Mood Disorders, Personality and Grief in Women and Men undergoing in vitro Fertilization Treatment

HELENA VOLGSTEN
Dissertation presented at Uppsala University to be publicly examined in IX Universitetshuset, Övre Slottsgratan 2, Uppsala, Friday, November 27, 2009 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract


Psychological problems are common in infertile women undergoing in vitro fertilization (IVF) treatment. The aim of this thesis was to determine the prevalence of psychiatric disorders, such as mood and anxiety disorders, and related risk factors and personality traits in women and men undergoing IVF.

Participants were 1090 consecutive women and men, 545 couples, attending a fertility clinic in Sweden during a two-year period. The Primary Care Evaluation of Mental Disorders (PRIME-MD), based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), was used for evaluating mood and anxiety disorders. The participation rate was 862 (79 %) subjects.

Any psychiatric disorder was present in 31 % of females and in 10 % of males. Major depression was prevalent in 11 % of females and 5 % of males. Only 21 % of the subjects with a psychiatric disorder had some form of treatment. A negative pregnancy test and obesity (BMI ≥ 30) were risk factors for mood disorders in women and the only risk factor for depression in men was unexplained infertility. Anxiety disorders were less common than in the general population and no IVF-related risk factors were identified. The Swedish universities Scales of Personality (SSP), a self-rating questionnaire, was used for evaluation of personality traits. High scores of personality traits related to neuroticism were associated with mood and/or anxiety disorders among both women and men.

Another objective was to explore the experience of childlessness three years after unsuccessful IVF by a qualitative-approach, assessing data by interviews. Failure after IVF was experienced by women in terms of grief, whereas men took upon themselves a supportive role not expressing grief. A need for professional support and counselling in how to handle grief was described. An unstructured end after IVF treatment left unanswered questions. Three years after the end of treatment, men and women were still processing and had not adapted to childlessness, indicating the grieving process was unresolved.

Keywords: infertility, in vitro fertilization, depression, anxiety, personality, neuroticism, grief, unsuccessful IVF

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"Hoppas inte utan tvivel
och förtvivla inte utan hopp"

Seneca
The unknown child

That child will never lie in me, and you
Will never be its father. Mirrors must
Replace the real image, make it true
So that the gentle love-making we do
Has powerful passions and a parent’s trust

The child will never lie in me and make
Our loving careful. We must kiss and touch
Quietly, watch our reflexions break
As in a pool that is disturbed. Oh take
My watchful love; there must not be too much.

A child lies within my mind. I see
the eyes, the hand. I see you also there.
I see you waiting with an honest care,
Within my mind, within me bodily,
And birth and death close to us constantly.

Elizabeth Jennings (1926-2001)
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


III Volgsten H, Ekselius L, Sundström Poromaa I, Skoog Svanberg A. Personality traits associated with depressive and anxiety disorders in infertile women and men undergoing in vitro fertilization treatment. Acta Obstetricia et Gynecologica Scandinavica, Accepted for publication

IV Volgsten H, Skoog Svanberg A, Olsson P. Unresolved grief in women and men in Sweden three years after undergoing unsuccessful in vitro fertilization treatment Submitted

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<tr>
<td>ART</td>
<td>assisted reproductive technology</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CBT</td>
<td>cognitive behavioural therapy</td>
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<tr>
<td>DSM IV</td>
<td>diagnostic and statistical manual of mental disorders, fourth edition</td>
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<tr>
<td>ESHRE</td>
<td>European Society of Human Reproduction and Embryology</td>
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<tr>
<td>ET</td>
<td>embryo transfer</td>
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<tr>
<td>GAD</td>
<td>generalized anxiety disorder</td>
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<tr>
<td>GnRH</td>
<td>gonadotrophin releasing hormone</td>
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<tr>
<td>hCG</td>
<td>human chorionic gonadotrophin</td>
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<tr>
<td>ICSI</td>
<td>intra cytoplasmic sperm injection</td>
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<td>IVF</td>
<td>in vitro fertilization</td>
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<td>NOS</td>
<td>not otherwise specified</td>
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<tr>
<td>OCD</td>
<td>obsessive-compulsive disorder</td>
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<tr>
<td>PR</td>
<td>pregnancy rate</td>
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<td>SET</td>
<td>single embryo transfer</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction

Infertility
Infertility is a reproductive failure and a significant loss affecting women and men. Reproductive health, according to WHO’s definition of health as a state of complete physical, mental and social well-being, addresses reproductive functions at all stages of life. One of these functions is the individual’s capability to reproduce (1). The ability to have a biological offspring is an existential concern. In most cultures womanhood is considered the ability to bear and give birth to a child and creating a family is central to most couples. Therefore, reproductive failure, such as infertility, can cause reactions of crisis (2) and depressive symptoms (3). Previously it was assumed that mental factors such as depression caused infertility. Today, when assisted reproductive technology (ART) has become fairly routine, it has become apparent that the mental strain experienced by many infertile couples may be more of a consequence of infertility than a cause (3, 4). However, another hypothesis has been suggested; that there is a reciprocal relationship between mental health and infertility in that both effects may occur concurrently (5-7).

Causes of infertility
Infertility is defined as the inability to conceive after one year of regular intercourse without contraception and affects approximately 10 – 15 % of all couples of fertile age in industrialized countries (8). Infertility is considered primary when the female has never conceived and secondary when the female has not achieved subsequent pregnancy. Factors causing infertility can be explained by a female (such as a tubal factor, endometriosis or anovulation) or a male factor (such as oligo- or azoospermia). For some couples the cause can also remain unexplained after evaluation, and a complete diagnosis may not be established before treatment. The female’s age can be the cause of infertility, as fertility declines as the quality of the ovum are affected by age (9, 10). Thus, postponement of the first child is causing fertility problems (11, 12). In addition, there are lifestyle factors that may cause infertility, such as female obesity, smoking and psychological stress (12-15).
Treatment of infertility

*In vitro* fertilization (IVF) is routine treatment today for all types of causes of infertility. IVF was introduced in 1978 when the first child was born after IVF treatment (16). The first child after IVF treatment in Sweden was born in 1982 and 10 years later fertilization by intra cytoplasmic sperm injection (ICSI) was introduced. Almost 3,000 children are born each year in Sweden after IVF, which corresponds to nearly 3% of all newborn infants. Every third woman conceives and one out of four women has a live birth after one IVF treatment (17). Two out of three counties in Sweden offer three subsidized IVF attempts to the infertile couple and in the other counties one or two attempts are offered. Of couples undergoing IVF treatment between 30-40% will remain childless after treatment (18, 19).

At the time of the study IVF pre-treatment included follicular stimulation with daily injections of gonadotrophin (recombinant FSH), following down regulation with, in most cases, Gonadotrophin releasing hormone (GnRH) agonist (standard/long protocol) or in combination with a GnRH antagonist (short protocol). When follicular maturation was obtained, as monitored by regular examinations with transvaginal ultrasonography, oocyte retrieval was performed 34-36 hours after an injection of 10,000 IU hCG. Fertilization *in vitro* was performed either by IVF or ICSI. Embryo transfer (ET), in most cases of a single embryo (82%), was performed 2-3 days later. Good quality spare embryos were cryopreserved to be transferred later in subsequent cycles. Luteal support was given with intravaginal progesterone. The pregnancy test result (hCG in urine) was assessed at home by the woman 16-19 days after oocyte retrieval. The couple reported the result of the pregnancy test to the clinic. The IVF treatment with a long protocol lasted approximately 6-7 weeks from onset until the pregnancy test was assessed.

Outcome after IVF treatment can be reported as pregnancy rate (PR); either as the result of the pregnancy test (biochemical pregnancy) or the result verified by ultrasound (clinical pregnancy). The outcome can be reported either by treatment per started cycle or by embryo transfer (20). Few studies report the outcome as live birth rate, although a successful outcome of treatment for the infertile couple is not achieved until the result is a live birth (15, 21).

Hormone therapy during IVF

Gonadotrophin releasing hormone (GnRH) is a hypothalamic hormone used for down regulation during IVF treatment to prevent premature ovulation. Adverse effects from GnRH treatment include menopausal symptoms such as hot flashes, headache and mood changes (22). The mood changes induced
by GnRH treatment are usually not severe enough to fulfil the criteria for major depression, and have generally been attributed to low estradiol levels (22, 23). A short protocol (antagonist) has been shown to minimize the adverse mood effects in comparison to the prolonged ovarian suppression induced by standard/long treatment (24, 25). Fewer self-reported short-term symptoms of depression one week after the last IVF failure were found after short compared to standard/long treatment, as prolonged ovarian suppression may cause more depressive symptoms (25), whereas no differences in depressive symptoms were noted between the two treatment strategies following the first IVF (26). However, the mood effects of hormone therapy during IVF have been the focus of surprisingly little study.

Women usually express high expectations and hope for a successful outcome when IVF is initiated and disappointment and symptoms of depression following treatment failure (27-30). Thus, infertility and undergoing IVF treatment with hormone therapy is demanding and can cause stress symptoms and emotional reactions of crisis, grief and depressive symptoms.

**Stress symptoms**

Infertility and undergoing IVF treatment are stressful life events and can lead to stress symptoms, psychosomatic stress reactions and adjustment disorders. Adjustment disorders are more prevalent among infertile women than controls after evaluation and prior to fertility treatment (31). An adjustment disorder is a maladaptive reaction to an identifiable stressful event which is assumed to diminish when the stress ceases. IVF-related stress has been confirmed not only by psychometric measurements but also by increasing cortisol levels throughout the treatment course (32, 33). Adjustment disorders are characterized by emotional reactions to stressful events similar to depression, but they spontaneously resolve after adjustment over time without specific treatment (34). However, symptoms of an adjustment disorder do not correspond to normal grief reactions. Adjustment disorders are limited to a time period of less than six months after a stressful event (35). Stressful life events are reported more frequently in females than in males and are suggested to increase the risk of developing major depression (36-38).

**Crisis reactions**

Infertility is conceptualized as a major crisis in life. A crisis occurs after a stressful life event, threaten important life goals and unresolved problems from the past arise (2, 39). A crisis evoke emotional reactions that are classified into four main phases; the initial phase (shock, surprise, denial), the
reactive phase (frustration, anger, anxiety, guilt, grief, depression, isolation),
the adaptive phase (acceptance) and a resolution phase (planning for future
solutions) (2, 39). Reactions during a crisis are determined by factors such as;
influences of the event itself, pre-existing personality, cultural factors and
social support from significant others (40). A crisis is considered a transi-
tional period with opportunity for either personal growth or increased risk
for development of psychiatric disorders, depending on how the crisis is
handled (41).

The conceptual framework of the crisis theory (2, 41) is modified for the
purpose of the infertility crisis (39). Although the crisis theory may initially
be used the theory is less useful for the adaptive phase as infertility may
consist of recurring stressful events (42). Women who have undergone un-
successful tubal surgery for a female infertility factor mostly remain in the
reactive phase when interviewed two years after surgery according to Lalos
and co-workers (43). The infertility crisis differs from other life crises, that
are time-limited with duration of six weeks or less for the reactive phase and
an adaptive phase of up to one year (2, 39).

Grief reactions

Grief is a common reaction in women after a diagnosis of infertility (39).
Infertility represents many losses; the loss of fertility and reproductive abil-
ity, and the loss of a child and biological offspring (44). Grief is a normal
reaction to a distressing situation, such as a loss (45). The duration of normal
grief reactions depends on the grieving process, which is considered impor-
tant for successful adjustment to the infertility crisis (39, 44, 45). However,
when the loss is of a potential, not an actual loss, the couple may not realize
they are allowed to grieve (39).

The grieving process may be hampered or prolonged, thus causing compli-
cated or pathological grief. Symptoms that are not characteristic for normal
grief reactions are excessive guilt, suicidal ideation and feelings of worth-
lessness (35). Complicated grief occurs when grief reactions persist more
than two months after a loss and it is a psychiatric illness that requires
evaluation and treatment, and is consistent with the definition of major de-
pression (35).

Therefore, distinguishing between grief reactions, complicated grief and
depression is important but can be difficult (38, 46-48). Most clinical symp-
toms are similar, except grief reactions are often self-limited and with pre-
served self-esteem (46).
Psychiatric disorders in the general population

A psychiatric disorder is, according to the American Psychiatric Association (APA), conceptualized as “a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress or disability or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom. In addition, this syndrome or pattern must not be merely an expectable and culturally sanctioned response to a particular event, for example, the death of a loved one. Whatever its original cause, it must currently be considered a manifestation of a behavioral, psychological, or biological dysfunction in the individual” (49).

Psychiatric disorders, in this thesis, are diagnosed according to a descriptive criteria-system, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (49).

The lifetime prevalence according to epidemiological and national-based studies of major depression varies between 10 – 25 % in women and 5 - 12 % in men whereas the point prevalence of major depression is 5 – 9 % in women and 2 – 3 % in men. The lifetime and 12-month prevalence of anxiety disorders varies as follow; GAD 5 % and 3 %, panic disorder 1.5 – 3.5 % and 1 - 2 %, OCD 2.5 % and 1.5 – 2 %, social phobia 3 - 13 % and 8 % respectively, in both women and men (49).

The lifetime prevalence of mood disorders is approximately 24 % in women and 15 % in men and the 12-month prevalence 14 % in women and 8.5 % in men. The lifetime prevalence of anxiety disorders is approximately 30 % of women and 19 % of men and the 12-month prevalence 23 % in women and 12 % in men. The lifetime prevalence of any psychiatric disorder is 55 % in women and 49 % in men. The 12-month prevalence for alcohol abuse/dependence is 6 % in women and 16 % in men. (50-53).

Furthermore, there is a substantial co-morbidity between anxiety and depression in both females and males (50, 54, 55). Mood disorders are also associated with increased reporting of physical symptoms such as headache, fatigue, back pain and bowel complaints (56).
Major depression

Major depression is a disorder of mood or affect; mood refers to the internal emotional state and affect to the external expression of emotional experiences (46, 59). Major depression is two to three times as common in women as in men (60) and the peak incidence in females occurs during the reproductive years, with a mean age at onset of 30 years (61).

The two core symptoms of a diagnosis of a major depressive episode are either depressed mood or the loss of interest or pleasure in nearly all activities. The additional symptoms are changes in appetite or weight, sleep, and psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty thinking, concentrating, or making decisions. Recurrent thoughts of death or suicidal ideation, plans or attempts is another DSM-IV criteria for depression (49).

Five or more of the symptoms/criteria have to be fulfilled according to the DSM-IV criteria and persist for most of the day, nearly every day, for at least two consecutive weeks for the diagnosis of major depression. The episode must be accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning (49). Major depression can become recurrent (new episode of depression after full remission) and may substantially impair an individual’s ability to cope with daily life. Relapses (when depression is not in full remission) occur in 75 - 80 % of cases.

Most cases of depression can be treated with pharmacotherapy, such as SSRI (selective serotonin reuptake inhibitors) and/or with psychotherapy. However, pharmacotherapy during pregnancy is controversial and the first choice for treatment of depression in infertile females has been considered psychotherapy, as these women are attempting to conceive and consequently should avoid medication (47). A recent review suggests that SSRI should be used with caution during pregnancy (62). However, the current recommendations in Sweden are that antidepressants should not be avoided during pregnancy (63, 64). Psychotherapy, as cognitive behavioural therapy (CBT) has been demonstrated to be an efficient treatment for depression in the general population (65) and in infertile females undergoing IVF (66, 67). CBT has also been recommended for infertile women with anxiety disorders (47).

It has been predicted that major depression will be the second most common health problem and a leading cause of disease-related disability in the population by 2020 (57). Already, major depression imposes substantial impairment and a reduced quality of life among women throughout the world (50, 58).
Psychiatric disorders in infertile females and males

The prevalence of psychiatric disorders, based on DSM-IV criteria, has been found in one study of infertile women before IVF treatment, indicating that the prevalence of major depression and generalized anxiety disorder was 17 % and 23 %, in women respectively (68). Another study compared the prevalence of psychiatric disorders in infertile subjects specifically referred or not referred to psychosomatic care and found prevalence rates of anxiety and/or depressive disorders in the latter group to be 30 % in women and 17 % in men (69).

The use of a diagnostic interview to assess a psychiatric diagnosis, rather than self-report scales for depressive symptoms, is that the health professional knows who is in need of specific interventions or treatment. A limitation with the use of self-report screening scales is that they can merely suggest the likelihood of a psychiatric disorder (68, 70).

However, depression and anxiety have been reported more frequently by self-report scales in infertile women. Among infertile women approximately 37 % had depressive symptoms on the Beck Depression Inventory (BDI), which was twice as common as in the control group (3). According to the General Health Questionnaire, depressive symptoms were found in 33 % and 43 % of females prior to IVF and following IVF, respectively (71). Furthermore, anxiety symptoms in infertile women were encountered in 26 % of women at evaluation prior to IVF and in 22 % of women six months later using the State-Trait Anxiety Inventory (STAI) (72). Increased rates of depressive symptoms in females prior to IVF have also been reported in a recent review (73), whereas another review reported no difference in depression levels between infertile females and norm groups prior to IVF (74). Few studies report on depressive and anxiety symptoms among males. The prevalence of depressive symptoms in infertile men according to the BDI varied between 3.5 % prior to IVF and 8 % after failed IVF (75). Furthermore, anxiety symptoms in infertile men were encountered in 9 % of men at evaluation prior to IVF and in 11 % of men six months later using the STAI (72). No elevated scores for anxiety using the STAI were reported among males in another assessment prior to IVF treatment (27).

The variability in prevalence rates of depressive and anxiety symptoms in infertile samples is largely determined by differences in time-points for the assessments (before, during and/or after IVF), and methodological issues such as the use of different standardized psychometric self-report instruments and the use of different cut-off scores (73).
Thus, the prevalence of psychiatric disorders, based on DSM-IV criteria, is largely unknown among unselected infertile couples undergoing IVF. To our knowledge there are no existing data about the prevalence among infertile men undergoing IVF.

Risk factors for mood and anxiety disorders

A vulnerability to develop depression is suggested to depend on a previous history of depression, pre-existing stressful life events and personality factors (40, 46, 47, 60). Other factors are previous reproductive failure and genetic predisposition (46, 47). Exposure to stressful life events is also suggested to be higher among subjects with a history of depression (76, 77).

Risk factors for depression and anxiety in the general population include low socioeconomic status, smoking, drug and alcohol abuse, being single and being unemployed (55, 57, 78), which is fairly consistent with risk factors for psychiatric disorders in a population-based sample of Swedish pregnant women (79). Obesity is another major health concern associated with depressive and anxiety disorders (80, 81). However, results from a systematic review suggest that firm conclusion can not be made of the effect of obesity on depression (82).

Prospective studies of risk factors for mental health in infertile females undergoing treatment are scarce (74). Compared to the general population, it can be assumed that other risk factors are of importance as IVF couples are by definition in stable relationships (83) and presumably avoid smoking and alcohol use to a greater extent. IVF-related factors, such as female age, duration of infertility and cause of infertility have been suggested to be risk factors for anxiety and/or depression in the IVF setting (28), whereas other studies show no correlation between female age, duration of infertility and depressive symptoms (3, 84). Furthermore, given the variation in emotional reactions to infertility, it is of importance to identify risk factors for adverse reactions and individuals at risk to develop depression undergoing IVF.
Personality traits

Personality traits are an individual’s characteristic relatively lasting ways of thinking, feeling and behaving (85). Once adulthood is reached, personality traits are considered to be fairly stable over time (86-88). Personality traits related to neuroticism can be used to identify individuals at risk for development of psychiatric disorders (89). An association between neuroticism-related personality traits and major depression has been established (88, 90, 91) and according to the “vulnerability model” these traits are considered a risk factor for the development of depression (92).

Individuals with high scores of neuroticism, or negative affect, are anxious, vulnerable to stress, lack self-confidence and are easily frustrated (85, 93). The relationship between neuroticism and major depression is suggested to be the result of common genetic factors that predispose to both neuroticism and major depression (94). Furthermore, certain personality traits may affect the possibility of experiencing major life events as stressful, and stressful life events may, in turn, predispose to development of a depressive episode (95).

These relationships raise the possibility that certain personality traits, such as neuroticism, could predispose to development of depression and anxiety in response to the infertility crisis and the emotional burden of IVF treatment. Studies of personality traits in relation to emotional response to IVF treatment are limited (30) and associations between personality traits and psychiatric disorders in infertile females and males undergoing IVF have not been previously assessed.

Experiences of childlessness after the end of IVF

Emotional reactions to infertility have been explored in women before (39, 44) and during fertility treatment (84, 96, 97). However, long-term follow-up after the end of unsuccessful IVF has not been conducted to the same extent (98-100). Grief is one of the main experiences of being childless two years after ending unsuccessful IVF (101). However, qualitative studies focus on women (101-103) or interviews have been made with the couple together (104-106). Hence, there is a need to obtain a more in-depth understanding of both men’s and women’s experiences after unsuccessful IVF treatment.

The conceptual framework of crisis theory, modified for the purpose of infertility, was used in the qualitative-approach study (2, 39).
Aims

The specific aims of the following Papers were;

I. to determine the prevalence of mood and anxiety disorders in infertile women and men undergoing IVF treatment

II. to identify IVF-related risk factors for mood and anxiety disorders in infertile women and men undergoing IVF treatment

III. to determine whether certain personality traits, such as neuroticism, are associated with mood and/or anxiety disorders in infertile women and men undergoing IVF treatment

IV. to explore the experience of childlessness in infertile women and men three years after unsuccessful IVF treatment
Materials and methods

Study sample papers I - III
All female and male partners in consecutive couples undergoing IVF or ICSI treatment at the Centre of Reproduction, Uppsala University Hospital, Uppsala, Sweden, were approached for participation in the study between April 2005 and April 2007.

Study setting papers I-IV
In Sweden, ART is offered by public and private clinics. The Centre of Reproduction is public, and infertile couples are offered three subsidised IVF treatments with a waiting list of three months at the time of the study. The upper age limit for IVF at the Centre of Reproduction is 40 years for females and 55 years for males. After the subsidised treatments are completed the couple may decide to continue privately paid treatment at the public clinic or at a private clinic. The cost for IVF treatment at the public clinic at the time of the study was about 22 000 SEK. Counselling was offered to all couples at their first visit to the clinic. Couples can seek medical care with or without referral; those who are referred from areas outside Uppsala County are pre-treated at the referring clinic. Subjects pre-treated at their home clinic visit the Centre of Reproduction for the first time on the day of oocyte retrieval. The pregnancy test (hCG in urine) is assessed at home by the female 16-19 days after oocyte retrieval.

Study design papers I-III
On the day of oocyte retrieval, each eligible subject was asked for written consent to participate in the study and to individually complete and return the two questionnaires included in the study. The personality questionnaire (paper III) was included in the study a few months later (August 2005). Study exclusion criteria were (1) unable to read and understand the questionnaire because of language difficulties and (2) couples undergoing cycles with gamete donation, i.e. oocyte and sperm donation. Furthermore, subjects
already evaluated at the time of an earlier IVF treatment during the study period were not approached to participate.

Psychiatric assessment

The PRIME-MD (Primary Care Evaluation of Mental Disorders) system was developed to screen, evaluate, and diagnose psychiatric disorders according to DSM-IV criteria in primary care settings and has been validated (70, 107). Prior studies have indicated good agreement between PRIME-MD diagnoses and those of independent mental health professionals, with a sensitivity of 83 %, a specificity of 88 % and a positive predictive value of 80 % (70). Given its utility and ease of use, the PRIME-MD was considered a suitable tool for assessing the prevalence of psychiatric disorders in the IVF setting.

The original PRIME-MD system (70) consists of two components: a one-page patient questionnaire (PQ), appendix I, and a 12-page clinician evaluation guide (CEG), which is a structured interview guide that is followed when evaluating the responses on the PQ. The CEG contains modules for mood, anxiety, eating disorders, alcohol abuse, social phobia, and obsessive-compulsive disorder. Only those modules that are indicated by the patient on the PQ are administered. A modified form of the PRIME-MD patient questionnaire, containing 24 questions evaluating somatoform disorders, mood disorders, anxiety disorders and eating disorders, was used for this study.

The PRIME-MD system evaluates the presence of 20 possible psychiatric diagnoses, of which this study focused on 11. Among these 11 diagnoses, eight correspond to the specific requirements of “full” DSM-IV diagnoses, such as major depressive disorder, dysthymia, partial remission of major depressive disorder, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder (OCD), social phobia and bulimia nervosa, specified in appendix II (49). Three additional diagnoses are considered to be “subthreshold” diagnoses, minor depressive disorder, anxiety not otherwise specified (NOS) and eating disorder NOS. Subthreshold diagnoses have fewer symptoms than required for a specific DSM-IV diagnosis but are included in the study as they are also associated with considerable disability, as in the case of minor depressive disorders (108). Furthermore, in this thesis questions concerning bipolar disorder, somatoform disorders and alcohol abuse were not assessed. In addition, the PRIME-MD system does not assess the distress/impairment criteria.
Along with the PRIME-MD patient questionnaire (PQ) the subjects were asked to provide their name, date of birth, telephone (cellphone) number, and a signed informed consent form allowing for a telephone interview (in case of positive responses on the PQ). Subjects were considered to be screen-positive if a response to any key question on the PQ indicated a psychiatric disorder. Screen-negative subjects were those whose responses on the PQ did not include items suggesting psychiatric symptoms.

To confirm a diagnosis a telephone interview, using a highly structured computerized version of the CEG, was conducted individually with the screen-positive women and men. Prior to the interviews subjects were informed that additional questions would be left until after the interview. In case of a PRIME-MD diagnosis, the subject was asked about current antidepressant drug therapy and/or psychotherapy and about previous history of depression. All subjects who fulfilled criteria for a DSM-IV diagnosis were offered referral to psychiatric specialist care. The telephone interview was conducted 21 days after screening, i.e. after the pregnancy test had been performed. At the time of the telephone interview the interviewer had no knowledge of the pregnancy test result.

**Personality assessment**

The Swedish universities Scales of Personality (SSP) is a self-rating questionnaire based on the Karolinska Personality Scales (109). Compared to KSP, the SSP has a reduced number of items and improved psychometric quality (110). The SSP contains 91 items divided into 13 scales each with seven items: *Somatic Trait Anxiety, Psychic Trait Anxiety, Stress Susceptibility, Lack of Assertiveness, Embitterment, Detachment, Social Desirability, Trait Irritability, Mistrust, Verbal Trait Aggression, Physical Trait Aggression, Impulsiveness* and *Adventure Seeking* (110), paper III.

The participants rated the items on a scale from 1 to 4, where 1 equals ”does not apply at all” and 4 equals “applies completely”. The SSP scores were transformed into normative T-scores with means of 50 and standard deviations of 10 based on a representative Swedish non-patient sample, (110). The SSP scores were adjusted for age and gender (111).

Sociodemographic data were collected by asking the subjects to fill in a separate questionnaire with questions on socioeconomic factors. The fertility history and outcome of IVF (pregnancy test result and live birth rate) were obtained from the subjects’ medical records after all subjects had participated in the study.
Statistical/Data analyses papers I-III

Continuous variables were compared by the use of independent t-tests and are presented as means ± SD. Frequencies were compared between groups using the chi square test. A p-value less than 0.05 was considered significant. Demographic and fertility data were compared between subjects with a psychiatric disorder and subjects with no psychiatric disorder; the latter group consisted of screen-negative subjects and screen-positive subjects in whom no psychiatric diagnosis was established during the telephone interview.

Statistical/Data analyses papers II-III

Multiple logistic regression analysis was used to calculate adjusted odds ratios (OR) and 95 % confidence interval (CI) (112). All variables were dichotomized and assessed in unadjusted analyses before entered into multiple logistic regression analyses. The reason for dichotomizing the variables was to obtain variables of clinical importance for IVF treatment (113). Multiple logistic regression analyses were performed with the forced entry method. In this approach all independent variables are tested in one block, not stepwise (114). Only variables with a p-value of 0.25 or less in the unadjusted analysis were included in the final model with any mood or any anxiety disorder as dependent variable, in paper II (113). The exception were age, smoking, duration of infertility, cause of infertility and pregnancy test result, as they are factors of clinical importance for the IVF treatment and possible risk factors in subjects undergoing IVF. Detailed descriptions of other included variables have been presented in paper II. All statistical analyses were performed with SPSS 15.0. A two-sided p-value less than 0.05 was considered significant.

In paper III, variables with a p-value of 0.25 or less were included in the logistic regression model with any psychiatric disorder (mood and/or anxiety) or live birth as dependent variable. Factor analysis with varimax rotation was performed to identify factors with eigenvalues > 1. The limit for factor loading was set at > 0.45. The analysis yielded a three-factor model that was related to the personality factors neuroticism, aggressiveness and sensation-seeking (110).

Study design, participants and data analyses paper IV

Women and men who had undergone IVF/ICSI treatment at the Centre of Reproduction, Uppsala University Hospital, Sweden after August 2001 par-
ticipated in the study. The methodological approach was qualitative with semi-structured interviews and qualitative content analysis (115, 116).

Participants were identified from the database at the clinic and recruitment was in two steps. First, an invitation letter including a written consent to participate was sent to women and men who had undergone IVF (and/or frozen embryo transfer) and had no more IVF treatments at this clinic during a minimum of three years. Forty-nine letters were sent out before the desired sample was recruited. Second, the men and woman were contacted by phone by the first author (HV) about a week after the letter was received; this provided an opportunity for the potential participants to ask questions, to check for exclusion criteria unavailable in the database and to book a place and time for an interview. The exclusion criteria were (1) unable to understand the questions because of language difficulties, (2) having a biological child from previous relationship and (3) already adopted a child.

The participants were individually interviewed in the same non-clinical research room at the hospital. All interviews were conducted in 2006 by the first author. Prior to the interview written informed consent was obtained and socio-demographic and fertility data were collected via a questionnaire. Fertility history was obtained from the medical records. The interviews started after informing the participant that she or he could choose to end the interview at any time.

In the individual semi-structured interviews a pre-tested and revised interview-guide covering the following topics was used; life situation as involuntary childless, partner relationship and social network and support, mental health during and three years after IVF and decision-making when to end IVF. All interviews were tape recorded, lasted a mean of 40 minutes and then they were transcribed verbatim by the first author. The interviewer was known to some participants due to working as a midwife at the Centre of Reproduction.

The interviews were analyzed by qualitative content analysis (115), by the first author and interpretations were checked against the co-authors in 2009. After careful reading the transcribed interview text was divided into meaning units. A meaning unit is a piece of text with a specific content that relates to the aim of the study. All meaning units were thereafter condensed; a process of shortening the text while still preserving the core content, into condensed meaning units. The condensed meaning units were further shortened into codes; a labeling that allows the data to be understood in relation to the context. Codes were then grouped into categories depending on similarities and differences in content (115).
Ethical considerations

Women and men gave their written informed consent prior to inclusion to the studies I-IV. The study procedures were in accordance with ethical standards and the Research Ethics Committee, Uppsala University, Uppsala, Sweden approved the study. All women and men who participated in the main study (I-III) and revealed a psychiatric diagnosis were offered referral to a psychiatrist. Participants in the qualitative study (IV) were offered contact with one of the physicians in the study if that was considered needed.

The research topic, assessing the prevalence of psychiatric disorders and experiences after the end of unsuccessful IVF treatment, must be considered as one of the most sensitive topics to address in clinical research. However, participation was voluntarily and did not affect the IVF treatment for those included in the main study, as the IVF team was not told who was participating or not participating. For the participants in the qualitative study the treatment had already ended. In the main study the participants could decline to participate by either not accepting or not handing in the questionnaire or by declining to participate in the following telephone interview. In the qualitative study no reminders were used after the first telephone invitation, as the topic could be sensitive for subjects and remind them of the treatment failure. The aim of the semi-structured interview was described in the covering letter. Information that the participant could choose to end the interview at any time during the interview was given.
Prevalence of mood and anxiety disorders (paper I)

A detailed description of the study population is presented in paper I. The study sample wherein a possible confirmation of a psychiatric diagnosis could be made consisted of 825 subjects (413 females and 412 males), see Figure I.
Demographic and fertility data are given in paper 1 for female and male subjects included and not included in the study. The only difference was that ICSI treatment and previous IVF/ICSI were more prevalent in men who declined to participate than in men who participated in the study, $p < 0.05$. Demographic and fertility data are given in Table 1 for female and male subjects with or without psychiatric diagnoses.

Three out of four couples were undergoing their first IVF and one in 10 couples (11 %) was undergoing their third IVF. When unadjusted analyses were made between females undergoing their first IVF (n=308) and females undergoing subsequent IVF (n=105) no differences were found for females with or without any psychiatric disorders. Males with anxiety disorders were more often undergoing their first IVF n=11 (55 %) compared with those with previous IVF n=9 (45 %), $p < 0.02$, data not shown in paper I.

Among subjects who filled out the PQ, 287 (65 %) women and 165 (39 %) men were screen-positive in that they triggered any of the key questions for psychiatric disorders. Of the total of 413 women in the study sample, 127 (31 %) had one or more psychiatric disorders. The corresponding figure for the 412 men was 42 (10 %). Mood disorders were the most prevalent psychiatric disorder and were found in 108 (26 %) females and 38 (9 %) males. Major depression, the most prevalent mood disorder, was present in 45 (11 %) women and 21 (5 %) men. Anxiety disorders were prevalent in 61 (14 %) women and 20 (5 %) men see Table 2.

Of the subjects with full DSM-IV diagnoses (n = 111); 20 (18 %) subjects had received some form of psychotherapy and seven (3 women and 4 men) subjects (6 %) had been prescribed antidepressant treatment with or without psychotherapy. Forty-nine (60.5 %) of the females (n = 81) and 16 (53 %) of the males (n = 30) with full DSM-IV diagnoses reported a previous history of depression. Recurrent thoughts of death during the last two weeks were reported by 8 (18 %) females and 5 (24 %) males diagnosed with a major depression.
Table 1 Demographic and fertility data for infertile women and men with or without psychiatric diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Female subjects</th>
<th></th>
<th>Male subjects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 413</td>
<td></td>
<td>n = 412</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychiatric</td>
<td>No psychiatric</td>
<td>Psychiatric</td>
<td>No psychiatric</td>
</tr>
<tr>
<td></td>
<td>diagnosis</td>
<td>diagnosis</td>
<td>diagnosis</td>
<td>diagnosis</td>
</tr>
<tr>
<td></td>
<td>n = 127</td>
<td>n = 286</td>
<td>n = 42</td>
<td>n = 370</td>
</tr>
<tr>
<td>Age, years</td>
<td>32.7 ± 4.1</td>
<td>32.9 ± 3.7</td>
<td>35.5 ± 4.5</td>
<td>34.6 ± 4.8</td>
</tr>
<tr>
<td>BMI, kg/m²¹</td>
<td>24.7 ± 4.1</td>
<td>23.9 ± 4.1</td>
<td>26.1 ± 4.4</td>
<td>25.5 ± 3.3</td>
</tr>
<tr>
<td>Smokers, n</td>
<td>10 (7.9 %)</td>
<td>13 (4.5 %)</td>
<td>4 (9.5 %)</td>
<td>15 (4.1 %)</td>
</tr>
<tr>
<td>Snuff taking status, n</td>
<td>3 (2.4 %)</td>
<td>11 (3.8 %)</td>
<td>10 (23.8 %)</td>
<td>101 (27.4 %)</td>
</tr>
<tr>
<td>University/College, n</td>
<td>64 (50.4 %)</td>
<td>156 (54.5 %)</td>
<td>17 (40.5 %)</td>
<td>165 (44.6 %)</td>
</tr>
<tr>
<td>High school education, n</td>
<td>63 (49.6 %)</td>
<td>130 (45.5 %)</td>
<td>25 (59.5 %)</td>
<td>205 (55.4 %)</td>
</tr>
<tr>
<td>Employee/student², n</td>
<td>75 (59.1 %)</td>
<td>165 (57.7 %)</td>
<td>19 (45.2 %)</td>
<td>222 (60.0 %)</td>
</tr>
<tr>
<td>Unemployed², n</td>
<td>8 (6.3 %)</td>
<td>8 (2.8 %)</td>
<td>3 (7.1 %)</td>
<td>10 (2.7 %)</td>
</tr>
<tr>
<td>Duration, months</td>
<td>38.3 ± 20.2</td>
<td>38.8 ± 19.2</td>
<td>39.7 ± 20.6</td>
<td>38.0 ± 19.4</td>
</tr>
<tr>
<td>Infertility factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>41 (32.3%)</td>
<td>81 (28.3%)</td>
<td>8 (19.0%)</td>
<td>115 (31.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>42 (33.0%)</td>
<td>86 (30.1%)</td>
<td>14 (33.3%)</td>
<td>111 (30.0%)</td>
</tr>
<tr>
<td>Unexplained³</td>
<td>41 (32.3%)</td>
<td>105 (36.7%)</td>
<td>17 (40.5%)</td>
<td>128 (34.6%)</td>
</tr>
<tr>
<td>Other³</td>
<td>3 (2.4%)</td>
<td>14 (4.9%)</td>
<td>3 (7.1%)</td>
<td>16 (4.3%)</td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81 (63.8%)</td>
<td>208 (72.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46 (36.2%)</td>
<td>78 (27.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nullipara</td>
<td>113 (89.0%)</td>
<td>261 (91.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multipara</td>
<td>14 (11.0%)</td>
<td>25 (8.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVF</td>
<td>78 (61.4%)</td>
<td>175 (61.2%)</td>
<td>23 (54.8%)</td>
<td>233 (63.0%)</td>
</tr>
<tr>
<td>ICSI</td>
<td>49 (38.6%)</td>
<td>111 (38.8%)</td>
<td>19 (45.2%)</td>
<td>137 (37.0%)</td>
</tr>
<tr>
<td>Previous IVF/ICSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>92 (72.4%)</td>
<td>215 (75.2%)</td>
<td>27 (64.3%)</td>
<td>285 (77.0%)</td>
</tr>
<tr>
<td>Yes</td>
<td>35 (27.6%)</td>
<td>71 (24.8%)</td>
<td>15 (35.7%)</td>
<td>85 (33.0%)</td>
</tr>
</tbody>
</table>

No significant differences were found between the groups.
¹BMI = body mass index
²missing data; a total of 157 (38.0%) females and 158 (38.3%) males. (This question was included later in the study)
³other causes or not evaluated
<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Females n = 413</th>
<th>Males n = 412</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any psychiatric diagnosis</strong></td>
<td>127 (30.8 %)</td>
<td>42 (10.2 %)</td>
</tr>
<tr>
<td>Full DSM-IV diagnoses¹</td>
<td>81 (19.6%)</td>
<td>30 (7.3%)</td>
</tr>
<tr>
<td>Subthreshold diagnoses²</td>
<td>46 (11.1%)</td>
<td>12 (2.9%)</td>
</tr>
<tr>
<td><strong>Any mood disorder</strong>³</td>
<td>108 (26.2 %)</td>
<td>38 (9.2 %)</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>45 (10.9 %)</td>
<td>21 (5.1 %)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>6 (1.4 %)</td>
<td>1 (0.2 %)</td>
</tr>
<tr>
<td>Partial remission of major depressive disorder</td>
<td>25 (6.1 %)</td>
<td>8 (1.9 %)</td>
</tr>
<tr>
<td>Minor depressive disorder</td>
<td>35 (8.5 %)</td>
<td>9 (2.2 %)</td>
</tr>
<tr>
<td><strong>Any anxiety disorder</strong>³</td>
<td>61 (14.8 %)</td>
<td>20 (4.9 %)</td>
</tr>
<tr>
<td>Anxiety NOS</td>
<td>46 (11.1 %)</td>
<td>16 (3.9 %)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>7 (1.7 %)</td>
<td>3 (0.7 %)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>5 (1.2 %)</td>
<td>2 (0.5 %)</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>8 (1.9 %)</td>
<td>1 (0.2 %)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>5 (1.2 %)</td>
<td>2 (0.4 %)</td>
</tr>
<tr>
<td>Eating disorder NOS</td>
<td>1 (0.2 %)</td>
<td>0</td>
</tr>
</tbody>
</table>

¹ Full DSM-IV diagnoses; major depressive disorder, dysthymia, partial remission of major depressive disorder, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, social phobia and bulimia nervosa
² Subthreshold diagnoses; minor depressive disorder, anxiety NOS and eating disorder NOS
³ subjects can have one or more psychiatric diagnoses within any mood and/or any anxiety disorders
Risk factors for mood and anxiety disorders (paper II)

The overall treatment outcome in the study population of 413 females was 136 (32.9 %) positive pregnancy tests, resulting in 100 live births (24.2 %) after treatment cycle. Fertility factors and outcome of IVF treatment for women with or without any psychiatric disorder are presented in Table 3. There were no differences in fertilization factors such as number of oocytes retrieved, fertilization rate and number of frozen embryos or treatment outcome (pregnancy test result) between females with or without any psychiatric disorder.

Following multiple logistic regression, a negative pregnancy test and obesity (BMI ≥ 30) were independent risk factors for depressive disorders in females. Among males the only independent risk factor for depression was unexplained infertility. No IVF-related risk factors for anxiety disorders could be identified, see paper II.

A negative pregnancy test, previous pregnancy and smoking were independent risk factors for major depression in females (n = 45), see Table 4. Previous extrauterine pregnancies had occurred in 11 % (n = 5) of females with major depression compared to 2.8 % (n=8) of females with no psychiatric diagnosis, p < 0.008. For females with major depression the live birth rate was 9 % (n = 4) compared to a live birth rate of 26 % among women with no psychiatric diagnosis (n = 74), OR 3.57; 95% CI, 1.23 - 10.32, p < 0.02.

Language difficulties were an exclusion criterion in the study. However, it was possible to include a few subjects, 24 women (6 %) and 19 men (5 %) with other ethnical background than Swedish. Therefore, the variable native language other than Swedish was used in the unadjusted analyses.
<table>
<thead>
<tr>
<th>Females</th>
<th>Any psychiatric disorder (n = 127)</th>
<th>No psychiatric diagnosis (n = 286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes at oocyte retrieval (n)</td>
<td>11.4 ± 6.6</td>
<td>10.4 ± 6.0</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>55.3 ± 27.4</td>
<td>55.3 ± 28.3</td>
</tr>
<tr>
<td>Embryo Transfer (ET)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>115 (90.6%)</td>
<td>245 (86.3%)</td>
</tr>
<tr>
<td>No</td>
<td>12 (9.4%)</td>
<td>39 (13.7%)</td>
</tr>
<tr>
<td>Embryos at ET (n)</td>
<td>1.1 ± 0.5</td>
<td>1.0 ± 0.5</td>
</tr>
<tr>
<td>Numbers of frozen embryos after ET</td>
<td>2.1 ± 2.6</td>
<td>1.6 ± 2.4</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>35 (27.6%)</td>
<td>101 (35.3%)</td>
</tr>
<tr>
<td>Negative</td>
<td>92 (72.4%)</td>
<td>185 (64.7%)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>27 (21.3%)</td>
<td>88 (30.8%)</td>
</tr>
<tr>
<td>Biochemical</td>
<td>3 (2.4%)</td>
<td>8 (2.8%)</td>
</tr>
<tr>
<td>Empty gestational sac</td>
<td>5 (3.9%)</td>
<td>5 (1.7%)</td>
</tr>
<tr>
<td>Miscarriages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrauterine pregnancy</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Miscarriage &lt; week 12</td>
<td>1 (0.8%)</td>
<td>12 (4.2%)</td>
</tr>
<tr>
<td>Miscarriage &gt; week 12</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Live birth rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (20.5%)</td>
<td>74 (25.9%)</td>
</tr>
<tr>
<td>No</td>
<td>101 (79.5%)</td>
<td>212 (74.1%)</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>22 (84.6%)</td>
<td>54 (73.0%)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>4 (15.4%)</td>
<td>20 (27.0%)</td>
</tr>
</tbody>
</table>
Table 4  Associations between socio-demographic, fertility data and major depression in females

<table>
<thead>
<tr>
<th></th>
<th>Major depression females (n=45)</th>
<th>No psychiatric diagnosis females (n=286)</th>
<th>Adjusted Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>9 (20.0%)</td>
<td>101 (35.3%)</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>36 (80.0%)</td>
<td>185 (64.7%)</td>
<td>2.23*</td>
<td>1.01 – 4.94</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>29 (64.4%)</td>
<td>183 (64.0%)</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>≥ 35</td>
<td>16 (35.6%)</td>
<td>103 (36.0%)</td>
<td>0.71</td>
<td>0.35 – 1.45</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>40 (88.9%)</td>
<td>273 (95.5%)</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>5 (11.1%)</td>
<td>13 (4.5%)</td>
<td>3.28*</td>
<td>1.03 – 10.40</td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24 (53.3%)</td>
<td>208 (72.7%)</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (46.7%)</td>
<td>78 (27.3%)</td>
<td>2.17*</td>
<td>1.11 – 4.25</td>
</tr>
<tr>
<td>Infertility duration (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 36</td>
<td>31 (68.9%)</td>
<td>176 (61.5%)</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>≥ 36</td>
<td>14 (31.1%)</td>
<td>110 (38.5%)</td>
<td>0.70</td>
<td>0.35 - 1.40</td>
</tr>
<tr>
<td>Infertility causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (24.4%)</td>
<td>86 (30.1%)</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20 (44.4%)</td>
<td>85 (29.7%)</td>
<td>1.77</td>
<td>0.77 – 4.03</td>
</tr>
<tr>
<td>Unexplained</td>
<td>14 (31.1%)</td>
<td>115 (40.2%)</td>
<td>1.02</td>
<td>0.43 – 2.41</td>
</tr>
</tbody>
</table>

*p < 0.05, Multiple logistic regression based on 331 subjects
Personality traits associated with mood and anxiety disorders (paper III)

For this sub-study 856 eligible women and men, 428 couples, were approached to participate. In all 643 (75 %) subjects filled out the SSP questionnaire. The response rates were 75.5 % for women (n = 323) and 75 % for men (n = 320). The overall treatment outcome in this study population of 323 women was 111 positive pregnancy tests (pregnancy rate of 34.4 %), resulting in 80 live births (live birth rate of 24.8 %). Any mood and/or anxiety disorder was prevalent among 100 (31 %) of the 323 women and 30 (9 %) of the 320 men. Mood disorders were present in 84 (26 %) women and in 27 (8 %) men and anxiety disorders in 53 (16 %) women and in 11 (3 %) men, due to co morbidity, data not shown.

Both women and men with mood and/or anxiety disorders had higher mean scores on somatic trait anxiety, psychic trait anxiety, stress susceptibility, lack of assertiveness and embitterment compared to women and men without mood and/or anxiety disorders, see paper III. The 13 personality scales yielded a three-factor model in the factor analysis, neuroticism, aggressiveness and sensation-seeking (extraversion). To simplify the multiple logistic regression models, these personality factors were used instead of the individual personality traits.

High scores of the personality factor neuroticism and a negative pregnancy test after IVF were independently associated with mood and/or anxiety disorders among infertile women, see Table 5. Among men high scores of neuroticism and unexplained or male infertility factor were independently associated with mood and/or anxiety disorders, see paper III.

The final multiple regression model indicated that high scores of neuroticism were negatively associated with live birth (p < 0.04) after IVF. Live birth was also negatively associated with low scores of aggressiveness (p < 0.02), see paper III.
Table 5  Associations between personality traits, socio-demographic, fertility data and any psychiatric disorder in women

<table>
<thead>
<tr>
<th></th>
<th>Any psychiatric disorder (n = 100)</th>
<th>No psychiatric diagnosis (n = 223)</th>
<th>Unadjusted Odds ratio</th>
<th>Adjusted Odds ratio</th>
<th>95.0% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuroticism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low scores</td>
<td>29 (30.5%)</td>
<td>113 (51.1%)</td>
<td>ref</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>High scores</td>
<td>66 (69.5%)</td>
<td>108 (48.9%)</td>
<td>2.38*</td>
<td>2.21*</td>
<td>1.26 – 3.85</td>
</tr>
<tr>
<td><strong>Aggressiveness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low scores</td>
<td>42 (44.7%)</td>
<td>113 (52.3%)</td>
<td>ref</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>High scores</td>
<td>52 (55.3%)</td>
<td>103 (47.7%)</td>
<td>1.35</td>
<td>1.09</td>
<td>0.63 – 1.87</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>65 (65.0%)</td>
<td>146 (65.5%)</td>
<td>ref</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>≥ 35</td>
<td>35 (35.0%)</td>
<td>77 (34.5%)</td>
<td>1.02</td>
<td>0.90</td>
<td>0.52 - 1.58</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>87 (87.9%)</td>
<td>199 (92.1%)</td>
<td>ref</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>12 (12.1%)</td>
<td>17 (7.9%)</td>
<td>1.61</td>
<td>1.65</td>
<td>0.73 – 3.72</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>93 (93.0%)</td>
<td>214 (96.0%)</td>
<td>ref</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>7 (7.0%)</td>
<td>9 (4.0%)</td>
<td>1.79</td>
<td>1.52</td>
<td>0.52 – 4.48</td>
</tr>
<tr>
<td><strong>Previous pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>64 (64.0%)</td>
<td>161 (72.2%)</td>
<td>ref</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 (36.0%)</td>
<td>62 (27.8%)</td>
<td>1.46</td>
<td>1.28</td>
<td>0.73 – 2.23</td>
</tr>
<tr>
<td><strong>Pregnancy test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>27 (27.0%)</td>
<td>84 (37.7%)</td>
<td>ref</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>73 (73.0%)</td>
<td>139 (62.3%)</td>
<td>1.63</td>
<td>1.80*</td>
<td>1.02 – 3.15</td>
</tr>
</tbody>
</table>

BMI = body mass index, * p < 0.05
Multiple logistic regression based on 303 subjects, 20 subjects had missing data.

Experiences of childlessness three years after unsuccessful IVF (paper IV)

The study group consisted of 19 participants; seven were couples and two male and three female participants did not bring their partners to the study. Of the latter participants, two of the men and two of the women had partners with a biological child from a previous relationship and these partners were excluded. One female participant was divorced. The participants had their last IVF treatment at the public clinic at a mean of 38 months prior to data collection. The analyses resulted in two main categories and seven sub-categories describing the experiences of the participants.
Experiences in relation to IVF treatment and failure

*Hope turned into grief*

Prior to IVF both men and women described they felt optimism and hope. Unsuccessful IVF had affected mental health negatively. Grief and symptoms of depression after IVF failure were disclosed by women. The experience was described as losing someone close, and suicidal thoughts after treatment failure were revealed. Men had no knowledge of possible emotional reactions following unsuccessful treatment, and the grief reactions of their wives were unexpected. Not allowing oneself to grieve, ignoring the grief and continuing with the next treatment were described by men and women.

*Late realisation of the need for professional support*

A lack of professional support during IVF or following unsuccessful treatment was described by both men and women. Men felt that they were expected to take a supportive role and they showed no sadness or grief when treatment failed. Handling their own and their partner’s grief reactions after treatment failure were experienced as difficult. Individual support and counselling for men was suggested, as this would enable them to ask about and better understand their spouse’s unexpected grief reactions without the spouse being present.

*Frustrating and unstructured ending of treatment*

After the last IVF treatment a final consultation with a health professional was lacking according to both men and women. Treatments were described as being too forced with too many doctors involved and the end was often abrupt. Reasons for discontinuing IVF treatment were the women’s emotional reactions after IVF failure, medical factors and financial factors. Men described that it had been the wife’s decision not to continue further IVF and that they were not always in agreement with their spouse about ending IVF and feelings of frustration over the decision were expressed.

*Affected partner relationship*

The partner relations had been both positively and negatively affected by IVF. Men and women described both a strengthened relationship and strain and temporary separations. A lack of self-esteem, expressed as worthlessness, was described by women. The subject of sexuality was spontaneously mentioned during the interview by women but not by men. Sexual life had been negatively affected during IVF and for some women it was still a problem three years later.
Experiences as childless after IVF failure

Unanswered questions after ending IVF
Remaining unanswered questions three years after IVF were described by both men and women. Not having the infertility factor finally explained and therefore not knowing the cause of infertility were reasons mentioned as hampering the processing of childlessness among both men and women. No fertilization after IVF was explained as a reason for understanding that the chance of treatment success was over.

Feeling left out and lacking understanding
Both men and women expressed a lack of understanding on the part of their closest family and friends about infertility and its treatment. Another reason for a lack of understanding was that men and women had provided information and was communicated about their fertility problems differently. Having social support was not described as often among men as by women. Men described feeling excluded in social situations when friends and colleagues were talking about their children. Experiences of not being like others, not being able to have children, and not being able to create a family were described by the women.

Meaning of life affected
Adaptation to childlessness had not been reached three years after IVF. Men described how they were trying to learn to live with the pain by denying it. Women described how they was physically and rationally close to accepting childlessness however there would never be an emotional acceptance. Three years after ending IVF mental health was described as relatively stable among men. Women were more emotionally stable than during IVF but some still had symptoms of depression. Not knowing how to handle and process grief was revealed. Feelings of guilt were described by women, but not by men, and a loss of control of the situation as childless. The loss of parenthood, of not having a family including a child, was described as a different life situation. At the same time, a life with more freedom was described. Still having hope for a spontaneous pregnancy was expressed among women, but also how their hope for a child had taken up a great deal of time in their life. The future was described in thoughts of being alone in old age. Both men and women described disappointment of not being able to give their parents the joy of grandchildren and not being able to have their own grandchildren.
Discussion

Methodological considerations papers I-III

Psychiatric disorders were assessed by the use of the PRIME-MD screening questionnaire followed by a highly structured interview conducted by telephone. Diagnostic interviews can also be conducted by semi-structured interviews, such as the SCID (Structured clinical interview for DSM-V disorders), with more open-ended questions for psychiatric assessments. A limitation of the PRIME-MD is that questions concerning distress/impairment are not assessed.

The use of the clinician evaluation guide (CEG) in PRIME-MD by a telephone interview has been validated in comparison with face-to-face interviews conducted by primary care physicians with good agreement (70, 107, 117). Telephone interviews are commonly used in large-scale population-based studies of psychiatric disorders because of their demonstrated comparability with face-to-face research interviews (70, 118, 119). For this reason, and because approximately 40 % of the subjects were living outside of Uppsala County, the structured computer-based interview by telephone was used for the psychiatric assessments in this study.

The choice of time-points for the assessment of psychiatric disorders may be considered as a limitation of the study. We chose a time-point for the final evaluation (CEG) which we thought would be most relevant to the couples undergoing IVF, i.e. after the pregnancy test result. A number of considerations were taken into account when this decision was finalized. First, a baseline assessment at the start of the infertility evaluation or at the onset of IVF treatment was discussed. From a clinical perspective this would have been a valuable time-point as we then would have been able to assess which subjects were depressed already at onset of IVF and in need of specific interventions during the course of treatment. However, almost half of the couples were referred from other counties, and by the time they first came to the Centre of Reproduction infertility evaluation and pre-treatment for IVF had been initiated by the referring clinic. With such a design, we would have ended up having a smaller sample or extending the inclusion period substantially.
Furthermore, whether this time-point would have resulted in a more valid estimate of the prevalence rates for depression and/or anxiety is uncertain. Increased rates of depressive symptoms in females prior to IVF have been reported in a review by Williams and co-authors (73), whereas a review by Verhaak and co-authors reported no significant difference in depression levels between infertile females and norm groups prior to IVF (74). Also, it has been shown that women express unrealistically high expectations when treatment is initiated, which may underestimates the clinical problem (27-30).

Another time-point that was discussed was whether the initial screening (PQ) should be performed on the day of oocyte retrieval or on the day of embryo transfer. In order to increase the sensitivity of our assessments we chose the day of the oocyte retrieval, which is considered as more stressful than the ET procedure. In doing so, we presumably had to perform more telephone interviews with screen positive women but there is little or no evidence that this difference in time-points (two to three days in between procedures) would have had any real relevance for our outcome measures. However, by screening before treatment outcome was known to the couple we have no knowledge if there were any of the screening negative women or men that could have developed a depression.

The time-point chosen for the telephone interview was after the pregnancy test had been performed. We considered performing the telephone interview prior to the pregnancy test, but this idea was rejected as this period has been shown to be the most stressful during the course of IVF (29). As the purpose of the study was to describe the prevalence rates of depression and anxiety during IVF we decided that the best time-point for the final evaluation would be after the treatment outcome was known to the couple. It is also important to stress that more than 25% of women with depression and/or anxiety had a positive pregnancy test.

A further limitation of the study was the time-point for the assessment of personality traits. Personality assessment at an earlier time-point in life, before the first onset of depression (120) or before the infertility crisis started, would have been preferable, although this was not feasible. Personality traits related to neuroticism are considered to be associated with major depression, although it is still debated as to whether neuroticism actually predispose to development of depression or are the result of one or several depressive episodes (120, 121).

Another methodological consideration was that alcohol abuse was not assessed in the modified version used for this study, even though this question was initially included in the PRIME-MD. Couples who are attempting a pregnancy are generally presumed to abstain from alcohol but the alcohol-
related questions could nevertheless have been of value for the study. Among men in the general population, high rates of substance-related disorders such as alcohol abuse, that disguise a depression have previously been reported (52, 122). Furthermore, in one study assessing alcohol abuse in primary care by the PRIME-MD the prevalence of alcohol abuse or dependence was estimated to 19% in men to compare with 4% for women (123).

Most women and men with language difficulties were excluded from the study. Although a few were included (5%), the rate of subjects with other native language than Swedish in the general population is about 16% (8). The exclusion of individuals with other native languages is a problem in most studies where data are collected by questionnaires and interviews. It can be assumed that these individuals more often suffer from depression, as heightened depression scores have been reported previously (124).

Furthermore, a variable of importance when analysing risk factors for psychiatric disorders is a history of depression. A previous history of depression was reported by every second subject with full DSM-IV diagnoses (paper I). However, a history of depression was only reported by females and males who received a psychiatric diagnosis during the telephone interview, and not by any other subjects included in the study. This information could have been assessed by including the question in the demographic questionnaire given to all participants in the study. For this reason prior depressive episodes could not be used in the multiple logistic regression model. Similarly, the number of previous stressful life events, except for the negative reproductive events, was not documented in this study. However, risk factors for development of depression and anxiety are fairly well-known from previous studies and the current study aimed at evaluating possible IVF-related risk factors for depression and anxiety.

It can also be argued that at a control or comparison group would have been of value in interpreting the study. However, the aim of the study was not to investigate whether IVF couples suffer more from depression and/or anxiety in comparison with other fertile women or the general population, but rather to describe the extent of this clinical problem within the IVF setting. However, in comparison with previously conducted population-based studies (52, 53), mood disorders were more common among infertile couples, whereas prevalence rates of anxiety disorders were similar or even lower than in the general population. Prevalence rates of psychiatric disorders among infertile females were similar to what was found in unselected gynaecological outpatients (125). Likewise, compared to a population-based study of pregnant women, the prevalence rates of depression and/or anxiety disorder were higher in the infertile females (126).
However, strengths of the present study include the relatively large sample size for an infertility/IVF setting, and the inclusion of male subjects, the high response rate and the possibility of obtaining follow-up data on pregnancy outcomes in all subjects. Furthermore, because medical records were kept on all eligible subjects, separate analyses could be performed among subjects who declined to participate.

Methodological considerations Paper IV

A qualitative approach was used for paper IV to complement the main study. A qualitative method can be used to reach a in-depth understanding of a given topic by describing in words and not in numbers, and by not explaining or analyzing differences in the sample (127, 128). A qualitative approach makes it possible to retrieve those answers that might be hard to assess from a quantitative study conducted by collecting data from questionnaires. One concern with assessment by questionnaires is that self-report measures may be susceptible to social desirability bias, as infertile couples want to present as well-adjusted emotionally especially prior to IVF. Participants are suggested to respond more as expected or more positively in questionnaires than in interviews (129, 130). Thus, open-ended interviews have a potential for a more in-depth understanding of the participant’s experiences.

Validity and reliability in qualitative studies is described by credibility, dependability and transferability to reach trustworthiness (115). Credibility depends on the sampling and the interpretation of the collected data according to the given topic (131) and refers to the similarities within and differences between categories (115), by using citations from different participants in the interviews. Another way is to test for inter-rater reliability, to avoid bias when interpreting. Thus, the co-authors checked the achieved codes and categories to reach an agreement and in this manner the interpretation was also checked for. Another way to reach inter-rater reliability can be to randomly choose a sample of interviews to be separately coded by the co-authors. By using qualitative content analysis the results can be described in terms of both manifest (explicit) and latent (implicit) content, which was the case in this study. This study mainly focused on the manifest content in the interviews. However, the underlying meanings, thus addressing the latent content, were also described as in the case of men not explicit expressing grief.

Dependability is the possible change over time in data collection and analysis and if different answers are given to different interviewers (115, 116). All interviews in this study were conducted and transcribed during the same year (2006) by the same person. The interviews were assessed by an interview
guide to maintain the same questions to all participants, and a structured analysis including discussion among the researchers minimized the change over time. All transcribed interviews were re-checked by listening to the tapes on several occasions. The description of bias and being compliant towards the collected data and transcribing verbatim are of importance (116, 131).

Limitations of qualitative studies are often the relatively small sample size, thus making transferability, such as to generalizing results to other settings less possible. Therefore, the extent of the transferability of the result of a study to other infertility settings depends on cultural and traditional similarities or differences (116). However, qualitative research does not aim at being representative in sampling, but at reaching meaning and understanding of each individual’s experience (128, 132). The experiences of individuals with ethnic backgrounds other than Swedish were not included nor were certain characteristics occurred of those declining to participate. Further, men with a male infertility factor and women with university level education who were fewer in number than in our previous infertility sample at the same clinic. Another limitation of the study was that sexual problems that some women brought up spontaneously were not a topic guiding the interviews, and thus there is no knowledge of male participants’ experiences of sexuality.

However, strengths of the qualitative study, was to assess the individual male perspective after the end of unsuccessful IVF treatment, as this provides new knowledge in the infertility/IVF setting. Also, to combine the main study with a qualitative method may increase the understanding of the experience of childlessness after unsuccessful IVF treatment.
Main outcome findings

The main study (papers I-III) is to our knowledge the first to describe prevalence, IVF-related risk factors and personality traits and associations with depressive and/or anxiety disorders in both women and men undergoing IVF treatment.

Mood disorders are more prevalent than anxiety disorders

Mood disorders were common in both women and men undergoing IVF. Major depression was the most common mood disorder, prevalent in one of 10 women and twice as common as in men. However, anxiety disorders were less common than in the general population. The relatively high prevalence rates of mood disorders may reflect the fact that the studied population was a clinical sample. Prevalence rates of psychiatric disorders among infertile females were similar to what was found in unselected gynaecological outpatients, where 30.5 % suffered from any psychiatric disorder and 10 % had a major depression (125). However, the prevalence of mood disorders is even higher in the primary care setting; 35 % in women and 25 % in men assessed by the PRIME-MD (123).

The prevalence rates of depression and anxiety disorders can also be affected by the difficulties involved in dealing with infertility and/or the emotional burden of undergoing IVF treatment. The hormone therapy used during IVF may also affect the self-reported symptoms such as mood, headache and fatigue at the time of the initial screening. However, three out of four women in this study were undergoing their first IVF and according to de Klerk and co-workers no difference in self-reported symptoms of depression were detected after the first IVF treatment or between different treatment regimens (26).

The majority of subjects with depressive disorders were undiagnosed. One plausible explanation for why depression is not recognized in the infertility setting is that infertile couples are reluctant to report depressive symptoms to the IVF team as they want to appear well adjusted, in concern that IVF treatment will be postponed if psychological problems are revealed (28, 73). Therefore, their positive attitudes before the start of the first treatment may disguise an ongoing depression.

Another finding was that only a small proportion of those identified with mood or anxiety disorders had ongoing treatment. Only a few women with a psychiatric disorder had antidepressant treatment during the IVF treatment, although the current recommendations are not to avoid antidepressants during pregnancy (63, 64). Psychotherapy, in the form of counselling, was re-
ceived by only one fifth of the subjects with a psychiatric diagnosis and by one in 10 of all subjects in this study. This is surprisingly few, as all couples are informed about and offered counselling at their initial visit to the clinic. However, similar low rates of counselling have previously been reported by Boivin and colleagues, who found that only 11 % of females and males received counselling (133). Counselling is suggested according to ESHRE to be offered to all couples considering medical, psychological and social questions, as an integral part of the IVF programme and may be performed by health professionals in the IVF team or by professional counsellors (12, 25). Another alternative explored is an intervention by extended encounters with a midwife during IVF treatment, however no impact was noticed on psychological well-being (134). Furthermore, a recent meta-analysis examining psychological interventions for infertile women found no significant effects in mental health (135). Therefore, for those individuals at risk to develop depression psychological/psychiatric consultants and adequate evidence based treatment need to be provided.

IVF-related risk factors for mood disorders

A negative pregnancy test after IVF treatment was associated with an increased risk of mood disorders among women, in particular major depression. As the pregnancy test is taken at home by the female, a negative test result will be revealed to the couple outside the fertility clinic. Therefore, it is clinically important to follow couples after treatment failure. Infertile couples need to be informed at an early time point prior to IVF that the outcome after treatment can be unsuccessful and of the emotional reactions that may follow (74). A mandatory appointment for follow-up booked prior to IVF is therefore strongly recommended. In case of treatment failure the follow-up visit at the clinic should take place within a few weeks after the negative pregnancy test. Not only is unsuccessful treatment associated with increased risk of depression, a failed treatment may lead to an increase in pre-existing depressive symptoms, which are unlikely to diminish shortly after treatment. An unsuccessful first treatment is a less favourable starting point for the next treatment cycle and may be a risk for later development of depression (74, 136). Therefore, to identify females with depression and to assure that adequate evidence based treatment is initiated before the next treatment is of importance.

Previous pregnancy was, beside a negative pregnancy test, a risk factor for major depression in females. The prevalence of early miscarriages is between 10 - 20 %. The knowledge of the prevalence of spontaneous abortions in relation to any underlying depression is limited. It is still unknown whether depression with or without treatment with antidepressants is associated with spontaneous abortions (137 - 138). However, having recurrent
miscarriages and extrauterine pregnancies may lead to depression. Therefore, the IVF team needs to be aware of and identify those women with previous negative reproductive events, such as miscarriages or extrauterine pregnancies, as these women are particularly vulnerable to develop major depression after unsuccessful IVF treatment.

Obesity (BMI ≥ 30) was another independent risk factor associated with mood disorders in females. The prevalence of obesity in the population is increasing and it is likely that obesity and depression may occur together (139). However, no firm conclusion can be made of the effect of obesity on depression (82). Obesity may negatively affect the live birth rate after IVF and weight reduction before the onset of IVF has been shown to improve treatment outcome (13, 140, 141). Information about the negative effects of obesity is important and many clinics recommend weight reduction and have limits for BMI prior to IVF.

Unexplained infertility was the only independent risk factor for depression among males. Not having an infertility diagnosis is suggested to be a stressful factor (142) and has to be taken into account in men undergoing IVF. Previous studies have indicated that an unexplained infertility factor can be a risk factor for distress in women (105, 143). Explaining the infertility diagnosis may increase the sense of control (43) and decrease the risk of developing depression. Today when the waiting time for infertility evaluation and treatment is shorter than a decade ago (104) and visits to the clinic are few, there is less time and opportunity for explaining the cause of infertility prior to or during IVF. Therefore, the infertility factor need to be explained not only undergoing IVF but also at a final consultation after IVF treatment.

Surprisingly, fertility factors such as female age, duration of infertility, infertility diagnosis and number of previous IVF treatments were not associated with psychiatric disorders, although these findings are consistent with other studies (3, 84).

Personality related to mood and/or anxiety disorders

High scores of personality traits related to neuroticism were independently associated with mood and/or anxiety disorders in women. Our results are in line with findings of Verhaak and co-workers, thus suggesting that pre-existing neuroticism in women are one of the most important predictors of the emotional response after IVF failure (30). High scores of neuroticism were also independently associated with mood and/or anxiety disorders among men. However, as these disorders were less prevalent among men the results in this group must be interpreted with caution.
Certain personality traits may increase the probability of experiencing life events as stressful (95). Infertility and treatment failure, independently or taken together qualify as stressful life events. Consequently, not only may women with high scores of personality traits related to neuroticism be more likely to perceive unsuccessful IVF treatment as more stressful than women without such an underlying predisposition, but they may also be more vulnerable developing a depressive episode during or after unsuccessful IVF treatment.

An increased awareness of these vulnerability factors for developing depression is of importance for health professionals in care of infertile couples. Although personality is considered to be fairly stable and resistant to change, implications for intervention may be useful, as to modify the high expectations of a positive treatment outcome and to reduce depression after treatment failure (144). Therefore, there is a need for a specialized IVF-team able to identify subjects at risk of depression and to provide evidence based treatment after treatment failure or before undergoing further IVF treatment.

**Mood disorders and personality in relation to treatment outcome**

Some of the results derived from paper II and III need to be further addressed, although they must be regarded as preliminary. The live birth rate (9 %) for females with major depression was significantly lower than for other females in this study population (approximately 25 %) in women without psychiatric diagnoses. However, in spite of the relatively small sample of women with major depression (n = 45) these findings may suggest that major depression is associated with negative outcome of IVF treatment. A review of the literature indicates that mood disorders may be associated with decreased pregnancy rates (73), although there is great controversy in this area. An association between anxiety and/or depressive symptoms and lower pregnancy rates has been suggested (28, 145-147), whereas other studies have failed to reveal any associations (27, 148-150). Few studies have addressed the association between anxiety and/or depressive symptoms and live birth rate as endpoint. In a study by Klonoff-Cohen and co-workers live birth rate was negatively influenced by baseline stress prior to IVF (21), but this was not the case in another study by de Klerk and co-workers (151).

The association between personality factors, such as neuroticism, and treatment outcome following IVF was explored in paper III. In contrast to paper II, the assessment of personality traits were made at the time-point of oocyte retrieval, and consequently before the result of the pregnancy test was known to the subject. The results indicate that high scores of neuroticism are negatively associated with live birth after IVF. Successful outcome after IVF depends on multiple factors such as female age and good quality embryos.
(9, 10). According to our results, neuroticism as a vulnerability factor for depression may also be associated to treatment outcome after IVF.

Unresolved grief after IVF failure

Grief and symptoms of depression were described by women both after IVF failure and three years after the end of IVF in paper IV. If the grieving process is hampered or prolonged, it may lead to complicated grief which is consistent with the definition of major depression (2, 47). Major depression includes feelings of worthlessness, such as loss of self-esteem which is contrary to normal grief reactions where self-esteem is not affected (46). Feelings of guilt and lost control and suicidal thoughts after IVF failure were described among women indicating symptoms of depression. Guilt and sense of loss of control is considered a vulnerability factor for distress after IVF (28, 96). Another study revealed that a substantial proportion of childless women had high scores of complicated grief and depressive symptoms when fertility treatment was no longer an option (152). Furthermore, unresolved grief can lead to substantial disability and impairment, increased health service use and sick leave, although those questions were not assessed in this study. Therefore, it is important for health care professionals to distinguish between normal grief and complicated grief (47, 48) and to identify and follow the individuals at risk of developing major depression after treatment failure. Furthermore, informing and counselling about emotional reactions of grief and depression after IVF failure already at an early phase prior to IVF may help the individual in the grief process of childlessness after IVF treatment.

Social support is depending on if there has been information given about the fertility problems, as there is no visible loss. Therefore, it is plausible that infertile individuals will be more vulnerable to depression if there is a lack of support (40, 152). If the loss is visible, as after a stillbirth, the social network will be supportive and thus facilitate an adjustment process. Social isolation, as feelings of being excluded with no understanding from their social network, was described mostly by men. Men and women were communicating differently about fertility problems with significant others, resulting in less social support among men. A lack of social support or discontent with support given leads to complicated grief and depression in women (48, 152). A study of parents of preterm infants indicates those who actively seek social support and express negative feelings have healthier mental health outcome than those who deny negative feelings and do not seek or accept support from their social network (40). A lack of professional support and how men took the supportive role after treatment failure were also described and indicated men asked for and were in need of their own individual support while
undergoing IVF treatment. This raised the question of, if and when, will men grieve or realise they need an opportunity to grieve.

A consequence of the emotional reactions after IVF failure was to discontinue IVF treatment. The decision-making to end treatment was described by the men as being the woman’s decision, and one reason for this was the grief reactions experienced after treatment failure. The most common reason for discontinuing treatment is emotional burden after IVF failure (153, 154). Hence, to limit drop-out from further treatment mandatory professional support should be offered all couples after treatment failure. If symptoms of depression can be identified and adequately treated, the chance may be that more couples continue and may optimise the chance of successful outcome after treatment (154).

Lack of a structured end after IVF treatment is a plausible factor to hamper the processing of childlessness. Furthermore, the cause of infertility could be explained at a final consultation, thus reducing the number of unresolved questions after treatment (100). However, there are no rituals in the experience of ongoing childlessness for facilitating an adaptation (39, 42, 44, 155). Achieving closure, having some kind of ending, is of importance for being able to process childlessness. Ending treatment means closure of options for having a biological child and giving up hope of pregnancy. However, the cessation of treatment does not end infertility for women, as there is no emotional closure, indicating an increased vulnerability to develop depression (156).

The theoretical framework of life crisis was not applicable for all phases during an infertility crisis, as most men and women were still processing and had not adapted to childlessness three years after IVF treatment. Infertility differs from life crisis by an extended reactive phase resulting in a state of prolonged or chronic crisis (43). A crisis model for infertility has implications for understanding the emotional adjustment of the grief process and can be of use for successful adjustment (4). However, as infertility is not a single stressful event but a complex process, often with recurrent reproductive losses (156) the crisis model may not be as useful. Crises are considered time-limited and for many individuals infertility is not limited in time because of recurrent losses.

Differentiating between the emotional reactions, such as stress, crisis and grief and psychiatric disorders as major depression can be difficult. Furthermore, there is no clear definition of the psychological problems associated with infertility (135). For a childless woman the loss is an ongoing stressful life event, first the loss of fertility and then the loss after undergoing failed treatment when childlessness will be considered as definite. Thus, the crisis
can constitute lifelong grief with the risk of developing depression. Not only is infertility a reproductive health problem it may also lead to mental health problems, as major depression. IVF failure was affecting women and men differently, by women experiencing grief and men were not expressing grief. Most infertile individuals will adjust to infertility and IVF failure. However, some of the individuals with previous negative reproductive events and neuroticism-related personality traits will be more vulnerable to develop depression.

Identify risk factors
Screening women and men prior to IVF to identify individuals vulnerable to develop depression may be possible by assessing the risk factors found in this study; such as previous miscarriage, obesity and the infertility factor among men. A medical and psycho-social history at the time of admission to IVF should therefore include assessment of risk factors and also a history of depression and social network/support.

Although assisted treatment has developed during the last two decades, little has improved in terms of support and counselling for couples undergoing IVF, a situation described by Schmidt already a decade ago (104). Some of the suggestions given by men in paper IV included individual and mandatory support before and after IVF, an introduction prior to IVF and a treatment-plan to follow during IVF. Patient education and information for infertile couples undergoing treatment is in need of improvement (157). Therefore, these suggestions are clinical implications that are possible for the IVF team to assess for all couples undergoing IVF. These improvements are needed to facilitate the grieving process after undergoing unsuccessful IVF treatment. Furthermore, for those individuals at risk to develop depression psychological/psychiatric consultants and evidence based treatment is the option.
Conclusions

Mood disorders were common in both women and men undergoing IVF. Major depression was prevalent in one of 10 women and twice as common as in men. The majority of subjects with psychiatric disorders were undiagnosed and untreated. Anxiety disorders were less common than in the general population and no IVF-related risk factors were identified.

A negative pregnancy test was associated with an increased risk for depression in women, whereas the pregnancy test result was not a risk factor for depression in men. An unexplained infertility factor was the only risk factor for mood disorders in men. High scores of personality traits related to neuroticism were associated with any mood and/or anxiety disorders among both women and men.

Unsuccessful IVF was experienced by women, in the qualitative-approach study, in terms of grief whereas men took upon themselves a supportive role and did not express grief. Professional support and counselling in how to handle the grief was requested. An unstructured end after IVF treatment left unanswered questions. Three years after the end of treatment, both men and women were still processing and had not adapted to being childless, indicating the grieving process was unresolved.
Clinical implications

A midwifery perspective

A midwife within reproductive health meets women during different transitions in a woman’s life; from the adolescent girl reaching puberty, the pregnant woman before, during and after childbirth to the menopausal woman at the end of her reproductive life. A midwife will also meet the couple when it is not possible to reach one of these transitions, or life goals, when fertility treatment does not result in the birth of a child. At this time point it is important to be aware of the mental strain, of grief and depression that can occur. Not only reproductive health is affected, mental health may be affected as well. Therefore, involuntary childlessness, as the inability to transition from pregnancy to childbirth and parenthood is to be considered as one of the most stressful events in a woman’s life.

With this knowledge and awareness in mind reproductive health professionals, such as the midwife, can meet the couple prior to their first IVF. By asking questions about previous negative reproductive events and history of depression it may be possible to identify those individuals vulnerable to develop depression. By also using the suggestions given by men in this study, such as providing additional individual support before IVF including information about possible emotional reactions and how to handle them after IVF failure, it may be possible to facilitate the grieving process after IVF failure.

Furthermore, these clinical implications can also be used to try to limit dropout from further IVF so that more couples will continue, thereby optimizing the chance of successful outcome after treatment. Patient information and education are important not only for the infertile couple prior to and during IVF. Information to the general population is of importance to obtain increased understanding of the difficulties involved during infertility and IVF treatment. Therefore, psychiatric education for health professionals in the IVF team in care of the infertile couple is of importance.
Future research

Clinical research often aims at describing prevalence and causes/risk factors for a given problem for those individuals requesting treatment. Thus, there is no knowledge in this respect regarding those not requesting treatment. When the result is assessed and there is a problem or risk factor revealed, one need to start addressing the problem through implementation, not only by identifying and recommending. Support and counselling, concerning grief reactions following unsuccessful treatment, by a specialized midwife in the IVF-team during and after IVF offered to all couples to decrease the mental burden of treatment failure and ongoing childlessness is an intervention of further research.

Furthermore, there have been few long-term follow-up studies after the end of IVF treatment and no study thus far has addressed the prevalence of psychiatric disorders following IVF failure. Clearly, grief is a common finding in women three years after failed IVF, but our qualitative study was not designed to address whether these women suffered from an unresolved infertility crisis, complicated grief or even major depression. The women and men who participated in studies I-III started their first (in most cases) IVF treatment almost five years ago and may thus be targeted for a long-term follow-up study focusing on prevalence of major depression. Possible questions to address include whether there is a difference in the prevalence rates of depression between women who have conceived and women who are still childless. Also, it would be possible to assess why couples discontinue IVF when treatment outcome is unsuccessful and to establish the reasons for drop-out from further IVF in a larger sample. Another issue that was brought up by women in paper IV was the negative effect infertility and IVF treatment had had on their sexual life. Further studies in both women and men concerning sexuality are warranted.

Another topic for future research would be to describe the resolution of childlessness, such as plans for adoption, which was not assessed in the current study. Will biological childlessness result in a resolution of the infertility crisis and if so how is it solved; by adoption or other alternatives? Development of a theoretical explanation-model for the infertility crisis in order to improve the understanding of involuntary childlessness is a topic that could be of use for future research.
Infertilitet och att genomgå behandling med in vitro fertilisering (IVF) kan vara förenat med psykisk ohälsa, som depression. Egentlig depression kan fastställas med psykiatiska diagnoskriterier enligt DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). Personlighetsdrag relaterade till neuroticism kan öka sårbarheten att utveckla depression.

Syftet med detta avhandlingsarbete var att fastställa förekomsten av depressions- och ångestsyndrom, hos ofrivilligt barnlösa kvinnor och män som genomgår IVF behandling. Syftet var också att undersöka vilka riskfaktorer och personlighetsdrag som är relaterade till depressions- och ångestsyndrom. Ett ytterligare syfte var att intervjuar kvinnor och män för att ta reda på deras upplevelse av barnlöshet tre år efter avslutad IVF.

Studien genomfördes på Reproduktionscentrum, Akademiska sjukhuset, Uppsala under en tvåårsperiod mellan 2005 – 2007 där samtliga kvinnor och män (545 par) erbjöds att delta. Svarsfrekvensen var totalt 79 % (413 kvinnor och 412 män). Två frågeformulär ingick i studien; PRIME-MD (The Primary Care Evaluation of Mental Disorders) ett psykiatriskt diagnostiskt instrument bestående av två delar; ett screeningformulär med 24 frågor, samt en uppföljande intervjua som i denna studie genomfördes per telefon med screeningpositiva kvinnor (65 %) respektive män (39 %). Screening skedde i samband med äggaspiration (OPU) och följdes upp med en individuell högstrukturerad diagnostisk telefonintervju tre veckor senare, efter graviditetstesten. SSP (The Swedish universities Scales of Personality) ett personlighetsformulär med 91 frågor som användes för att undersöka personlighetsdrag.

Resultatet från undersökningen visade att förekomsten av depression och/eller ångestsyndrom var 31 % bland kvinnor och 10 % bland män. Vanligast förekommande var egentlig depression som diagnostiserades hos 11 % kvinnor och 5 % män. Ångestsyndrom var inte mer vanligt bland infertila kvinnor och män än i normalbefolkningen. Riskfaktorer för depression hos kvinnor var ett negativt graviditetstest efter IVF samt fetma (body mass index ≥ 30). Oförklarad barnlöshetsfaktor var den enda riskfaktorn för depres-
sion hos män. Inga IVF-relaterade riskfaktorer för ångestsyndrom påvisades hos kvinnor eller män. Personlighetsdrag relaterade till neuroticism var assoцииerat med depression och/eller ångestsyndrom.


Avhandlingsarbetet har visat behov på ökad kunskap och förståelse om risk och sårbarhetsfaktorer för depression i samband med infertilitet och misslyckad IVF behandling. Det finns ett behov av utbildning inom psykiatri och psykisk ohälsa, för att öka kunskapen om bemötandet av individer i psykisk kris. Barnmorskan inom reproduktiv hälsa möter kvinnor i viktiga vändpunkter i livet; från tonårsflickan i puberteten, kvinnan i samband med graviditet och barnafödande fram till den fertila periodens slut, menopaus. Barnmorskan möter också det infertila paret, som inte uppnår sitt livsmål - att få barn efter genomgången IVF behandling.

Kliniska implikationer för IVF-teamet, exempelvis en specialiserad barnmorska, är att i samband med inskrivningssamtalet inför IVF ställa frågor om riskfaktorer, som i denna studie var tidigare misstank, samt om tidigare depression, för att underlätta identifiering av personer som kan ha en ökad risk att utveckla depression efter misslyckad IVF behandling. För dessa individer som tidigare varit deprimerade bör psykiaterkonsult samt evidensbaserad behandling erbjudas. Betydelsen av kontinuitet, samt ett avslutande samtal efter IVF framkom i studien och viken av att informera om orsaken till barnlösheten. Andra implikationer för att underlätta bearbetande av barnlösheten är att erbjuda stöd och råd, både individuellt och för paret, redan i ett tidigt skede av IVF om de emotionella reaktioner och den sorgeprocess som kan uppstå efter att ha genomgått misslyckad IVF behandling.
Förslag på framtida forskning är en långtidsuppföljning av de par i studien som påbörjade IVF behandlingen för närmare fem år sedan. Syftet är att ta reda på förekomsten av psykisk ohälsa beroende på utfallet efter IVF, dvs. om paren fått barn eller inte. Dessutom kan orsaker till att avsluta misslyckad IVF behandling i förtid undersökas. Frågor som inte tagits upp i denna studie; som alkoholvänor, sexualitet samt tidigare depression kan ställas.

Ett annat forskningsområde är att beskriva om och hur kvinnor och män har bearbetat barnlöshetskrisen; genom adoption eller andra alternativ. Utvecklande av en teoretisk förklaringsmodell för barnlöshetskrisen kan vara ett sätt att öka kunskapen om och förståelsen för de barnlösa parens livssituation.
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1. DSM-IV criteria

**Major depressive episode**

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either

1. (1) depressed mood or
2. (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (for example, feels sad or empty) or observations made by others (for example, appears tearful). Note: In children and adolescents, can be irritable mood.

2. (2) Marked diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).

3. (3) Significant weight loss when not dieting or weight gain (for example, change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

   Note: In children, consider failure to make expected weight gains.

4. (4) Insomnia or hypersomnia nearly every day.

5. (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

6. (6) Fatigue or loss of energy nearly every day.

7. (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8. (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

9. (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a mixed episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication) or a general medical condition (for example, hypothyroidism).

E. The symptoms are not better accounted for by bereavement, that means, after the loss of a loved one, the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

**Dysthymic disorder**

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least two years. Note: In children and adolescents, mood can be irritable and duration must be at least one year.

B. Presence, while depressed, of two (or more) of the following:

1. poor appetite or overeating
2. insomnia or hypersomnia
3. low energy or fatigue
4. low self-esteem
5. poor concentration or difficulty making decisions
6. feelings of hopelessness

C. During the two-year period (one year for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than two months at a time.

D. No major depressive episode has been present during the first two years of the disturbance (one year for children and adolescents); i.e., the disturbance is not better accounted for by chronic major depressive disorders, or major depressive disorder, in partial remission. Note: There may have been a previous major depressive episode provided there was a full remission (no significant signs or symptoms for two months) before development of the dysthymic disorder. In addition, after the initial two years (one year in children or adolescents) of dysthymic disorder, there may be superimposed episodes of major depressive disorder, in which case both diagnoses may be given when the criteria are met for a major depressive episode.

E. There has never been a manic episode, a mixed episode, or a hypomanic episode, and criteria have never been met for cyclothymic disorders.
F. The disturbance does not occur exclusively during the course of a chronic psychotic disorder, such as schizophrenia or delusional disorder.

G. The symptoms are not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication) or a general medical condition (for example, hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**Generalized anxiety disorder**

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least six months, about a number of events or activities (such as work or school performance).

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past six months. Note: Only one item is required in children.

   1. restlessness or feeling keyed up or on the edge
   2. being easily fatigued
   3. difficult concentrating or mind going blank
   4. irritability
   5. muscle tension
   6. sleep disturbance (difficult falling or staying asleep, or restless unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of an axis I disorder, for example, the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder.

E. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication) or a general medical condition (for example, hyperthyroidism) and do not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.
Panic disorder without agoraphobia

A. Both (1) and (2):
   (1) recurrent unexpected panic attacks
   (2) at least one of the attacks has been followed by one month (or more) of one
   (or more) of the following:
      (a) persistent concern about having additional attacks
      (b) worry about the implications of the attack or its consequences
         (for example., losing control, having a heart attack, "going crazy")
      (c) a significant change in behavior related to the attacks

B. Absence of agoraphobia.

C. The panic attacks are not due to the direct physiological effects of a substance (for example, a
drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).

D. The panic attacks are not better accounted for by another mental disorder, such as social
phobia (for example, occurring on exposure to feared social situations), specific phobia (for
example, on exposure to a specific phobic situation), obsessive-compulsive disorder (for example,
on exposure to dirt in someone with an obsession about contamination), posttraumatic stress
disorder (for example, in response to stimuli associated with a severe stressor), or separation
anxiety disorder (for example, in response to being away from home or close relatives).

Obsessive-compulsive disorder

A. Either obsessions or compulsions:

   Obsessions as defined by (1), (2), (3), and (4):
   (1) recurrent and persistent thoughts, impulses, or images that are experienced, at
       some time during the disturbance, as intrusive and inappropriate and that cause
       marked anxiety or distress
   (2) the thoughts, impulses, or images are not simply excessive worries about real-
       life problems
   (3) the person attempts to ignore or suppress such thoughts, impulses, or images,
       or to neutralize them with some other thought or action
   (4) the person recognizes that the obsessional thoughts, impulses, or images are a
       product of his or her own mind (not imposed from without as in thought
       insertion)
Compulsions as defined by (1) and (2):

(1) repetitive behaviors (for example, hand washing, ordering, checking) or mental acts (for example, praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly

(2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. Note: This does not apply to children.

C. The obsessions or compulsions cause marked distress, are time consuming (take more than one hour a day), or significantly interfere with the person’s normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (for example, preoccupation with food in the presence of an eating disorder; hair pulling in the presence of trichotillomania; concern with appearance in the presence of body dysmorphic disorder; preoccupation with drugs in the presence of a substance use disorder; preoccupation with having a serious illness in the presence of hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a paraphilia; or guilty ruminations in the presence of major depressive disorder).

E. The disturbance is not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication) or a general medical condition.

Specify if:

With poor insight: if, for most of the time during the current episode the person does not recognize that the obsessions and compulsions are excessive or unreasonable.

Social phobia

A. A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. Note: In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.
B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack. Note: In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.

C. The person recognizes that the fear is excessive or unreasonable. Note: In children, this feature may be absent.

D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.

F. In individuals under age 18 years, the duration is at least 6 months.

G. The fear or avoidance is not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (for example, panic disorder with or without agoraphobia, separation anxiety disorder, body dysmorphic disorder, a pervasive developmental disorder, or schizoid personality disorder).

H. If a general medical condition or another mental disorder is present, the fear in criterion A is unrelated to it; for example, the fear is not of stuttering, trembling in Parkinson’s disease, or exhibiting abnormal eating behavior in anorexia nervosa or bulimia nervosa.

Specify if: Generalized: if the fears include most social situations (also consider the additional diagnosis of avoidant personality disorder).
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Editor: The Dean of the Faculty of Medicine

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