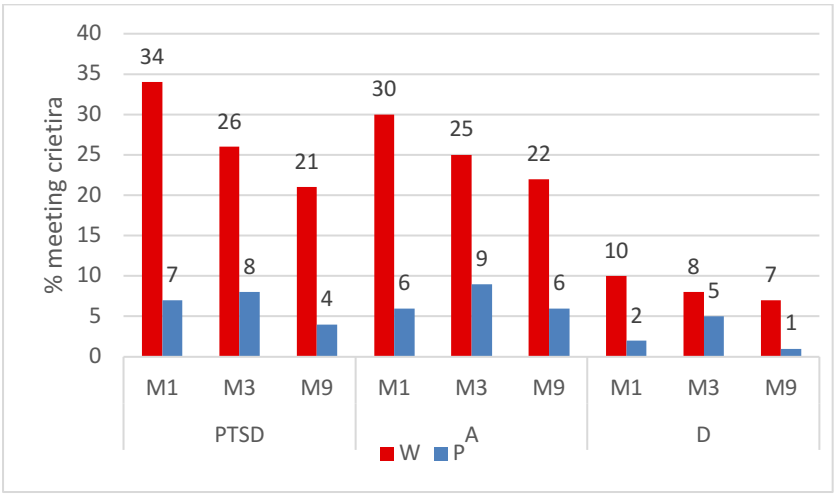
9.5 Results: PTSD in partners

A small proportion of patients met criteria for PTSD at every time point (7%, 8% and 4% at months 1, 3 and 9). The most commonly endorsed symptom cluster at all three timepoints was the re-experiencing cluster, followed by the avoidance cluster. A high proportion identified interruption of activities at every time point: at month interruption of sex life was most common; at subsequent time points it was 'general satisfaction with life'.

9.6 Results: comparison between women and partners

192 couples were included in this analysis. Women have a higher prevalence of PTSD, moderate-severe anxiety and depression, and higher mean scores at every timepoint than partners.

Figure 9.2 *Bar chart demonstrating proportions of women and partners meeting criteria for PTSD, moderate or severe anxiety (A) or depression (D) at 1-, 3- and 9-month assessments*



Abbreviations: M1 – month 1 questionnaire; M3 – month 3 questionnaire, M9 – month 9 questionnaire, P – partners; PTSD – posttraumatic stress disorder, W – women

Table 9.7 *Mean score, and proportion of partners meeting overall criteria, and criteria of each symptom cluster (subdivided by severity), according to the Posttraumatic Diagnostic Scale, in partners of women with losses, at three time points following early pregnancy loss*

	Month 1 N=107	**Month 3 N=83**	**Month 9 N=70**
Helpless	92/107 (86%)	69/83 (83%)	62/70 (88%)
Terrified	34/107 (32%)	28/83 (34%)	30/70 (43%)
Helpless OR Terrified	93/107 (87%)	70/83 (84%)	64/70 (91%)
Proportion meeting each symptom cluster*:			
Re-experiencing	84/107 (79%)	60/83 (72%)	46/70 (65%)
Avoidance	38/107 (36%)	28/83 (34%)	22/70 (31%)
Hyper-arousal	42/107 (39%)	31/83 (37%)	21/70 (30%)
All three clusters	24/107 (22%)	17/83 (20%)	13/70 (19%)
Interruption of activities			
Work	32/107 (30%)	18/83 (22%)	14/70 (20%)
Household chores	18/107 (17%)	11/83 (13%)	7/70 (10%)
Relationships with family	20/107 (19%)	16/83 (19%)	13/70 (19%)
Relationships with friends	22/107 (21%)	14/83 (17%)	15/70 (21%)
Fun and leisure activities	27/107 (25%)	16/83 (19%)	12/70 (17%)
Sex life	48/107 (45%)	30/83 (36%)	19/70 (27%)
General satisfaction with life	36/107 (34%)	33/83 (40%)	21/70 (30%)
Overall level of functioning	18/107 (17%)	19/83 (23%)	14/70 (20%)
Any interruption of activities	66/107 (62%)	47/83 (57%)	31/70 (44%)
>= 2 activities interrupted or interruption of overall functioning	48/107 (45%)	29/83 (35%)	24/70 (34%)
Score			
Score >=18	8/107 (7%)	10/83 (12%)	3/70 (4%)
Total proportion meeting Ehring criteria:			
Posttraumatic stress	7/107 (7%)	7/83 (8%)	3/70 (4%)

Abbreviations: M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire; PDS – Posttraumatic stress diagnostic scale;

Table 9.8 *Mean and standard deviation of anxiety, depression (according to HADS) and PDS scores, and the percentage of participants with moderate-severe symptoms (HADS) or meeting criteria for cases (PDS), following early pregnancy loss*

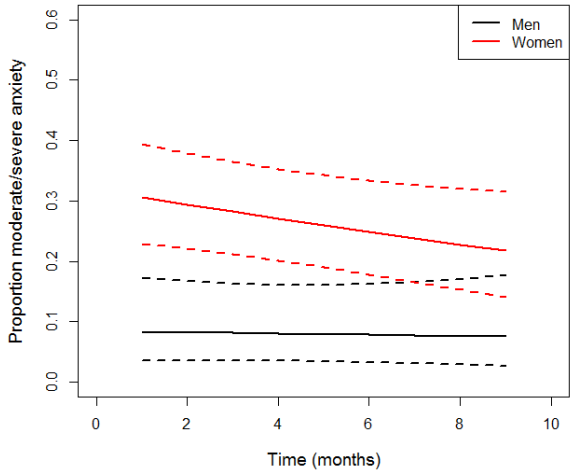
	Women			Partners		
	M1	**M3**	**M9**	**M1**	**M3**	**M9**
Number of HADS respondents	145	130	109	109	87	72
Mean Anxiety score (SD)	7.43 (4.41)	7.73 (4.20)	6.75 (4.41)	4.80 (3.60)	4.83 (3.75)	4.90 (3.97)
Anxiety moderate-severe cases (%)	44 (30%)	32 (25%)	24 (22%)	7 (6%)	8 (9%)	4 (6%)
Mean depression score (SD)	4.23 (4.32)	4.35 (4.01)	3.80 (3.82)	2.28 (2.72)	2.78 (3.53)	2.65 (3.21)
Depression moderate-severe cases (%)	15 (10%)	11 (8%)	8 (7%)	2 (2%)	4 (5%)	1 (1%)
Number of PDS respondents	144	129	108	107	83	70
Mean PDS score (SD)	14.1 (10.3)	11.8 (9.4)	10.4 (10.5)	7.1 (7.1)	6.7 (8.0)	5.2 (6.0)
PDS cases (%)	49 (34%)	33 26%)	23 (21%)	7 (7%)	7 (8%)	3 (4%)

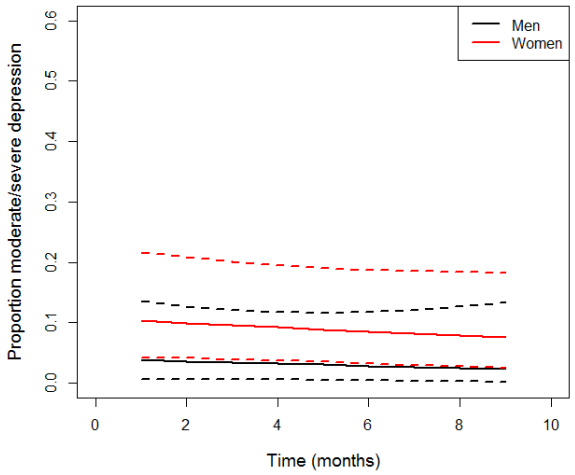
Abbreviations: HADS – Hospital Anxiety and Depression Scale; M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire; PDS – Posttraumatic stress diagnostic scale; SD - Standard Deviation

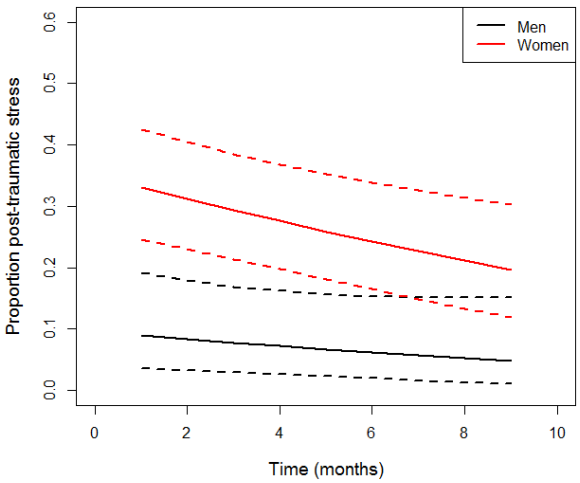
The evolutions of anxiety, depression and PTSD, based on a simple mixed effect model (including time (continuous) and gender), is shown in Figure 9.3. This demonstrates lower prevalence over the entire 9 months in partners, and little change in this prevalence over time. Further details of the statistical analysis can be seen in Appendix 8.

Based on this model, the odds ratio for anxiety in partners compared to women at M1 is 0.05, (95% CI 0.01-0.19). For depression it is 0.15 (95% CI 0.02- 0.96). For PTSD caseness at M1 it is 0.02 (95% CI 0.004-0.12). Thus, the probability of suffering from PTSD, or moderate or severe anxiety or depression is significantly lower for men than for women.

Figure 9.3 *Average evolutions for anxiety, depression and PTSD over time for women and partners after pregnancy loss based on a mixed effects model*







9.7 Discussion

At one month, 6% partners self-report symptoms suggestive of anxiety, 2% depression, and 7% PTSD. There is no appreciable decline in caseness over time. The probability of reporting symptoms suggestive of anxiety, depression and PTSD is significantly lower for partners than for women following EPL.

A strength of this study is that it involved a large, consecutively recruited group of partners, with assessment at set timepoints. It is the first study to assess for PTSD in partners.

However, a minority of women's partners were present at the appointment to be approached, and only half of those present agreed to take part. This is likely to introduce participation bias. It is reassuring that clinical encounters appeared similar between the recruited and non-recruited group, and also that that women whose partners were recruited had similar levels of anxiety, depression and PTSD overall to the whole group (30%, 10% and 34% respectively at M1, compared to 24%, 11% and 29%). The attrition rate was also very high; even higher for partners than it was for women. It is reassuring that partners had similar baseline psychometric scale scores regardless of how long they participated for. Non-participation is an inevitability in studies of this nature.

As previously discussed, there may be debate as to whether the experience of early pregnancy loss fulfils criteria of a 'traumatic event' for the diagnosis of PTSD. The requirement for exposure to real or threatened death or serious injury to be directly witnessed may be fulfilled when the partner plays an active role in supporting a woman with catastrophic bleeding. This may also be considered fulfilled when the partner witnesses the 'death' of a fetus (though whether a pre-viable fetus can 'die' may be subject to debate, as may the degree to which seeing an ultrasound image, or blood perhaps, is classed as 'witnessing'). On balance, these criteria were clearly not established to deliberately exclude EPL – and, in cases where partners experience symptom clusters suggestive of PTSD otherwise, it does not seem appropriate to disregard the diagnosis. The PDS has, however, not been validated in partners in this context, and this would be a priority before PTSD-specific treatment for partners after loss was considered.

Our results for anxiety and depression are similar to two other studies, one in Hong Kong and one in the UK, from a decade previously (100, 111). One small study of 25 partners suggested considerably higher results, but this is likely to reflect small numbers (and potentially participant selection) (106).

9.8 Conclusions

Partners do not seem to suffer from significant anxiety or depression above the level seen in the background population. A small minority meet screening criteria for PTSD relating to the loss. In view of the high frequency of losses, they potentially contribute significantly to the overall burden of psychopathology in men. Whether such impact is amenable to treatment should be the subject of further research.

Chapter 10: Conclusions

10.1 Introduction

This thesis set out to explore the extent and determinants of the psychological impact of early pregnancy loss. This chapter discusses the key findings of the presented work in relation to each hypothesis. It concludes with a discussion of the broad methodological limitations of the research to date, directions for future research, and consideration of the wider implications of the findings.

10.2 Summary of evidence

Hypothesis 1: Women have a higher prevalence of moderate and severe anxiety and depression following an early pregnancy loss than in a healthy early pregnancy

The systematic review presented in Chapter 2 summarises past evidence that both anxiety and depression scores (17, 120) and caseness (115) are higher after EPL than in a pregnant comparison group within the first two months after a loss.

In our study, 24% women met the threshold for moderate or severe anxiety, and 11% for depression, one month after a loss, compared to 13% and 3% respectively in the control group in healthy pregnancy. These translate into an adjusted odds ratio for anxiety of 2.14 (95% CI 1.14 to 4.36), and for depression of 3.88 (95% CI 1.27-19.16). We have thus found evidence to support this hypothesis.

Hypothesis 2: The prevalence and severity of anxiety and depression declines over time in those who do not experience further losses

Our evidence suggests that, in the average individual, who does not experience further losses or pregnancies, the odds of experiencing moderate or severe anxiety decrease by 31% each month (OR 0.69, 95% CI 0.50-0.94) and of depression by 13% (OR 0.87, 95% CI 0.53 – 1.44) each month. Mean scores also decline.

This is consistent with a general decline in anxiety and depression caseness seen in papers with multiple assessments (64, 93, 100, 109, 114, 118, 121). Importantly, however, ours is the first study to control for further losses or pregnancies.

Hypothesis 3: There is a high incidence of posttraumatic stress in women following a loss, and the prevalence and severity decline over time.

In our study, 29% met criteria suggestive of PTSD using the posttraumatic diagnostic scale at one month, 21% at three months and 18% at nine months. Severity scores also decline over time. This was by far the largest study to date assessing PTSD.

Our structured interview assessment in 10% of participants verified a similar proportion (27%) of individuals meet DSM-5 criteria for PTSD at interview a mean of two months after EPL.

Hypothesis 4: Women who have experienced an ectopic pregnancy will suffer psychological sequelae

Overall, the rates of psychopathology in the group with ectopic pregnancy and those with miscarriage are similar.

Modelling the evolution over time for the average individual suggests that the decrease in probability of experiencing moderate to severe anxiety and depression seems to be slightly steeper following miscarriage than following ectopic pregnancy (p values 0.14 for anxiety and 0.06 for depression).

Hypothesis 5: Anxiety, depression and posttraumatic stress at 1 month can be predicted by pre-existing and encounter-related factors

There was some evidence from our research that a higher likelihood of reaching a threshold for depression, anxiety or posttraumatic stress symptoms may be associated with a past or current diagnosis of psychiatric disorder, worry for wellbeing and sense of responsibility. There is also a slight association with previous loss.

In addition to the above, previous studies have suggested that IVF pregnancy and childlessness may be risk factors for greater distress.

Overall, these factors explain very little of the variation in psychological morbidity from one individual to the next, and it is unlikely that a useful predictive model could be developed. All women after EPL should be deemed at risk of psychopathology.

Hypothesis 6: Partners suffer from anxiety, depression and posttraumatic stress, but to a lesser degree than women, and with quicker resolution.

Evidence suggests that the average partner has significantly lower odds of experiencing either depression or anxiety one month after loss (odds ratio 0.05 for anxiety and 0.15 for depression). A small proportion of partners exhibit symptoms suggestive of PTSD (7% at one month), with an odds ratio compared to women of 0.02.

10.3 Methodological limitations

10.3.1 Non-participation, non-response and drop out

The majority of quoted studies, including our own, suffered high non-participation, non-response and drop-out. Our own methodology, with consecutive approach for participation, and in which consent was generally taken on the day of approach, and relying on email invitations to participate, is bound to suffer lower response rates. Response relied on the participant: 1) receiving the email (often to a work address) at a convenient moment – or remembering to fill it in later; 2) without incentive, being sufficiently generous with their time to complete it. Inevitably, our requests served of reminders of sad or uncomfortable events, and it is easy to see why an individual may prefer to ignore them. Although we found no evidence that those with high psychopathology at M1 were more or less likely to drop out, it is possible that the group who did not respond throughout are different. They may have been more affected: research in the context of industrial disasters has indicted that those most affected by trauma will avoid participation (124). In the context of terminations of pregnancy, research has also shown lower participation in those most likely to be vulnerable to psychological morbidity (123). Conversely, those less affected may not see the importance of the research, and choose not to invest time in it.

It is important to interpret all research in this field in this context. However, even if results are inflated by involvement of those more affected (and this is not balanced by avoidant behaviour of those most affected), one must keep sight of the fact that even much lower proportions, in the context of high frequency of EPL, would still point to a significant public health issue.

10.3.2 Potential impact of participation

There may be an unintended therapeutic benefit of taking part. One would expect our own online questionnaire to be less at risk of this than studies involving interviews – but all studies with

repeated assessments may be at risk of underestimating pathology in an unassessed group at later time points, and overestimating resolution.

10.3.3 PTSD as a diagnosis

PTSD itself is a diagnosis more often associated with military combat, and central to its understanding is of response to an 'extra-ordinary' stressor. Can an event that happens to 1:4 women be considered extra-ordinary?

Looking closely at the diagnostic criteria for PTSD (as in Chapter 2), it requires experiencing real or threatened serious injury to 'self or others' The most objectively horrifying versions of events – when a women suddenly expels a clearly identifiable fetus, or has life-threatening intra-abdominal bleeding associated with an ectopic - are easy to interpret in this context. However, less extreme events could qualify: even if they are not objectively threatening to the life or wellbeing of the patient, they may be interpreted as such, and they are clearly threatening to the fetus (if we consider an unborn child as the 'other'). DSM-5 actually specifies that medical incidents may quality if they involve 'sudden, catastrophic events' – a pregnancy loss is usually sudden, and always catastrophic to the pregnancy.

The response to the pilot study from members of the public was interesting: while the majority of those commenting appreciated the research, a small minority reported offence that the diagnosis was being "taken in vain" for something that was part of normal life, thereby belittling its use in the context of more extreme violence. This perhaps goes to the root of the issue: that women are expected to see a loss as 'normal'.

Of course, there is no doubt that PTSD as a diagnosis was not originally conceived in relation to such a common stressor. A case could in fact be made for its own specific diagnosis -of a 'post-pregnancy loss stress syndrome'. Such a diagnosis may differ in its diagnostic criteria in order to maximise specificity for those with an extreme and clinically important reaction. A case for such a diagnosis would require intensive exploration by interview of a large number of affected individuals.

10.3.4 Use of self-assessment screening tools

Screening for psychiatric disorders on a large scale for research relies on self-assessment tools. It also necessarily excludes those that don't speak English to a sufficient standard.

Our own study benefited from structured interview assessment for PTSD in a proportion of individuals, which seemed to corroborate our finding of high overall rates of PTSD, though the concordance with the self-assessment was slightly lower than expected. We have not validated the PDS in partners, and therefore cannot comment on its reliability as a measure in this population.

10.3.5 Cut-offs to define caseness

Research in psychology necessarily relies on defined cut-offs to identify pathology, with a high proportion of individuals exhibiting low level symptoms. For example, results from HADS in female respondents to M1 shows that only 6% did not endorse any anxiety symptoms, and 18% any depressive symptoms.

Cutoffs inevitably result in a gross oversimplification of the issue, with those falling beneath the score thresholds also likely to have important symptoms. While proportions with 'disease' are an important bottom-line to assess or change policy, to ignore those without is a mistake. Instead, the results should be viewed by policy-makers as the 'tip of the iceberg', with sub-syndromal symptoms having important implications.

10.3.6 Causality

It is plausible that pre-existing anxiety or depression increases the risk of pregnancy loss, with some evidence, as discussed in Chapter 2, to support this. Methodologically, none of the studies have been capable of assessing women prior to the pregnancy or complications. Consistent improvement over time after loss does provide some evidence to support the loss itself being at the root of an exacerbation. Moreover, PTSD is a diagnosis that relates to a particular trauma – in our research, questions specifically related to the EPL (though pre-existing psychopathology undoubtedly increases risk).

It is also important to consider that anxiety and depression maybe the result of involuntary childlessness and unwanted delays to conception, rather than the loss itself. Again, improvement over time in those without further losses or pregnancies suggests otherwise. Previous evidence suggests that childlessness, and antecedent subfertility are both risk factors for psychopathology after miscarriage: our data, however, did not support this.

10.4 Suggestions for future research

10.4.1 Assessment of intervention

Importantly, while we have established that psychological morbidity exists following EPL, it remains to be seen whether intervention is beneficial.

The Cochrane review, published in 2012, suggested little evidence that a broadbrush approach of 'counselling' (mostly one session, by a range of providers – midwives, nurses and psychologists)- in an unselected population was effective in improving symptoms of depression and anxiety (5). However, there was no assessment of interventions specifically targeted at psychiatric disorders, nor was an improvement in PTSD symptoms assessed for.

Evidence on PTSD in other contexts reveals that it warrants specific treatment by professionals. Single session interventions ('debriefing') with a focus on the traumatic incident are not recommended and may even be counterproductive (167). The recommended management for those presenting within three months of the event is 'trauma-focused cognitive behavioural therapy (CBT)'. This generally requires 8 to 12 sessions (though if it is started within one month, fewer sessions may be needed), and should be delivered by the same person, on a regular (usually weekly) basis. Drug treatment may be considered second line.

A first suggested line of investigation would thus be to see if trauma-focused CBT may be of benefit in the pregnancy loss population. It is probable that treatment focusing on elements specific to pregnancy loss could be optimized. There is also some emerging evidence for the use of Acceptance and Commitment Therapy (which targets symptoms of avoidance) in PTSD (168).

10.4.2 Assessment of screening

The performance and cost-efficacy of a screening instrument (potentially similar to the PDS) after a loss should be robustly assessed. The introduction of systematic screening at, for example, six weeks after a loss would require evidence that such a policy would be capable of improving outcome by correctly triaging those in need of, and benefitting from, intervention.

10.5 Suggestions for clinical practice

10.5.1 Optimisation of routine care

Key to the development of PTSD is the cognitive appraisal of the event. Thorough, accurate explanations of what to expect during the course of routine appointments may be preventative. Contributing to a women's sense of control by giving a choice of management strategies where appropriate, and timely access to surgical management (such that unplanned conservative management is less likely) may also be helpful.

We have found evidence that those who felt responsible for the loss scored more highly in measures of anxiety, depression and posttraumatic stress. Evidence also suggests self-blame is promoted by the absence of a medical explanation(101). Discussing likely aetiology may thus be helpful (such as the high possibility of a genetic cause, which is likely to be incompatible with life). Conversely, care should be taken when, for example, conveying normal cytogenetic analyses that the patient is not left feeling at fault.

While awaiting evaluation of the efficacy of screening, clinicians should utilize existing opportunities to enquire about mental health. Symptoms in the immediate aftermath of EPL may resolve spontaneously, but a clear plan should be made for further assessment of symptoms of anxiety, depression and PTSD. Until the efficacy of pregnancy-loss specific treatment is proven, these conditions should prompt treatment or referral as they would otherwise, in accordance with national guidance.

10.5.2 General awareness of psychological sequelae

In view of the high levels of anxiety, depression and posttraumatic stress symptoms in the aftermath of EPL, women, and those caring for them, must be made aware of this risk. There is currently much less awareness amongst healthcare professionals than of post-natal depression (169).

Legitimation and understanding of emotional symptoms are likely to be an important step in recovery. Moreover, early recognition and treatment, especially with PTSD, may be more effective. Thus, discussion of emotional responses should be a standard part of each consultation. It should also form part of a discharge letter to a GP – for example:

"we have advised the patient that it is common following early pregnancy loss to experience psychological symptoms, including anxiety, depression and posttraumatic stress. If they, or those

around them, are concerned that they may be developing symptoms of these conditions, they have been advised to see you to discuss treatment".

There is often a stark contrast between the hospital management of early and late losses: in the hospitals involved in this research, there is a cut-off of 20 weeks above which there is access to specialist bereavement midwife support. The implication that those beneath this threshold do not need as much support is not founded in research, and should be challenged.

10.6 Concluding remarks

Pregnancy loss is ubiquitous, and complications in early pregnancy form a significant element of the clinical work of gynaecologists and general practitioners. In the context of such frequency, it is all too easy to forget how profound the diagnosis of the end of a pregnancy can be. Pregnancy itself represents the most major of life's transitions: the unexpected and involuntary loss of an object of such intense emotional investment is undeniably significant.

The response to the pilot study indicated that this is a subject that struck a chord with many. Amongst the vitriole of ex-army officers (concluding that PTSD was a diagnosis that should be saved for those returning from the battlefield) was a humbling level of gratitude from women who felt that for too long, their story – of bitter disappointment, unacknowledged bereavement, self-blame, fear and often intense physical trauma – had been untold. As journalist Anna Whitehouse wrote in a personal interview in response to our pilot publication:

" miscarriage is deeply traumatic. If you know what it is to love someone, you know what it is to lose someone…. The post-miscarriage questioning is relentless, the guilt overwhelming. Yet I boxed this all up – other people seemed to navigate it without any public displays, I thought, and so should I"

Allowing women to talk about the trauma, and not to attempt to ignore it, is an essential first step. It remains to be seen exactly what intervention may be helpful, and in whom – but there is little doubt that a more widespread awareness of the emotional sequelae, such that it is identified and treated more readily, will be helpful.

It has been a privilege, albeit a sad one, to attempt to raise awareness of these issues, in the hope that doing so will change the narrative of the average clinical encounter to acknowledge a justified sense of horror, loss and fear for the future.

Appendices:

Appendix 1: Systematic Review Search Criteria

Embase search criteria
1. blighted ovum/ or incomplete abortion/ or missed abortion/ or recurrent abortion/ or spontaneous abortion/ 2. ectopic pregnancy/ 3. (Miscarriage or ectopic pregnanc*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 4. (pregnancy loss or pregnancy losses).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 5. 1 or 2 or 3 or 4 6. anxiety disorder/ or acute stress disorder/ or generalized anxiety disorder/ or "mixed anxiety and depression"/ or posttraumatic stress disorder/ 7. depression/ 8. (Anxiety or depress* or post-traumatic stress).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 9. 6 or 7 or 8 10. 5 and 9

Medline search criteria
1. abortion, spontaneous/ or abortion, habitual/ or abortion, incomplete/ or abortion, missed/ or abortion, septic/ or abortion, threatened/ or embryo loss/ 2. pregnancy, ectopic/ or pregnancy, abdominal/ or pregnancy, angular/ or pregnancy, cornual/

or pregnancy, heterotopic/ or pregnancy, ovarian/ or pregnancy, tubal/ or pregnancy, interstitial/

3. (Miscarriage or ectopic pregnanc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4. (pregnancy loss or pregnancy losses).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

5. 1 or 2 or 3 or 4

6. "trauma and stressor related disorders"/ or adjustment disorders/ or stress disorders, traumatic/ or psychological trauma/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/

7. Anxiety Disorders/

8. Depression/

9. (Anxiety or depress* or post-traumatic stress).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

10. 6 or 7 or 8 or 9

11. 5 and 10

Psychinfo search criteria

1. exp Spontaneous Abortion

2. (ectopic adj1 pregnanc*).mp. [mp=title, abstract, heading word, table of contents, key concep original title, tests & measures]

3. (pregnancy adj1 loss).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

4. exp ANXIETY/

5. exp MAJOR DEPRESSION/

6. exp Posttraumatic Stress Disorder/ or exp Post-Traumatic Stress/

7. 1 or 2 or 3

8. 4 or 5 or 6

9. 7 and 8

Appendix 2: Newcastle-Ottowa Quality Assessment Scale for Cohort Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community ✵

b) somewhat representative of the average _____ in the community ✵

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort ✵

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) ✵

b) structured interview ✵

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ✵

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) ✹

b) study controls for any additional factor ✹ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment ✹

b) record linkage ✹

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) ✹

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for ✹

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✹

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

Appendix 3: HADS

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Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Appendix 4: PDS

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PDS

Part 1

Many People have lived through or witnessed a very stressful and traumatic event at some point in their lives. Below is a list of traumatic events. Put a checkmark in the box next to ALL of the events that have happened to you or that you have witnessed.

(1) ☐ Serious accident, fire, or explosion (for example, an industrial, farm, car, plane, or boating accident)

(2) ☐ Natural disaster (for example, tornado, hurricane, flood, or major earthquake)

(3) ☐ Non-sexual assault by a family member or someone you know (for example, being mugged, physically attacked, shot, stabbed, or held at gunpoint)

(4) ☐ Non-sexual assault by a stranger (for example, being mugged, physically attacked, shot, stabbed, or held at gunpoint)

(5) ☐ Sexual assault by a family member or someone you know (for example, rape or attempted rape)

(6) ☐ Sexual assault by a stranger (for example, rape or attempted rape)

(7) ☐ Military combat or war zone

(8) ☐ Sexual contact when you were younger than 18 with someone who was 5 or more years older than you (for example, contact with genitals, breasts)

(9) ☐ Imprisonment (for example, prison inmate, prisoner of war, hostage)

(10) ☐ Torture

(11) ☐ Life-threatening illness

(12) ☐ Other traumatic event

(13) If you marked item 12, specify the traumatic event below.

_____

IF YOU MARKED ANY OF THE ITEMS ABOVE, CONTINUE. IF NOT, STOP HERE.

Part 2

(14) If you marked more than one traumatic event in Part 1, put a checkmark in the box below next to the event *that bothers you the most*. If you marked only one traumatic event in Part 1, mark the same one below.

☐ Accident
☐ Disaster
☐ Non-sexual assault by family or someone you know
☐ Non-sexual assault by a stranger
☐ Sexual assault by family or someone you know
☐ Sexual assault by a stranger
☐ Combat
☐ Sexual contact under 18 with someone 5 or more years older
☐ Imprisonment
☐ Torture
☐ Life-threatening illness
☐ Other

In the lines below, briefly describe the traumatic event you marked above.

_____
_____
_____
_____

Below are several questions about the traumatic event you just described above.

(15) How long ago did the traumatic event happen? (circle ONE)

1 Less than 1 month
2 1 to 3 months
3 3 to 6 months
4 6 months to 3 years
5 3 to 5 years
6 More than 5 years

For the following questions, circle Y for Yes or N for No.

During this traumatic event:

(16) Y N Were you physically injured?
(17) Y N Was someone else physically injured?
(18) Y N Did you think that your life was in danger?
(19) Y N Did you think that someone else's life was in danger?
(20) Y N Did you feel helpless?
(21) Y N Did you feel terrified?

Part 3

Below is a list of problems that people sometimes have after experiencing a traumatic event. Read each one carefully and circle the number (0-3) that best describes how often that problem has bothered you IN THE PAST MONTH. Rate each problem with respect to the traumatic event you described in Item 14.

0 Not at all or only one time
1 Once a week or less/once in a while
2 2 to 4 times a week/half the time
3 5 or more times a week/almost always

(22)	0	1	2	3	Having upsetting thoughts or images about the traumatic event that came into your head when you didn't want them to
(23)	0	1	2	3	Having bad dreams or nightmares about the traumatic event
(24)	0	1	2	3	Reliving the traumatic event, acting or feeling as if it was happening again
(25)	0	1	2	3	Feeling emotionally upset when you were reminded of the traumatic event (for example, feeling scared, angry, sad, guilty, etc.)
(26)	0	1	2	3	Experiencing physical reactions when you were reminded of the traumatic event (for example, breaking out in a sweat, heart beating fast)
(27)	0	1	2	3	Trying not to think about, talk about, or have feelings about the traumatic event
(28)	0	1	2	3	Trying to avoid activities, people, or places that remind you of the traumatic event
(29)	0	1	2	3	Not being able to remember an important part of the traumatic event
(30)	0	1	2	3	Having much less interest or participating much less often in important activities
(31)	0	1	2	3	Feeling distant or cut off from people around you
(32)	0	1	2	3	Feeling emotionally numb (for example, being unable to cry or unable to have loving feelings)
(33)	0	1	2	3	Feeling as if your future plans or hopes will not come true (for example, you will not have a career, marriage, children, or a long life
(34)	0	1	2	3	Having trouble falling or staying asleep
(35)	0	1	2	3	Feeling irritable or having fits of anger
(36)	0	1	2	3	Having trouble concentrating (for example, drifting in and out of conversation, losing track of a story on television, forgetting what you read)
(37)	0	1	2	3	Being overly alert (for example, checking to see who is around you, being uncomfortable with your back to a door, etc.)
(38)	0	1	2	3	Being jumpy or easily startled (for example, when someone walks up behind you)

(39) How long have you been experiencing the problems that you reported above? (circle ONE)

1 Less than 1 month

2 1 to 3 months

3 More than 3 months

(40) How long after the traumatic event did these problems begin? (circle ONE)

1 Less than 6 months

2 6 or more months

Part 4

Indicate below if the problems you rate in Part 3 have interfered with any of the following areas of your life DURING THE PAST MONTH. Circle Y for Yes and N for No.

(41)	Y	N	Work
(42)	Y	N	Household chores and duties
(43)	Y	N	Relationships with friends
(44)	Y	N	Fun and leisure activities
(45)	Y	N	Schoolwork
(46)	Y	N	Relationships with your family
(47)	Y	N	Sex life
(48)	Y	N	General satisfaction with life
(49)	Y	N	Overall level of functioning in all areas of your life

Appendix 5: Detailed recruitment data

Recruitment according to hospital site

Table A5.1 *Women and their partners with early pregnancy loss: A summary of time available for recruitment, numbers approached and recruited, and reasons for non-recruitment (broken down by site)*

	Hammersmith 13/11/13 – 6/1/16 (Mean 0.5 days/week)		**St Mary's** 11/4/14 – 15/3/16 (Mean 3 days/week)		**Chelsea & Westminster** 18/11/14 – 3/3/16 (Mean 3 days/week)	
	Women (number)	**Partners (number)**	**Women (number)**	**Partners (number)**	**Women (number)**	**Partners (number)**
Approached	220	90	639	178	342	118
Not present (partners only)	n/a	168	n/a	458	n/a	224
Recruited % of all approached	134 (61%)	52 (58%)	405 (63%)	85 (48%)	198 (58%)	55 (47%)
Declined % of all eligible	62 (32%)	36 (41%)	181 (31%)	82 (49%)	124 (39%)	58 (51%)
Ineligible % of all approached	24 (11%)	2 (2%)	53 (8%)	11 (6%)	26 (8%)	5 (4%)
Reason (if volunteered) for declining participation:						
No reason given	30	27	96	56	51	34
Requested time to consider, but consent not returned by post	18	8	47	16	42	22
Unplanned pregnancy	1	0	5	0	8	2
Doesn't want to be reminded	6	0	15	2	13	0
Time commitment	5	1	7	8	2	0
No access to email	2	0	11	0	2	0
Reason ineligible:						
Insufficient English	16	2	45	11	23	3
Already in study from previous loss	8	0	7	0	3	2
No mental capacity	0	0	1	0	0	0

Table A5.2 *Women in healthy pregnancy (Control Group): A summary of time available for recruitment, numbers approached and recruited, and reasons for non-recruitment (according to site of recruitment)*

	Hammersmith 12 individual mornings between 23/11/13 and 20/3/14	**St Mary's** 10 individual mornings between 20/08/15 and 21/12/15	**Chelsea & Westminster** 6 individual days between 10/8/15 and 9/2/16
Approached	76	60	59
Recruited **% of all approached**	69 (91%)	53 (88%)	49 (83%)
Declined **% of all eligible**	6 (8%)	3 (5%)	7 (12%)
Ineligible **% of all approached**	1 (1%)	4 (7%)	3 (5%)
Reason (if volunteered) for declining participation:			
No reason given	4	2	2
Felt 'tempting fate'	0	1	0
Requested time to consider, but consent not returned by post	1	0	4
Time commitment	1	0	1
Reason ineligible:			
Insufficient English	1	4	3

Response rates in women according to hospital site

Table A5.3 *Response rates, non-response and withdrawal in women with early pregnancy loss, according to hospital of recruitment*

	Hammersmith	**St Mary's**	**Chelsea & Westminster**	**All Sites**
Recruited	134	405	198	737
E-mail address invalid	0	6 (1%)	2 (1%)	8 (1%)
Active withdrawal before P1 completed	4 (3%)	5 (1%)	2 (1%)	11 (1%)
P1 respondents **%**	92 (69%)	265 (65%)	147 (74%)*	504 (68%)
Passive non-response to P1	38 (28%)	129 (32%)	47 (24%)	214 (29%)
E-mail address invalid	0	6 (1%)	2 (1%)	8 (1%)
Active withdrawal before P2 completed	5 (4%)	10 (2%)	4 (2%)	19 (3%)

P2 respondents %	73 (54%)	222 (55%)	131 (66%)*	426 (58%)
Passive non-response to P2	56 (42%)	167 (41%)	61 (31%)	284 (39%)
E-mail address invalid	0	9 (2%)	3 (1%)	12 (2%)
Active withdrawal before P3 completed	7 (5%)	14 (3%)	6 (3%)	27 (4%)
P3 respondents %	68 (51%)	178 (44%)	97 (49%)	343 (47%)
Passive non-response to P3	59 (44%)	204 (50%)	92 (46%)	355 (48%)

P1 Part One: P2 Part 2: P3: Part 3: HH Hammersmith Hospital: SMH St Mary's Hospital: CW Chelsea and Westminster

*significantly (at P<0.05) higher response rate than SMH

Table A5.4 *Response rates, non-response and withdrawal, in women in healthy early pregnancy (control group), according to hospital of recruitment*

	Hammersmith	**St Mary's**	**Chelsea and Westminster**	**All sites**
Recruited	69	53	49	171
Subsequent miscarriage*	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Unable to confirm viability*	1 (2%)	1 (2%)	0 (0%)	2 (1%)
E-mail address invalid	0 (0%)	2 (4%)	2 (4%)	4 (2%)
Active withdrawal	4 (6%)	1 (2%)	0 (0%)	5 (3%)
Respondents	31 (45%)	27 (51%)	30 (61%)	88 (51%)
Passive non-response	33 (48%)	21 (40%)	17 (35%)	71 (42%)

*In the control group, the questionnaire was only sent after viability on the first routine scan (aimed to be performed between 11 and 13+6 weeks) was confirmed. In one case we were a miscarriage was confirmed after recruitment, and in two cases we could not identify the results of this scan.

Comparison of women whose partners were and were not recruited

Table A5.5 *Table of clinical details of those women with EPL with and without recruited partners*

	Women without partner recruited (n=545)	**Women with partners recruited (n=192)**
Gestation at diagnosis of loss *(days)*	Mean 65.4 (SD 20.0) Range 2-138	Mean 66.0 (SD 20.7) Range 22-123
Reason for referral		
Pain/bleeding	402/545 (73%)	120/192 (63%)
Incidental finding on scan	39/545 (7%)	56/192 (29%)
Clear passage of pregnancy	5/545 (1%)	1/192 (1%)
Other	96/545 (17%)	15/192 (8%)
No clear reason documented	3/545 (0%)	0/192 (0%)
IVF pregnancy	37/545 (7%)	13/192 (7%)
Final diagnosis		
Miscarriage	394/545 (72%)	143/192 (74%)
Ectopic pregnancy	90/545 (17%)	26/192 (14%)
Failed PUL	43/545 (8%)	15/192 (8%)
Persistent PUL	5/545 (1%)	0/192 (0%)
Molar pregnancy	13/545 (2%)	8/192 (4%)
Fetal heart pulsations previously seen on scan (miscarriage/molar pregnancy)		
Yes	91/407 (22%)	34/151 (23%)
Yes with concerns	7/407 (2%)	0/151 (0%)
No	306/407 (75%)	116/151(77%)
Unknown	4/407 (1%)	1/151 (1%)
Final management		
No active intervention necessary	187/545 (34%)	57/192 (30%)
Medical management of miscarriage	33/545 (6%)	18/192 (9%)
Surgical management of miscarriage	237/545 (43%)	93/192 (48%)
Methotrexate	17/545 (3%)	5/192 (3%)
Salpingectomy	50/545 (9%)	16/192 (8%)
Salpingotomy	5/545 (1%)	0/192 (0%)
Other surgical intervention	6/545 (1%)	1/192 (1%)
Lost to follow-up	10/545 (2%)	2/192 (1%)
Emergency surgical management‡	97/545 (17%)	27/192 (14%)
Emergency admission	110/545 (14%)	38/192 (20%)
Blood transfusion	18/545 (2%)	3/192 (2%)

Abbreviations: IVF – in vitro fertilization; PUL – pregnancy of unknown location

Response rates in partners according to site of recruitment

Table A5.6 *Response rates in partners of women with early pregnancy loss, according to hospital of recruitment*

	Hammersmith	St Mary's	Chelsea & Westminster	All Sites
Recruited	52	85	55	192
E-mail address invalid	0	3 (4%)	0	3 (2%)
Active withdrawal before M1 completed	0	1 (1%)	0	1 (1%)
M1 respondents **%**	26 (50%)	53(35%)	35 (64%)	114 (59%)
Passive non-response to M1	26 (50%)	28(33%)	20 (36%)	74 (39%)
E-mail address invalid	0	3 (4%)	0	3 (2%)
Active withdrawal before P3 completed	0	2 (2%)	0	2 (1%)
P3 respondents **%**	21 (40%)	39 (46%)	29 (53%)	89 (46%)
Passive non-response to M3	31 (60%)	41 (48%)	26 (47%)	98 (51%)
E-mail address invalid	1 (2%)	4 (5%)	0	5 (3%)
Active withdrawal before M9 completed	1 (2%)	2 (2%)	0	3 (2%)
M9 respondents	18 (35%)	30 (35%)	25 (45%)	73 (38%)
Passive non-response to M9	32 (62%)	49 (58%)	30 (55%)	111 (58%)

Response pattern in partners according baseline data

Table A5.7 Baseline data according to response status (non-responders, versus last information at M1/M3, versus last information at M9) in partners of women with EPL

Variable	No response (n=67)		Last info at M1/M3 (n=53)		Last info at M9 (n=72)	
	Mean (SD), or n (%)	Missings	Mean (SD), or n (%)	Missings	Mean (SD), or n (%)	Missings
Background demographic and clinical data						
Type of loss:						
Miscarriage (inc molar)	55 (82%)	0	43 (81%)	0	53 (74%)	0
Ectopic	7 (10%)	0	6 (11%)	0	13 (18%)	0
Resolved PUL	5 (7%)	0	4 (8%)	0	6 (8%)	0
Age	n/a		35 (6)	9 (17%)	36 (5)	7 (10%)
Proportion with children	n/a		14 (31%)	8 (15%)	13 (20%)	7 (10%)
M1 responses						
Desire for pregnancy *Likert scale 1 – not at all, 4 – very much*	n/a		3.6 (0.9)	8 (15%)	3.6 (0.9)	7 (10%)
Distress about loss *Likert scale 1 – not at all, 5 – extremely*	n/a		3.8 (0.9)	8 (15%)	3.7 (0.9)	7 (10%)
Satisfaction with healthcare *Likert scale 1-not at all, 5 – very, excellent*	n/a		3.9 (0.9)	8 (15%)	4.0 (0.9)	7 (10%)
Highest level of education						
A-levels or lower	n/a		11 (24%)	8 (15%)	10 (15%)	6 (8%)
University degree			25 (56%)		36 (55%)	
Post-graduate degree/doctorate			9 (20%)		20 (30%)	
Annual income						
<£25000	n/a		3 (7%)	8 (15%)	0 (0%)	6 (8%)
£25-50 000			13 (29%)		8 (12%)	
£50-100 000			16 (35%)		25 (38%)	
>£100 000			13 (29%)		33 (50%)	

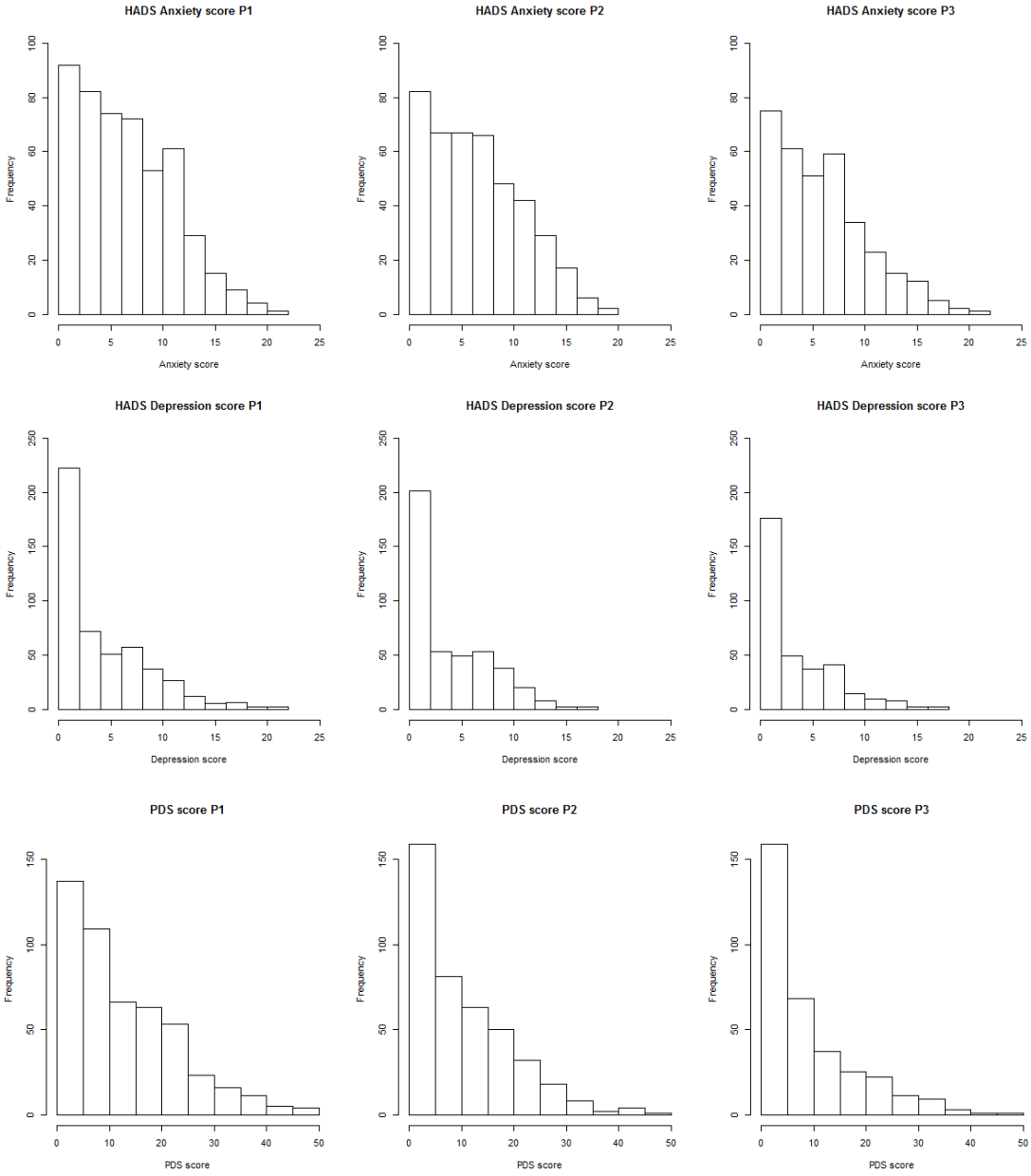
Psychiatric disorder						
No	n/a		39 (87%)	8 (15%)	56 (85%)	6 (8%)
Yes currently (< 6 months)			0 (0%)		0 (0%)	
Yes in past (> 6 months)			6 (13%)		10 (15%)	
Time taken to conceive						
< 3 months/unplanned	n/a		25 (56%)	8 (15%)	43 (65%)	6 (8%)
3-12 months			13 (29%)		12 (18%)	
> 12 months			7 (16%)		11 (17%)	
M3 responses						
Trying to conceive at M3						
Pregnant	n/a		4 (16%)	28 (53%)	7 (11%)	9 (13%)
Further EPL			1 (4%)		0 (0%)	
Not trying to conceive			13 (52%)		19 (30%)	
Trying to conceive			7 (28%)		37 (59%)	

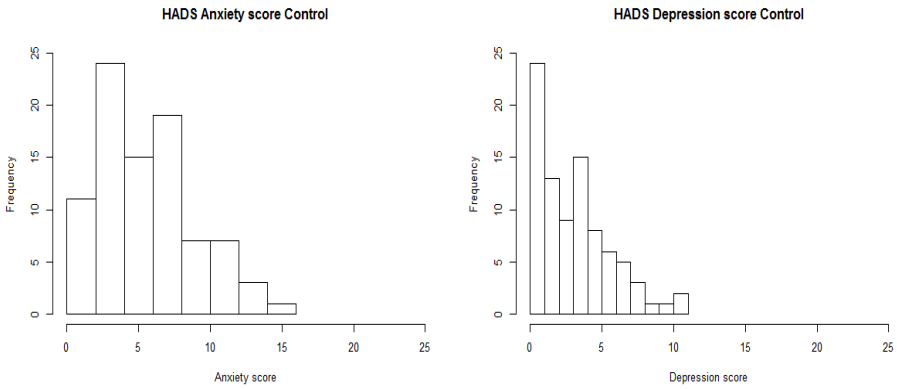
Abbreviations: EPL – Early Pregnancy Loss; M1 – month 1 questionnaire; M3 – month 3 questionnaire; M9 – month 9 questionnaire; PUL - pregnancy of unknown location

Appendix 6: Statistical analysis of anxiety, depression and PTSD after losses, compared to those with viable pregnancies, and over time

Histograms of HADS and PDS scores in women at each time point

Figure A5.1 *Histograms of HADS anxiety and depression scores, and PDS scores, at each time point*





Abbreviations: P1 – part 1 (1 month after EPL); P2 – part 2 (3 months after EPL); P3 – part 3 (9 months after EPL)

Comparison to control group: multivariate analysis

Table A6.1 *Estimated regression coefficients(B) with standard errors and odds ratios, together with confidence intervals, for the logistic regression using firth correction for anxiety and depression*

	Moderate/Severe Anxiety		Moderate/Severe Depression	
	B (SE)	OR (95% CI)	B (SE)	OR (95% CI)
EPL (1) vs control (0)	0.76 (0.34)	**2.14 (1.14; 4.36)**	1.35 (0.66)	**3.88 (1.27; 19.16)**
Maternal age (years)	-0.02 (0.02)	0.98 (0.94; 1.02)	-0.0005 (0.0304)	1.00 (0.94; 1.06)
IVF pregnancy: (yes=1;no=0)	-0.32 (0.42)	0.73 (0.30; 1.59)	0.28 (0.49)	1.32 (0.47; 3.27)
History of any EPL (yes=1; no=0)	0.75 (0.21)	2.12 (1.41; 3.19)	1.03 (0.29)	2.79 (1.57; 5.05)
Children (yes=1;no=0)	0.06 (0.21)	1.07 (0.70; 1.61)	0.10 (0.29)	1.11 (0.61;1.97)

Abbreviations: B – regression coefficient; CI – confidence interval; EPL – early pregnancy loss; OR – odds ratio; SE – standard error

Change over time: Random effects logistic regression model

We fitted random intercept and random slope logistic regression models for moderate/severe depression, anxiety and PTSD. Covariates were:

- type of EPL (miscarriage vs EP)
- maternal age (years)
- history of any EPL (yes/no)
- IVF pregnancy (yes/no)
- time (continuous)
- previous children (yes/no)
- whether a further loss was experienced (binary, time-varying)
- 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'. Further pregnancy was conceived per measurement.

In order to allow a different evolution for those who experienced miscarriage and those who experienced an ectopic pregnancy, an interaction between time and type of EPL was included.

This approach can use all available data, is valid under MAR conditional on the covariates in the model (Molenberghs et al, Biostatistics 2004), and can deal with variability in the time points. Since further loss or pregnancy are measured during follow up and are not constant 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 the woman's risk of depression or anxiety, the within-patient effect of the time-varying covariate will be estimated by adjusting for the patients' proportion of measurement points with any pregnancy loss since follow-up and any new pregnancy, to prevent bias.

- 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) while $FUPc_{ij}$ 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 $FULc_{ij}$ as they indicate the effects on the evolution of anxiety and depression when an individual experiences further loss or pregnancy during follow up.

$Y_{ij}|b_{1i},b_{2i} \sim Bin(\pi_{ij})$, 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 model is fitted using Adaptive Gaussian quadrature and 15 quadrature points to approximate the likelihood and Quasi-Newton is used as the optimizer.

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 on the time when patients filled out the questionnaire, therefore, the exact time since the loss was used in the model. This leads to the use of 1126 observations from 474 individuals for anxiety and depression.

Of the 474 individuals used in the analysis for depression and anxiety, 270 did not experience any previous loss, 188 did experience previous loss. 16 individuals did not have information about previous losses and 1 did not have information for previous children. For those individuals, single

imputation was used based on their age, type EPL, IVF pregnancy, imputed levels of depression and anxiety at the first measurement moment, previous losses and previous children.

It is important to note, that in representing the average individual, the values for history of EPL, IVF pregnancy and previous children are not 'realistic' as these variables can only take the values 0 (no) or 1 (yes).

Model not taking into account EPL group

First we show results from a model not taking into account EPL group (miscarriage versus ectopic), subsequently we add 'group' and an interaction effect between group and EPL as covariates.

Anxiety

Table A6.2 *Estimated regression coefficients and standard errors for the mixed effects logistic regression for anxiety, without the effect of type of previous EPL*

	Moderate/severe Anxiety
	B (SE)
Intercepts	-1.28 (1.36)
Time (months after event)	-0.37 (0.16)
Maternal age (years)	-0.02 (0.04)
History of any EPL (yes=1;no=0)	1.39 (0.41)
IVF pregnancy (yes=1;no=0)	-1.36 (0.79)
Previous Children (yes=1;no=0)	-0.10 (0.39)
Further Pregnant (within)	0.42 (0.53)
Further Loss (within)	2.58 (0.89)
Variance random intercept	6.10
Variance random slope	0.09
UN(2,1)	0.47

* Estimated between subjects effect of 'Further Pregnant' and standard error are -1.28 (0.94)

* Estimated between subjects effect of 'Further Loss' and standard error are 2.82 (1.58)

Table A6.3 *The exponent of the estimated regression coefficients (odds ratios) together with a 95% confidence interval for the mixed effects logistic regression for anxiety*

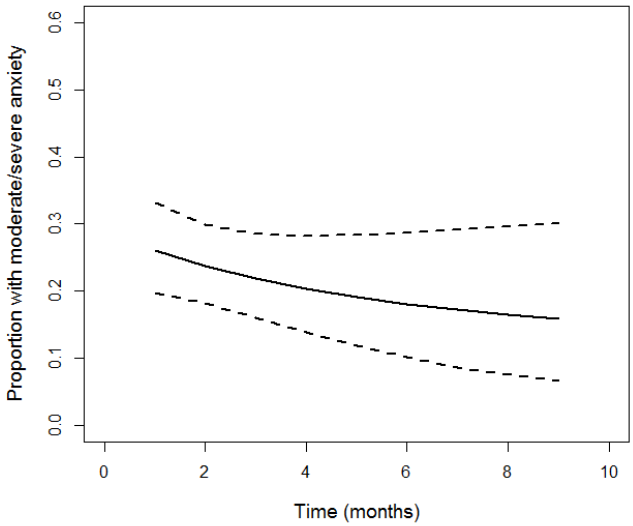
	Moderate/severe Anxiety
	Exp(B) (95% CL)
Time (months after event)	0.69 (0.50;0.94)
Maternal age (years)	0.98 (0.91;1.06)
History of any EPL (yes=1;no=0)	4.03 (1.79;9.06)
IVF pregnancy (yes=1;no=0)	0.26 (0.05;1.22)
Previous Children (yes=1;no=0)	0.91 (0.42;1.96)
Further Pregnant (within)	1.52 (0.54;4.30)
Further Loss (within)	13.18 (2.27;76.71)

* Estimated odds ratios for the between subjects effect of 'Further Pregnant' with 95% confidence interval for anxiety are 0.28 (0.04;1.79)

* Estimated odds ratios for the between subjects effect of 'Further Loss' with 95% confidence interval for anxiety are 16.83 (0.75;379.77)

Figure A6.1 *Average evolution for anxiety over time (with 95% confidence limits) based on a mixed effects model.*

We assume an average random intercept and slope, no further loss or pregnancy during follow-up, and average values for maternal age (35 years), history of any EPL (0.385), IVF pregnancy (0.079) and children (0.425)



Depression

Table A6.4 *Estimated regression coefficients and standard errors for the mixed effects logistic regression for depression*

	Moderate/severe Depression
	B (SE)
Intercepts	-4.42 (1.72)
Time (months after event)	-0.14 (0.26)
Maternal age (years)	-0.02 (0.05)
History of any EPL (yes=1;no=0)	1.86 (0.53)
IVF pregnancy (yes=1;no=0)	-0.03 (0.85)
Previous Children (yes=1;no=0)	0.30 (0.46)
Further Pregnant (within)	0.45 (0.73)
Further Loss (within)	2.60 (1.11)
Variance random intercept	10.83
Variance random slope	0.07
UN(2,1)	-0.48

* Estimated between subjects effect of 'Further Pregnant' and standard error are -1.55 (1.14)

* Estimated between subjects effect of 'Further Loss' and standard error are -0.47 (1.77)

Table A6.5 *The exponent of the estimated regression coefficients (odds ratios) together with a 95% confidence interval for the mixed effects logistic regression for depression*

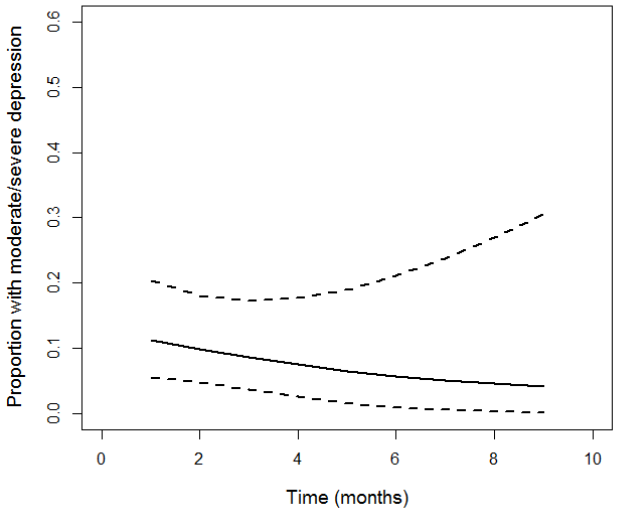
	Moderate/severe Depression
	Exp(B) (95% CI)
Time (months after event)	0.87 (0.53;1.44)
Maternal age (years)	0.98 (0.90;1.08)
History of any EPL (yes=1;no=0)	6.40 (2.24;18.29)
IVF pregnancy (yes=1;no=0)	0.97 (0.18;5.15)
Previous Children (yes=1;no=0)	1.36 (0.55;3.37)
Further Pregnant (within)	1.58 (0.37; 6.64)
Further Loss (within)	13.43 (1.50;120.01)

* Estimated odds ratios for the between subjects effect of 'Further Pregnant' with 95% confidence interval for anxiety are 0.21 (0.02;2.01)

* Estimated odds ratios for the between subjects effect of 'Further Loss' with 95% confidence interval for anxiety are 0.62 (0.02;20.30)

Figure A6.2: *Average evolution for depression over time (with 95% confidence limits) based on a mixed effects model.*

We assume an average random intercept and slope, no further loss or pregnancy during follow-up, and average values for maternal age (35 years), history of any EPL (0.385), IVF pregnancy (0.079) and children (0.425)



PTSD

Table A6.6 *Estimated regression coefficients and standard errors for the mixed effects logistic regression for posttraumatic stress*

	Moderate/severe Posttraumatic stress
	B (SE)
Intercepts	-0.38 (1.60)
Time (months after event)	-0.22 (0.05)
Maternal age (years)	-0.05 (0.05)
History of any EPL (yes=1;no=0)	1.64 (0.50)
IVF pregnancy (yes=1;no=0)	0.05 (0.88)
Previous Children (yes=1;no=0)	-1.03 (0.49)
Further Pregnant (within)	-1.35 (0.59)
Further Loss (within)	2.68 (0.71)
Variance random intercept	14.45

* Estimated between subjects effect of 'Further Pregnant' and standard error are -4.15 (1.21)

* Estimated between subjects effect of 'Further Loss' and standard error are 4.47 (1.70)

Table A6.7 *The exponent of the estimated regression coefficients (odds ratios) together with a 95% confidence interval for the mixed effects logistic regression for posttraumatic stress, without the effect of type of previous EPL*

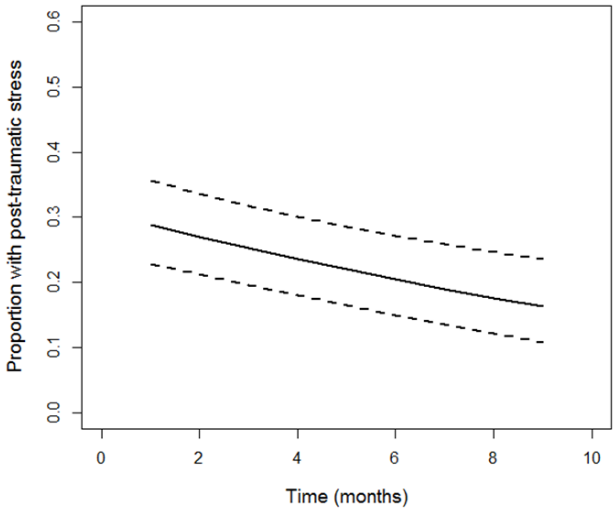
	Moderate/severe Posttraumatic stress
	Exp(B) (95% CI)
Time (months after event)	0.80 (0.72;0.89)
Maternal age (years)	0.95 (0.86;1.04)
History of any EPL (yes=1;no=0)	5.13 (1.92;13.75)
IVF pregnancy (yes=1;no=0)	1.05 (0.19;5.87)
Previous Children (yes=1;no=0)	0.36 (0.14;0.94)
Further Pregnant (within)	0.26 (0.08;0.83)
Further Loss (within)	14.66 (3.63;59.15)

* Estimated odds ratios for the between subjects effect of 'Further Pregnant' with 95% confidence interval for anxiety are 0.02 (0.001;0.17)

* Estimated odds ratios for the between subjects effect of 'Further Loss' with 95% confidence interval for anxiety are 87.07 (3.08;>999.99)

Figure A6.3 *Average evolution for posttraumatic stress over time (with 95% confidence limits) based on a mixed effects model.*

We assume an average random intercept and slope, no further loss or pregnancy during follow-up, and average values for maternal age (35 years), history of any EPL (0.385), IVF pregnancy (0.079) and children (0.425)



Model taking into account EPL group

Anxiety and Depression

Table A6.8 *Estimated regression coefficients and standard errors for the mixed effects logistic regression for anxiety and depression, taking into account type of pregnancy loss (miscarriage versus ectopic)*

	Moderate/severe Anxiety	Moderate/severe Depression
	B (SE)	B (SE)
Intercepts	-1.08 (1.49)	-5.15 (2.12)
Time (months after event)	-0.22 (0.16)	-0.05 (0.27)
Miscarriage (1) vs ectopic (0)	0.69 (0.61)	1.33 (0.93)
Time*Miscarriage (ectopic=reference)	-0.22 (0.15)	-0.38 (0.20)
Maternal age (years)	-0.04 (0.04)	-0.02 (0.05)
History of any EPL (yes=1;no=0)	1.43 (0.44)	1.88 (0.58)
IVF pregnancy (yes=1;no=0)	-1.19 (0.82)	0.22 (0.93)
Previous Children (yes=1;no=0)	-0.17 (0.41)	0.18 (0.51)
Further Pregnant (within)	0.40 (0.59)	0.73 (0.83)
Further Loss (within)	2.99 (1.04)	2.96 (1.28)
Variance random intercept	6.13	10.41
Variance random slope	0.14	0.11
UN(2,1)	0.51	-0.28

* Estimated between subjects effect of 'Further Pregnant' and standard error for anxiety are -1.63 (1.04) and for depression -1.13 (1.28)

* Estimated between subjects effect of 'Further Loss' and standard error for anxiety are 3.58 (1.72) and for depression 0.28 (1.99)

Table A6.9 *The exponent of the estimated regression coefficients (odds ratios) together with a 95% confidence interval for the mixed effects logistic regression for anxiety and depression.*

	Moderate/severe Anxiety	Moderate/severe Depression
	Exp(B) (95% CI)	Exp(B) (95% CI)
Miscarriage (1) vs ectopic (0) after 1 month	1.61 (0.54;4.79)	2.61 (0.53; 12.77)
Time (months after event) (Miscarriage)	0.65 (0.44;0.94)	0.66 (0.32;1.35)
Time (months after event) (Ectopic)	0.80 (0.59;1.10)	0.96 (0.57;1.61)
Maternal age (years)	0.96 (0.89;1.05)	0.98 (0.89;1.09)
History of any EPL (yes=1;no=0)	4.20 (1.76;10.01)	6.57 (2.10; 20.59)
IVF pregnancy (yes=1;no=0)	0.30 (0.06;1.53)	1.25 (0.20;7.73)
Previous Children (yes=1;no=0)	0.85 (0.37;1.91)	1.20 (0.43;3.30)
Further Pregnant (within)	1.50 (0.47;4.76)	2.07 (0.40;10.65)
Further Loss (within)	19.97 (2.60;153.41)	19.20 (1.55;237.47)

* Estimated odds ratios for the between subjects effect of 'Further Pregnant' with 95% confidence interval for anxiety are 0.20 (0.03;1.52) and for depression 0.32 (0.03;4.05)

* Estimated odds ratios for the between subjects effect of 'Further Loss' with 95% confidence interval for anxiety are 35.71 (1.20;>999.99) and for depression 1.32 (0.03;66.67)

PTSD

Table A6.10 *Estimated regression coefficients and standard errors for the mixed effects logistic regression for posttraumatic stress, , taking into account type of pregnancy loss*

	Posttraumatic stress
	B (SE)
Intercepts	-1.36 (1.84)
Time (months after event)	-0.17 (0.10)
Miscarriage (1) vs ectopic (0)	0.87 (0.77)
Time*Miscarriage (ectopic=reference)	-0.09 (0.11)
Maternal age (years)	-0.04 (0.05)
History of any EPL (yes=1;no=0)	1.57 (0.54)
IVF pregnancy (yes=1;no=0)	0.26 (0.94)
Previous Children (yes=1;no=0)	-1.18 (0.54)
Further Pregnant (within)	-1.10 (0.64)
Further Loss (within)	2.51 (0.76)
Variance random intercept	15.77

* Estimated between subjects effect of 'Further Pregnant' and standard error for posttraumatic stress are -4.17 (1.35)

* Estimated between subjects effect of 'Further Loss' and standard error for posttraumatic stress are 4.78 (1.88)

Table A6.11 *The exponent of the estimated regression coefficients (odds ratios) together with a 95% confidence interval for the mixed effects logistic regression for posttraumatic stress*

	Posttraumatic stress
	Exp(B) (95% CI)
Miscarriage (1) vs ectopic (0) after 1 month	2.20 (0.53;9.11)
Time (months after event) (Miscarriage)	0.77 (0.68;0.87)
Time (months after event) (Ectopic)	0.84 (0.69;1.03)
Maternal age (years)	0.96 (0.86;1.06)
History of any EPL (yes=1;no=0)	4.83 (1.66;14.02)
IVF pregnancy (yes=1;no=0)	1.30 (0.21;8.18)
Previous Children (yes=1;no=0)	0.31 (0.11;0.89)
Further Pregnant (within)	0.33 (0.10;1.16)
Further Loss (within)	12.32 (2.76;55.01)

* Estimated odds ratios for the between subjects effect of 'Further Pregnant' with 95% confidence interval for posttraumatic stress are 0.02 (0.001;0.22)

* Estimated odds ratios for the between subjects effect of 'Further Loss' with 95% confidence interval for posttraumatic stress are 118.86 (2.99;>999.99)

Appendix 7: Validation studies: breakdown of PDS scoring in those interviewed

The following tables show the PDS results for each of the women on whom a structured clinical interview (SCID) for PTSD was performed. The first two tables explore responses in those with PTSD according to SCID, and the final table for those who did not meet criteria for PTSD. In all tables, '1' corresponds to a criterion being endorsed for that individual, and '2' to it not being.

Endorsement for each cluster is as follows: at least one re-experiencing symptom, 3 avoidance symptoms, and 2 hyper-arousal symptoms. For all methods except Engelhard's, a score of 1 for each symptom (corresponding to "once a week or less/once in a while") is sufficient; for Engelhard, the score must be 2 (corresponding to 2-4 times a week or half the time).

For all aspects, results in which the criterion is not met are shaded (for the purposes of the severity score, the cut off is considered 18 for the purposes of shading). From this shading, it is clear that the duration criterion does not appear to be a useful criterion in identifying either cases or non-cases.

Table A7.1 *Posttraumatic stress diagnostic scale (PDS) results for 14 women meeting criteria for PTSD according to SCID*

Study number	H/T	Symptom cluster			Duration	Number of areas of interference	Total score	Scoring criteria		
		R	A	H				Foa	Foa – without durn	Ehring-clusters + >=18
CF164	1	1	1	1	<1m	8	17	2	1	2
CF190	1	1	1	1	none	3	22	2	1	1
SF350	1	1	1	1	<1m	7	33	2	1	1
SF374	1	1	1	1	<1m	6	26	2	1	1
SF375	1	1	1	1	>3m	5	40	1	1	1
SF399	1	1	1	1	<1m	8	27	2	1	1
SF400	1	1	2	1	1-3m	8	15	2	2	2
SF405	2	1	1	1	<1m	7	23	2	2	1
SF406	2	1	2	1	1-3m	0	17	2	2	2
HF209	1	1	1	1	1-3m	8	19	1	1	1
SF360	1	1	1	1	1-3m	7	31	1	1	1
SF363	1	1	1	1	<1m	0	10	2	2	2
SF385	1	1	1	1	<1m	6	25	2	1	1
SF404	1	1	1	1	1-3m	4	25	1	1	1

Abbreviations: H/T – helpless or terrified, R – Re-experiencing, A – Avoidance, H – Hyper-arousal

Table A7.2 *PDS results, scored according to criteria used by Engelhard in which a positive response is at least "2-4 times a week or half the time", for 14 women meeting criteria for PTSD according to SCID*

Study number	Symptom cluster			Number of areas of interference	Total score	Scoring criteria used by Engelhard
	R	A	H			
CF164	1	2	1	8	17	2
CF190	1	2	1	3	22	2
SF350	1	1	1	7	33	1
SF374	1	1	2	6	26	2
SF375	1	1	1	5	40	1
SF399	1	2	1	8	27	2
SF400	1	2	1	8	15	2
SF405	1	1	1	7	23	1
SF406	1	2	2	0	17	2
HF209	1	1	2	8	19	2
SF360	1	1	1	7	31	1
SF363	2	2	2	0	10	2
SF385	1	1	1	6	25	1
SF404	1	2	1	4	25	2

Abbreviations:, R – Re-experiencing, A – Avoidance, H – Hyper-arousal

Table A7.3 *PDS results for 37 women not meeting criteria for PTSD according to SCID*

Study number	H/T	Symptom cluster			Duration	No. areas interference	Total score	Scoring criteria			
		R	A	H				Foa	Foa – without durn	Erhing-clusters + >=18	Engleha rd
CF183	1	1	1	1	1-3m	4	6	2	2	2	2
CF197	1	1	1	1	1-3m	5	40	1	1	1	1
CF198	1	1	1	1	<1m	7	23	2	1	1	1
HF191	1	1	1	1	<1m	2	12	2	1	2	2
SF357	1	1	2	2	<1m	0	5	2	2	2	2
HF187	1	1	1	1	<1m	7	22	2	1	1	1
HF197	1	1	1	1	none	0	13	2	2	2	2
SF354	1	1	1	1	1-3m	0	15	2	2	2	2
SF364	1	1	1	1	<1m	6	15	2	1	2	2
SF403	1	1	1	1	1-3m	4	25	1	1	1	2
SF409	2	1	1	1	1-3m	3	15	2	2	2	2
SF410	1	1	1	1	>3m	5	17	1	1	2	2
CF159	1	1	2	2	<1m	0	3	2	2	2	2
CF162	1	1	1	1	<1m	3	8	2	2	2	2
CF166	2	1	2	2	none	0	1	2	2	2	2
CF168	1	2	2	2	none	0	3	2	2	2	2
CF171	1	1	2	2	<1m	0	4	2	2	2	2

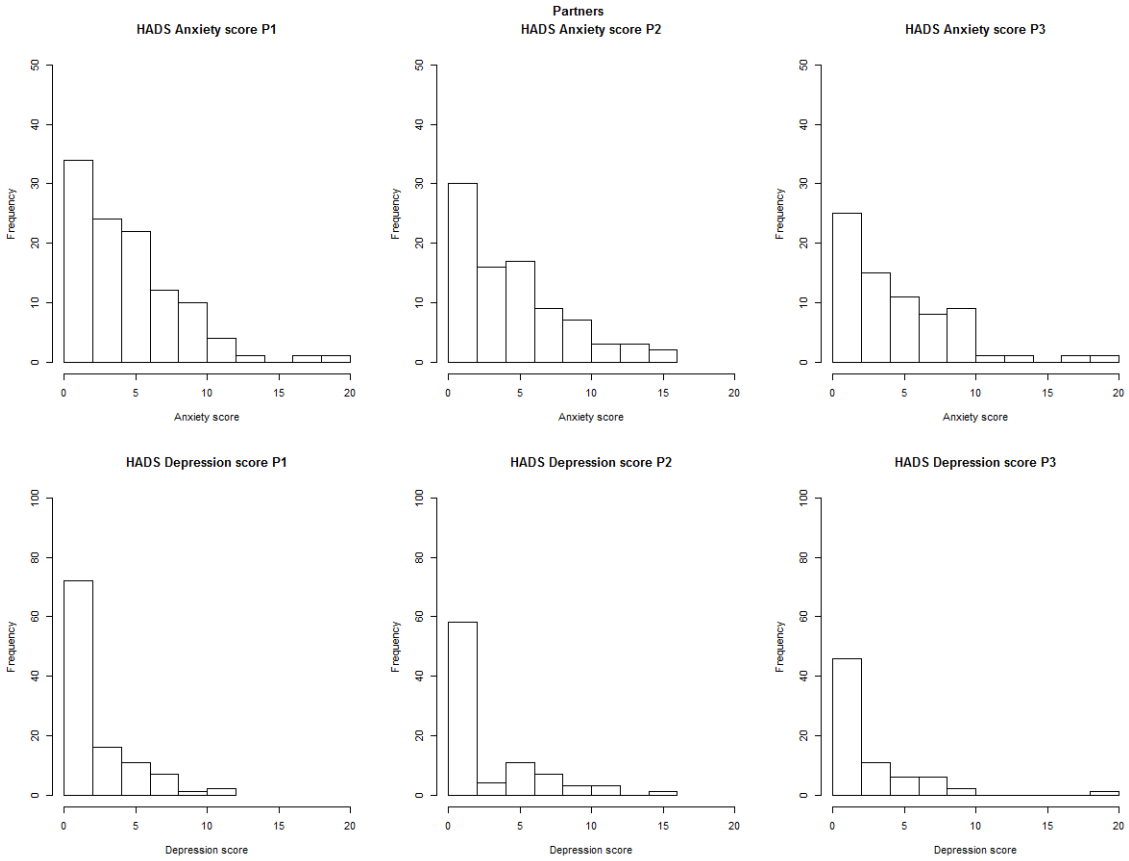
CF174	*1*	*1*	*2*	*2*	*1-3m*	*0*	*2*	*2*	*2*	*2*	*2*
CF176	*1*	*1*	*1*	*1*	*<1m*	*5*	*23*	*2*	*1*	*1*	*2*
CF178	*2*	*2*	*2*	*2*	*none*	*0*	*2*	*2*	*2*	*2*	*2*
CF179	*2*	*2*	*2*	*2*	*none*	*1*	*0*	*2*	*2*	*2*	*2*
CF191	*2*	*2*	*2*	*2*	*none*	*0*	*2*	*2*	*2*	*2*	*2*
CF193	*1*	*1*	*1*	*2*	*1-3m*	*5*	*12*	*2*	*2*	*2*	*2*
CF194	*1*	*1*	*2*	*1*	*1-3m*	*0*	*8*	*2*	*2*	*2*	*2*
HF186	*2*	*2*	*2*	*2*	*none*	*0*	*0*	*2*	*2*	*2*	*2*
HF189	*1*	*1*	*2*	*1*	*<1m*	*3*	*8*	*2*	*2*	*2*	*2*
HF194	*2*	*1*	*1*	*2*	*<1m*	*4*	*8*	*2*	*2*	*2*	*2*
HF201	*1*	*1*	*1*	*1*	*<1m*	*4*	*19*	*2*	*1*	*1*	*2*
SF355	*1*	*1*	*1*	*1*	*<1m*	*1*	*14*	*2*	*1*	*2*	*1*
SF365	*1*	*1*	*1*	*1*	*none*	*0*	*15*	*2*	*2*	*2*	*2*
SF368	*2*	*2*	*2*	*2*	*none*	*0*	*2*	*2*	*2*	*2*	*2*
SF372	*2*	*1*	*2*	*1*	*none*	*0*	*7*	*2*	*2*	*2*	*2*
SF377	*1*	*1*	*1*	*1*	*none*	*1*	*11*	*2*	*1*	*2*	*2*
SF380	*1*	*1*	*1*	*2*	*<1m*	*4*	*18*	*2*	*2*	*2*	*2*
SF386	*1*	*1*	*1*	*1*	*1-3m*	*5*	*9*	*1*	*1*	*2*	*2*
SF389	*1*	*1*	*1*	*1*	*<1m*	*5*	*12*	*2*	*1*	*2*	*2*
SF391	*2*	*2*	*2*	*2*	*none*	*1*	*1*	*2*	*2*	*2*	*2*

Abbreviations: H/T – helpless or terrified; R – Re-experiencing; A – Avoidance; H – Hyper-arousal, m – month(s)

Appendix 8: Statistical analysis of anxiety, depression and PTSD after losses in partners as compared to women

Histograms of HADS and PDS scores in partners at each time point

Figure A8.1 *Histograms of HADS anxiety and depression scores at each time point in partners*



Random intercept logistic regression model in women as compared to partners

We fitted a random intercept logistic regression model for moderate/severe depression and anxiety: A simple model including a main effect of time (continuous), a main effect of gender and an interaction effect between time and gender. Apart from these fixed effects, two random intercepts are included: a random intercept per couple and a random intercept per individual within a couple.

The model is fitted using adaptive Gaussian quadrature with 15 quadrature points to approximate the likelihood. 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 on the time when patients filled out the questionnaire, therefore, the exact time since the loss was used in the model. This leads to the use of 652 observations from 277 individuals in 170 couples.

Figure A8.1, based on tables A8.1 and A8.2, show the predicted probability together with a 95% prediction interval of suffering from moderate to severe anxiety or depression, or PTSD, for an average female patient and those for an average partner.

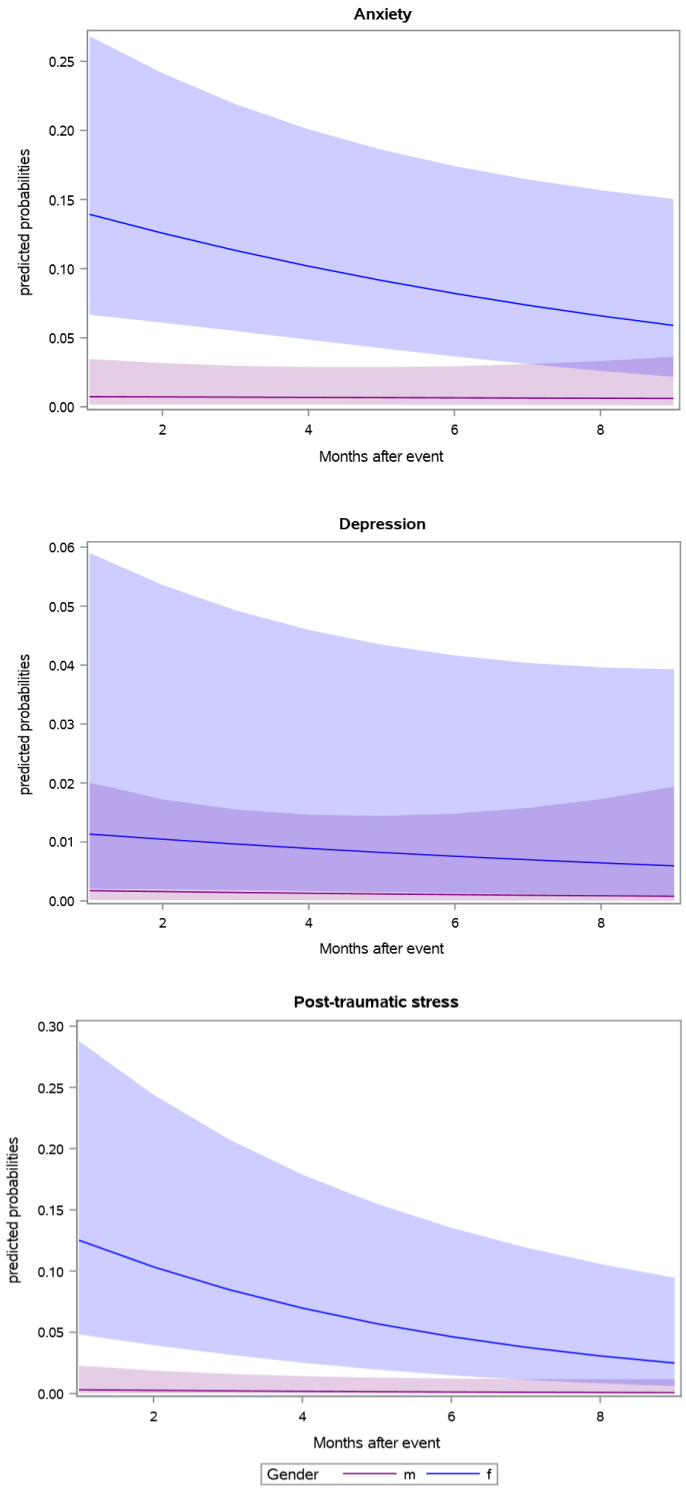
Table A8.1 *Estimated regression coefficients and standard errors for the mixed effects logistic regression for anxiety, depression and PTSD.*

	Moderate/severe Anxiety	**Moderate/severe Depression**	**PTSD**
	B (SE)	B (SE)	B (SE)
Intercepts	-1.70 (0.43)	-4.39 (0.88)	-1.73 (0.54)
Time (months after event)	-0.12 (0.06)	-0.08 (0.08)	-0.22 (0.07)
Gender (Reference = female)	-3.17 (0.79)	-1.86 (1.03)	-3.87 (0.94)
Time*Gender	0.09 (0.12)	-0.02 (0.19)	0.04 (0.15)
Variance random couple effect	4.93	2.04	10.93
Variance random effect for individuals within a couple	4.38	6.77	4.71

Table A8.2 *The exponent of the estimated regression coefficients (odds ratios) together with a 95% confidence interval for the mixed effects logistic regression for anxiety and depression.*

	Moderate/severe Anxiety	**Moderate/severe Depression**	**PTSD**
	Exp(B) (95% CI)	Exp(B) (95% CI)	Exp(B) (95% CI)
Gender (at month 1)	0.05 (0.01;0.19)	0.15 (0.02; 0.96)	0.02 (0.004;0.12)
Time (m)	0.98 (0.79;1.20)	0.91 (0.65;1.27)	0.84 (0.64;1.10)
Time (f)	0.89 (0.79;0.99)	0.92 (0.79;1.08)	0.81 (0.70;0.93)

Figure A8.2 *Predicted anxiety, depression and PTSD rates over time (with 95% prediction intervals) for and average woman and an average partner based on the mixed effects model.*



Appendix 9: Permissions

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