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**Blood- and Injection Phobia in Pregnancy**  
**Epidemiological, Biological and Treatment Aspects**

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”Many will swoon when they do see blood”  
As You Like It, Act IV, Scene III  
W. Shakespeare



## Abstract

Blood- and injection phobia is an anxiety disorder with a prevalence of approximately 3-5% in the general population. The etiology is often a combination of genetic factors and a conditioning experience. The symptoms of blood- and injection phobia are dizziness, confusion, nausea, epigastria discomfort, anxiety and sometimes panic attacks when receiving injections, seeing blood or having a blood sample taken. Unique for this specific phobia is the high probability of fainting when the phobic situation is encountered if there is no possibility to escape or to avoid the stimuli.

During pregnancy and labor, women with blood- and injection phobia are exposed to most of their fears and they therefore find themselves in anxiety-ridden situations. Stress and anxiety during pregnancy is known to be risk factors for adverse obstetric and neonatal outcomes. Studies have shown an altered hypothalamic-adrenal-pituitary axis in women with stress or/and anxiety during pregnancy and increased cortisol concentrations can imply negative consequences for the unborn child. Cognitive behavioral therapy (CBT) is known to be effective in treating specific phobias such as blood- and injection phobia.

The prevalence, obstetric and neonatal consequences, impact on the hypothalamic adrenal-pituitary axis and treatment aspects of blood- and injection phobia in a pregnant population have not been investigated before. The aims of this thesis were to study each of these phenomena.

During 2005 a total of 1606 pregnant women were approached at their first visit in an antenatal care clinic in the southeast region in Sweden. They were asked to complete the "Injection Phobia Scale-Anxiety" questionnaire. All women who scored  $\geq 20$  on the "Injection Phobia Scale-Anxiety" questionnaire ( $n=347$ ), were interviewed and either diagnosed for blood- and injection phobia or dismissed. In total, 110 women were diagnosed as having blood- and injection phobia. The prevalence of 7% shows that this condition is rather common among women in childbearing age.

In a study based on the same population as above, a prospectively collected cohort of 110 women with blood- and injection phobia showed a higher rate of obesity ( $p<0.001$ ), smoking ( $p=0.001$ ), fear of childbirth ( $p<0.001$ ), preeclampsia ( $p=0.01$ ), preterm labor ( $p=0.028$ ), elective cesarean section ( $p=0.032$ ) and having a baby born small for gestational age ( $p=0.009$ ) compared to a control group of 220 pregnant women without blood- and injection phobia.

Samples of cortisol in the saliva were collected in the morning and evening in gestational week 25 and 36 in both groups of pregnant women. The women with blood- and injection phobia had increased cortisol concentrations in the saliva indicating an altered hypothalamic-adrenal-pituitary axis during these weeks of pregnancy compared to the healthy controls ( $p=0.014$ ).

A treatment study was conducted using cognitive behavioral therapy in a group of pregnant woman with blood- and injection phobia. The results show that a two-session CBT in group for pregnant women with blood- and injection phobia is effective and stable for at least three months after partus ( $p<0.001$ ). This therapy also reduces anxiety ( $p<0.001$ ) and depressive ( $p<0.001$ ) symptoms during pregnancy, which is beneficial for both mother and fetus/baby. To enhance psychological well being in pregnant women with blood- and injection phobia this method could be applied.



## **List of original papers**

This thesis is based on the following papers, which are referred to by their Roman numerals I – IV:

I. Lilliecreutz C, Josefsson A. Prevalence of blood- and injection phobia among pregnant women. *Acta Obstet Gynecol Scand* 2008; 87:1276-1279

II. Lilliecreutz C, Josefsson A, Sydsjö G. An open trial with cognitive behavioural therapy for blood- and injection phobia in pregnant women - A group intervention program. *Arch Womens Ment Health* 2010; 13:259-65

III. Lilliecreutz C, Sydsjö G, Josefsson A. Obstetric and perinatal outcome among women with blood- and injection phobia during pregnancy. Accepted for publication in *J Affect Disord* Aug 2010

IV. Lilliecreutz C, Theodorsson E, Sydsjö G, Josefsson A. Salivary cortisol in pregnant women with blood- and injection phobia. Submitted to *Arch Womens Ment Health*



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## **Abbreviations**

11 $\beta$ -HSD: 11 $\beta$ -hydroxysteroid dehydrogenase

ACC: Antenatal care clinic

ACTH: Adrenocorticotrophic hormone

AT: Applied tension

BAI: Beck Anxiety Inventory

CAR: Cortisol awakening response

CBG: Corticosteroid binding globulin

CBT: Cognitive behavioral therapy

CI: Confidence Interval

CRH: Corticotrophin releasing hormone

CRH-BP: Corticotrophin releasing hormone binding protein

DHEAS: Dehydroepiandrosterone sulphate

DSM-IV: Diagnostic and Statistic Manual of Mental Disorders, fourth edition

EPDS: Edinburgh Postnatal Depression Scale

GR: Glucocorticoid receptor

HPA: Hypothalamic-pituitary-adrenal

IPSA: Injection Phobia Scale -Anxiety

IPSAV: Injection Phobia Scale -Avoidance

MPFC: Medial prefrontal cortex

MR: Mineralcorticoid receptor

OR: Odds ratio

PVN: Paraventricular nucleus

ROC: Receiver operating characteristic

SD: Standard deviation

SGA: Small for gestational age

Th: T helper cells

## **Introduction**

Pregnancy and becoming a mother constitute an important and overwhelming period in a woman's life. During pregnancy women are preparing themselves for giving birth as well as becoming a mother. Pregnancy includes extensive physiologic, hormonal and psychological changes and is also a period of life stress and psychological vulnerability.

Mental illness during this period has been of scientific interest for a long time. Depression and anxiety disorders are common health problems that affect women more often than they affect men, and mental illness during pregnancy concerns not only the mother to be, but also her partner and their child (Linzer et al. 1996, Deave et al. 2008). Relationships between the psychological conditions affecting the pregnant women and abnormalities occurring during pregnancy, labor and in the neonate have been the subject of several studies (Hoffman & Hatch 2000, Orr et al. 2002, Evans et al. 2007).

The complexity of the psychological, physiological and environmental processes involved in mental illness and the negative consequences for the fetus during pregnancy as well as for the child postpartum are now beginning to be understood (O'Connor et al. 2002a, O'Connor et al. 2002b, Buitelaar et al. 2003, O'Connor et al. 2005, Gutteling et al. 2005). Anxiety during pregnancy is known to be a risk factor for preterm labor and for giving birth to a small for gestational age baby among other things (Lobel 2000 et al., Diego et al. 2006, Lobel et al. 2008). Studies have shown an altered hypothalamic-adrenal-pituitary axis (HPA) in women with anxiety during pregnancy as a result of increased stress (de Weerth et al. 2003, Diego et al. 2006).

Mental illness among women in childbearing age has probably increased during the past years in combination with the fact that pregnant women are more frequently willing to report personal feelings, mood or a history of psychiatric illness than they might have been in the past.

Our health-care systems offer good opportunities for professionals to acquire information on each woman's emotional state and to offer help and support since nearly all pregnant women in Sweden attend an antenatal care clinic (ACC) where they make regular visits during pregnancy. Unfortunately, mental illness in childbearing women has been shown to be under-diagnosed (Wisner et al. 1993, Small et al. 1994) and to be all too often neglected by professionals (Small 1994 et al., Copper & Murray 1997, Johanson et al. 2000).

Anxiety disorders are common in the general population and affect the everyday life of many people. Approximately 15% of the female population suffers from the anxiety disorder -specific phobia (Kessler et al. 2005). Specific phobias that may affect pregnant women are blood- and injection phobia, tokophobia (phobia for childbirth) and to a certain extent claustrophobia (Hofberg & Brockington 2000). One of the research assumptions in this thesis was that blood- and injection phobia during pregnancy might create an intensive stress and anticipatory anxiety because of mandatory blood-sampling, being in a health care environment and the forthcoming delivery situation. Therefore would a pregnant woman with a phobia that affects her experience of the pregnancy and delivery probably have much to gain if she can receive treatment early in the pregnancy.

The purpose with this thesis was to try to find out if pregnant women with blood- and injection phobia constitute a group at risk for negative obstetric and neonatal outcomes and if so to evaluate a potentially effective treatment for these individuals.

Research to investigate the extent of blood- and injection phobia among pregnant women and to see if the phobia affected the levels of stress hormones during pregnancy were also performed.

## **Background**

### **Stress and anxiety in pregnancy**

From a biological perspective, stress is any challenge - psychological or physical - that threatens or is perceived to threaten homeostasis (i.e. the stability of the internal milieu of the organism). A stressor, which may be physiological or psychological, is, in general, any external stimulus to which there is a need for adaptation. A physiological stressor might be any physical action actually causing pain, even if only at a low level. Insertion of a needle is an example of such an action. A psychological stressor might simply be an actual threat or expected action that leads to a response even before the action is carried out.

Anxiety can be defined as an unpleasant emotional state with qualities of apprehension, dread, distress and uneasiness. Anxiety is often accompanied by physical sensations such as palpitations, nausea, chest pain and shortness of breath. Normal anxiety is a phrase applied to the states of arousal that occur in everyday life and are experienced by everyone at some time or other. Normal anxiety has an adaptive role and is a signal to take action. In normal anxiety the assessment of the danger is appropriate and the action, if taken, will be effective and useful. Pathological anxiety is a condition that may be diagnosed when the individual displays an inaccurate or excessive assessment of potential danger. The individual afflicted by pathological anxiety may be unable to make any response, or on the other hand, may make an excessively protective response. The person with pathological anxiety may be so disabled that it becomes impossible for him or her to conduct usual duties. Such an individual may overestimate a danger and make maladaptive adjustments in response to the threat. In summary; normal anxiety is a normal response to an abnormal situation and pathological anxiety is an abnormal

response to a normal situation. The distinction between “feeling stressed” and “feeling anxious” has not yet been fully elucidated.

Although no universally accepted definition of psychosocial stress exists, stress is clearly not a one-dimensional construct, but rather a person-environment interaction in which there is a perceived discrepancy between environmental demands and the individual’s biological, psychological or social resources (Wadhwa et al. 2001a).

### ***Maternal mental illness during pregnancy***

Hippocrates was already aware in 400 BC of the importance of emotional attitudes for the outcome of pregnancy. There is ample evidence from both animal and human studies showing the importance of maternal psychological functioning during pregnancy regarding maternal and fetal well-being (Weinstock 2001, van den Bergh et al. 2005, Herbert et al. 2006, Seckl & Holmes 2007, Talge et al. 2007) and the presence of psychiatric disorders in pregnancy is known to impact fetal and infant health outcomes (Stowe et al. 2001).

Maternal stress due to psychopathological factors such as depression and anxiety during pregnancy constitute a risk for adverse pregnancy outcomes e.g. premature labor, shortened pregnancy length, low-birth weight and adverse perinatal outcomes e.g. small for gestational age and development problems (Wadhwa et al. 1993, Lou et al. 1994, Sandman et al. 1994, Copper et al. 1996, Gitau et al. 1998, Wadhwa et al. 2001a, Rodriguez & Bohlin 2005, Wadhwa 2005, Diego 2006, Field et al. 2006, Alder et al. 2007, Li et al. 2009). Symptoms of anxiety and depression are more frequent during pregnancy than in the postpartum period and antenatal anxiety predicts not only postnatal anxiety but also postnatal depression (Heron et al. 2004, Sutter-Dally et al. 2004). Many subtypes of anxiety disorder are recognized; these include generalized anxiety, panic, specific phobia, post-traumatic stress, acute stress and obsessive-compulsive disorders. These disorders may involve quite different physiological processes but it has not been shown if these differences in process result in diverse effects on the fetus and the

child (Glover & O'Connor 2006). The fact that there is a high co-occurrence of symptoms of anxiety and depression raises questions about the specific predictions that are based on evaluation of levels of maternal anxiety. There is some evidence that the effect on the child is caused to a greater extent by prenatal anxiety in the mother than by depression (O'Connor et al. 2002a, Glover & O'Connor 2006).

### ***Maternal stress, obstetric and neonatal outcome***

Fetal growth and infant birth weight are important indices of infant health. Delivery prior to gestational week 37 is categorized as preterm delivery and poses risks for the infant, especially of low birth weight for later behavioral, cognitive and emotional problems. The risk of neurological and behavioral aberrations in offspring's with low birth weight and preterm birth are well described (Weinstock 2001). The prevalence of preterm birth in Sweden is at present 5.6% (The National board of Health and Welfare 2010) and in Europe between 5.5-11.4 % (Keller et al. 2010). Stress accounts for about 20% of the risk for preterm delivery and the effect of stress may be stronger after 32 weeks of gestation (Glover 2009 a). Women experiencing high levels of stress and/or low levels of social support are at approximately double the risk for premature delivery and having babies with low birth weight adjusted for gestational age and babies with a smaller head circumference (Lou et al. 1994, Dunkel-Schetter et al. 2000, Federenko & Wadhwa 2004). It is quite possible that there is a gene-environment interaction so that the effects of antenatal stress/anxiety become apparent only in those women and children who also have a genetic susceptibility. An example is the finding that African American women have a two-fold higher risk of premature birth than non-African American women have (Federenko & Wadhwa 2004).

Another study supporting the belief that stressful events can have a negative impact on the health of the fetus is the study by Eskenazi et al reporting low birth weight in babies delivered

in New York City and in upstate New York following the events of September 11<sup>th</sup> (Eskenazi et al. 2007).

Homelessness can lead to intense chronic stress which then is associated with both low birth weight and preterm birth after controlling for prenatal care and other risk factors (Stein et al. 2000). Maternal depression at 28 weeks in women with lower occupational status has been shown to be associated with the occurrence of small-for-gestational-age fetuses (Hoffman & Hatch 2000).

One of the effects of maternal stress/anxiety in pregnancy on the fetus is mediated by cortisol and raised cortisol causes the fetus to grow more slowly (Wadhwa et al. 1993). The connection between cortisol and low birth weight is also supported by the finding that prepartum treatment with cortisol has been found to reduce offspring birth weight (Bloom et al. 2001, Newnham & Moss 2001).

A study of women subject to anxiety of external origin during pregnancy found that these women had shorter labor times than women in the control group (Sjögren & Thomassen 1997). One might therefore speculate that anxiety may promote a hormonal balance which in turn stimulates the uterine contractions.

The possible influence of personality factors has been reported in several studies. In a study by Rini pregnant women reporting more stress had relatively short gestation times whereas women with stronger personal resources (mastery, self-esteem, optimism) had babies with higher birth weight (Rini et al. 1999). There are also reports that personality factors in this case, optimism, indirectly influence birth outcomes by minimizing or reducing the effect of stress (Lobel et al. 2000).

### ***Maternal stress and the child***

Maternal stress has implications not only for birth outcomes but also for fetal development in utero. The effects of stress on physical development are limited to the first trimester, which

makes sense given that this is when organogenesis is occurring (Glover & O'Connor 2006).

Two studies have shown that anxiety during this period increases the risk for congenital malformations. (Blomberg 1980, Hansen et al. 2000). In a cohort of 23859 pregnant women, those with very severe stress, such as death of an older child during the first trimester, had higher risk for cranial and neural crest malformations (Hansen et al. 2000).

There are several sensitive or critical periods in fetal development. These periods may be related to the time intervals during gestation corresponding to specific developmental events. In pregnant animals, induced stress has been shown to adversely affect behavioral adaptation, motor and mental development in the offspring (Weinstock 1997). Schneider and co-workers have shown in a series of studies that prenatal stressors adversely affect motor and mental development of rhesus monkeys with more anxiety and lower attention span (Schneider et al. 2002).

In 1973 Stott published a pioneering study linking antenatal stress with effects on the child. His major conclusion was that stresses during pregnancy and, in particular, marital discords were closely associated with child morbidity in the form of ill health, neurological dysfunction, developmental delays and behavior disturbance (Stott 1973).

The Avon Longitudinal Study of Parents and Children recruited a large prospective cohort of 14 000 pregnant women around Bristol in 1990-1991. The aim of the study was to determine the long term effects of antenatal stress or anxiety on the behavioral development of the child. Maternal anxiety and depression in gestational week 18 and 32 were determined using different questionnaires. The 15% most anxious mothers were compared with the rest. The behaviors of the children were assessed by maternal reports at 4, 7 and 11 years of age. The results showed that the children of mothers with high scores of anxiety in gestational week 32 had twice as high risk for hyperactivity, conduct- and emotional problems compared to the controls. The

difference between the groups was less marked at 18 weeks of gestation (O'Connor et al. 2002 a).

Research has shown that a stressful prenatal environment may contribute to a wide range of abnormalities in fetal brain morphology (limbic system and prefrontal cortex) and function (cognition, emotionality and behavior). This also includes glucocorticoid brain receptor development, behavioral inattention and anxiety, development and activity of the HPA axis, cardiovascular and immune functioning, sleep regulation and the time course of normal aging. Critical periods may exist in pregnancy during which the determinants of parturition are especially vulnerable to the effects of prenatal stress. (Wadhwa et al. 1993, Wadhwa et al. 2001a, van den Bergh et al. 2005, Glover & O'Connor 2006). Gender differences in susceptibility to maternal stress have also been discussed and may be due to the slower rate of cortical development in males than in females thereby making the male brain more vulnerable to insults for a longer period (Weinstock 2001). It could also be that the placenta of female fetuses imparts a relative protection from glucocorticoid excess due to increased glucocorticoid inactivation compared with males (Clifton & Murphy 2004).

An Israeli study comparing two groups of boys one consisting of boys born in the year of the Six-Day-War and the other of boys born two years later found that the children from the "war-exposed pregnancies" had significant developmental delays and regressive behavior (Meijer 1985).

In children from 4 to 11 years the association between antenatal stress and symptoms of attention deficit hyperactivity disorder (ADHD) has been established and large prospective studies have found that prenatal maternal anxiety predicted behavioral and emotional problems in children later in life (O'Connor et al. 2002b, Glover & O'Connor 2002, Essex et al. 2006, Rice et al. 2007).

Buitelaar et al showed that high levels of pregnancy-specific anxiety in mid-pregnancy predicted lower mental and motor development scores for the children at 8 months (Buitelaar et al. 2003). Self-reported anxiety during pregnancy in a large cohort of women in the United Kingdom is associated with increased salivary cortisol levels in offspring at 10 years of age (O'Connor et al. 2005).

In a cohort of 125 prospectively collected pregnant women who underwent amniocentesis around 17 weeks gestation Bergman et al found evidence that increased cortisol in utero is associated with impaired cognitive development, and that its impact is dependent on the quality of the mother- infant relationship (Bergman et al. 2010).

It is not known if prenatal stress/anxiety predicts psychiatric illness in the offspring. It has been suggested that depression, a psychiatric outcome rarely seen in children, might have an association with prenatal stress (Ryan 1998). Depression is the psychiatric disorder most closely linked with the neuroendocrine system and disturbances in the HPA axis.

Lou et al have suggested a “fetal stress syndrome” on the basis of their study, which showed that adverse antenatal life events resulted in a smaller head circumference, lower birth weight and lower neurological scores (Lou et al. 1994).

Several studies have supported “The Barker hypothesis of fetal programming of adult disease” which suggests that several chronic degenerative diseases in adult life, including hypertension, coronary heart disease, type II diabetes mellitus and some forms of cancer originate in development plasticity, in response to undernutrition during fetal life (Barker 1998, Kahn et al. 2003, Beltrand & Lévy-Marchal 2008, Bonamy et al. 2008, Whincup et al. 2008). This brings new perspectives to public health; diseases that were once thought to arise near the time of their manifestation in adult life are now known to have roots in prenatal life. Effects of antenatal stress are different with each child- many are not affected. This depends probably on genetic

vulnerability and gene environment interaction but outcome will also depend on postnatal care (Glover 2009a).

Being pregnant and suffer from blood- and injection phobia is a potentially strong stressful situation due to regular medical check-ups and the delivery coming up in the future. One might therefore speculate if these groups of women have an increased risk for adverse obstetric and neonatal outcome and if the children to these mothers are in risk for problems with normal mental and motor development.

### **Pathways for stress/anxiety from mother to fetus:**

There are three main pathways on how maternal stress and anxiety is transferred to the fetus:

#### *1. Neuroendocrine system*

The effect of maternal hormones on the uterus and the in-utero exposure of the fetus to abnormally high levels of maternal hormones, especially cortisol are plausible mechanisms by which maternal stress affects the fetus. The HPA axis is therefore an important mediating mechanism between anxiety/stress during pregnancy and outcome for the child. The HPA-axis in pregnancy is described later on in this thesis.

#### *2. Immune/inflammatory system*

In pregnancy T helper cells (Th) 2 cytokine production favoring humoral immunity is dominant whereas spontaneous abortion and preterm delivery have been associated with a maintained Th1 cytokine profile favoring cellular immunity.

Stress hormones regulate Th1/Th2 patterns and type1/type2 cytokine secretion and can thereby potentially altering the balance between these two arms of acquired immune responses (Wadhwa et al. 2001b).

Chronic stress and stress hormones appear to be associated with immunosuppression and changes in the normal pattern of cellular (Th1) and humoral (Th2) responses to antigens.

Herrera et al reported that high levels of maternal psychological stress and low levels of support were associated with depressed lymphocyte activity (Herrera et al.1988). Maternal prenatal stress has also been associated with altered immune responses in cord blood mononuclear cells and may impact the expression of allergic disease among the children (Wright et al. 2010). Maternal stress can also act via an immune/inflammatory pathway by modulating systemic and placental-decidual immunity, resulting in an increased susceptibility to intrauterine and fetal infection and inflammation, known risk factors for preterm birth (Andrews et al. 2000, Federenko & Wadhwa 2004). Stress could therefore modulate susceptibility to developing maternal genital tract infection during pregnancy and also contribute to a susceptibility to preterm birth in the presence of infection. Culhane et al has observed that high levels of maternal psychosocial stress are associated with a twofold increase in the prevalence of bacterial vaginosis in early human gestation (Culhane et al. 2001).

Proinflammatory cytokines are secreted as part of the maternal and/or fetal response to microbial invasion; these cytokines have been shown to promote spontaneous labor and rupture of membranes by stimulating the synthesis of prostaglandins and their release of metalloproteases in the gestational tissues (Federenko & Wadhwa 2004).

Integrated action of glucocorticoids, progesterone/prolactin and the immune system is crucial for optimal pregnancy outcome and is highly susceptible to environmental conditions (Parker & Douglas 2010).

### *3. Cardiovascular system*

The activation of the sympathetic nerve system during stress and anxiety results in a decreased uteroplacental perfusion. This might be explained by the fact that cortisol and catecholamines are known to affect vessel tone and could contribute to fetal growth restriction in women with stress and anxiety during pregnancy (Federenko & Wadhwa 2004).

In a study by Sjöström using doppler ultrasound examinations of the umbilical artery and fetal middle cerebral artery in gestational week 37- 40, it was found that the fetuses of women with anxiety, measured as a Spielberger's state anxiety score of 40 or more, had higher pulsatility index values in the umbilical artery and lower pulsatility index values in the fetal middle cerebral artery than those fetuses to women with lower scores. Maternal anxiety can therefore influence fetal cerebral circulation (Sjöström et al. 1997). Another study by Teixeira et al. confirmed this finding and reported associations between high levels of maternal anxiety and increased pulsatility index values in the uterine arteries of pregnant women (Teixeira et al. 1999). Associations between abnormal uteroplacental flow wave forms and elevated levels of placental corticotrophin releasing hormone (CRH) have also been reported (Donoghue et al. 2000).

Apart from anxiety and stress other factors that are concerns for the child to be are maternal health-related behaviors or lifestyles during pregnancy, such as diet, physical activity, smoking, alcohol and drug abuse which all have an impact on fetal development and infant birth outcomes including increased risk for fetal growth restriction, preterm delivery, spontaneous abortion, and cognitive and motor deficits of the central nervous system (Bishai & Koren 1999, Hannibal & Armand 2000, Higgins 2002, Hobel & Culhane 2003).

Many of these health related behaviors are of course associated with maternal health status and psychosocial factors, such as stress and social support.

## **Blood- and injection phobia**

### ***Specific phobia***

To have a specific phobia is one of the most prevalent psychological problems. The word phobia originates from Phobos (Greek) and means fear or terror. For a long time specific phobias were considered a common but inconsequential pathological problem. However, increasing evidence has shown that specific phobias are clinically significant and relatively understudied disorders (Becker et al. 2007). A person with a specific phobia has an extreme fear of a specific object or situation; fear that is out of proportion to the actual danger or threat. In addition, an individual with a specific phobia is distressed about having the fear, or experiences significant interference in his or her day-to-day life because of the fear. Many people have a fear of a particular object or situation, but most of the time these would not be considered phobias.

The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV 1994) provides the most commonly used classification of anxiety disorders such as specific phobias.

The DSM-IV defines five types of specific phobias: Animal (e.g. spiders), Natural Environment (e.g. heights, water), Blood- and Injection (e.g. blood, dentists), Situational (e.g. flying, closed spaces) type and "Other Types" such as fears of choking or vomiting, loud sounds etc. The most common specific phobias are fears of spiders, snakes, and heights.

The diagnostic criteria for blood- and injection phobia according to DSM-IV are:

- A. Marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipated presence of a specific object or situation.
- B. Exposure to the phobic stimulus almost always provokes an immediate anxiety response, which may take the form of a situational bound or situational predisposed panic attack.
- C. The person recognizes that the fear is excessive or unreasonable.
- D. The phobic situation is avoided or else endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared situation 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 anxiety can not be better explained by another anxiety disorder.

In the literature blood- and injection phobia is occasionally considered to comprise different phobias, "blood phobia", "injection phobia" and "injury phobia". In a study by Öst 81 patients with blood phobia were compared with 59 patients suffering from injection phobia. There were no differences between the two groups in age of onset, age at treatment, marital and occupational status, history of fainting in the phobic situation, and impairment. Higher proportions of the blood phobic subjects reported having a first-degree relative with the same phobia compared with those with injection phobia. The similarities were more marked than the differences and the authors suggested that these two specific phobias should be regarded as one diagnostic entity (Öst 1992 a).

Torgerson found that "mutilation" fears cluster together in a factor analysis of phobic fears.

These mutilation fears include fears of hospitals, surgical operations, open wounds, injections, blood, the smell of medicine and hospitals, pain and doctors (Torgerson 1979). Most authors have restricted their foci of study to one or several mutilation fears where the fears of blood, injections and dentists are the most common mutilation fears (Bienvenu & Eaton 1998). The research in this thesis has focused on phobia of blood and injections and the term blood- and injection phobia has been used.

There is a great range in the prevalence values reported in the literature for specific phobias as a general class, as is evident from this data: Serrano-Blanco et al. (2010) 6.6 %, Becker et al. (2007) 9.9 % (women only), Wells et al. (2006) 7.3 %, Kessler et al. (2005) 15.7 % (women

only), Fredriksson et al. (1996) 19.9 %, Kendler et al. (1992) 20.5 % (women only), Robins et al. (1984) 8.5-25.9 %, Agras et al. (1969) 7.7 %.

Additional studies include Costello who reported a 12-month prevalence rate of specific phobia in women varying between to 4.9 % and 12.5 % depending on the phobias included (Costello 1982), and finally Wittchen who used the DSM criteria and observed a 6-month prevalence of 4.1 % and a lifetime prevalence of 8 % for specific phobia in men and women (Wittchen 1986).

### ***Prevalence***

Of 184 teenaged maternity patients, 22 % were found to have a fear of blood drawing strong enough to make it hard for them to come to a public clinic for prenatal care (Cartwright et al. 1993). In a hospital-based study, 30.1% of 237 patients and 19.5% of 1263 healthy people reported fear of blood and injections. The fear of blood and injections was higher among patients with chronic disease and also among individuals with lower levels of education (Kose & Mandiracioglu 2007).

A great variation of the prevalence of blood- and injection phobia has been reported in the literature. See table 1. The prevalence of blood- and injection phobia in a pregnant population has never been described before. Part of the variation in prevalence is most likely due to the fact that in some, but not all, studies a decrease in the global assessment of functioning has been part of the definition of the phobia. The prevalence of blood- and injection phobia is probably lower in population samples from clinics and hospitals since those with this phobia tend to select themselves out of such populations. Therefore the studies done in those populations probably underestimate the true prevalence.

Point prevalence seems the best estimate since it has been argued that difficulties with recall over more extended time periods might pose reliability problems. It is therefore difficult to compare published prevalence rates because the definition of phobias differs from study to study, and because of differences in data collection methods, probably age, gender,

socioeconomic status and a varying number of feared objects or situations included in the survey.

**Table 1. Prevalence of blood- and injection phobia**

Study	Place	Period of prevalence	Sum of subjects	Age of subjects	Data collecting method	Phobia definition	Blood-and injection phobia
Agras et al. 1969	Burlington	One-point	325		Interview		3.1%
Costello 1982	Calgary	One-point	449	18-65	Interview	Intensity	4.5% (women)
Marks 1988					Review		2-4.5%
Kleinknecht & Lenz 1989	Bellingham	One-point students	204		Questionnaire		5.7%
Hamilton 1995					Clinical review	Needle phobia	10%
Fredriksson et al. 1996	Stockholm	One-point	704	18-70	Questionnaire	DSM	3.3% (women)
Page 1996		One-point	308		Questionnaire		8.8%
Bienvenu & Eaton 1998	Baltimore	Estimated lifetime	1920		Interview	DSM	3.5%
Nir et al. 2003	Haifa Patients	One-point	400	11-80	Questionnaire		1.8%
Deacon & Abramowitz 2006	Mayo clinic Patients	One-point	3315	19-99 M=57.5	Questionnaire	DSM	2.2%
Bracha et al. 2007	Baltimore	One-point	1724	27-49	Interview	DSM	3.3% (women)
Becker et al. 2007	Dresden	Life-time	2064	18-24	Interview	DSM	2.4% (women)

Blood- and injection phobia usually starts in childhood or adolescence and it is uncommon for adults to acquire this phobia. In a study by Becker almost 100% of the individuals with blood- and injection phobia had acquired the phobia before age 18 (Becker et al. 2007). In a study by Öst 60.5% of the blood phobic's and 69.5% of the injection phobic's experienced the onset of

blood- and injection phobia before age 10 (Öst 1992a). The mean age were 8.6 years (SD=3.9) for blood phobic's and 8.1 years (SD=4.9) for injection phobic's. The mean age of onset was 10.5 years in a study by Bienvenu who interviewed 1920 individuals using the DSM criteria for blood- and injection phobia (Bienvenu & Eaton 1998). However, the distribution in this study was highly skewed with only a few onsets at older ages; the median age of onset was 5.5 years. Other authors have described a median of 7-12 years for onset of this phobia (Thyer et al. 1985, Himle et al. 1989, Neale et al. 1994, Lipsitz et al. 2002).

Blood- and injection phobia show a sharply declining prevalence with age and the phobia is uncommon after the age of 65 whereas phobias for animals and enclosed spaces are long lived, once acquired (Agras et al. 1969, Costello 1982, Bienvenu & Eaton 1998). On the other hand; Fredriksson et al. (1996) have observed that the fear for blood- and injections decreases as a function of age in women but not in men.

Specific phobias in general are twice as common in women as in men (Fredriksson et al. 1996, Choy et al. 2007). Blood- and injection phobia is equally distributed in men and women in some studies and in others there is a female preponderance (Agras et al. 1969, Yule & Fernando 1980, Öst et al. 1984, Thyer et al. 1985, Fredriksson et al. 1996, Bienvenu & Eaton 1998, Deacon & Abramowitz 2006). Bienvenu also found higher prevalence of blood- and injection phobia in individuals with lower levels of education (Bienvenu & Eaton 1998).

### ***Etiology***

The etiology of specific phobias is complex and most reports include a history of negative experiences of the feared situation but also other psychological causes as well as biological and genetic factors are described (Davey et al. 1993, Menzies & Clark 1995).

Darwin presented a hypothesis in which he looked at fears as a mode of "biological preparedness having evolutionary significance" (Darwin 1877). The capacity for anxiety has been shaped by natural selection and blood- and injection phobia may represent a form of

prepared fear. A strong fear of puncturing the skin once had a clear value in preventing humans from injuries that could lead to death and incurable infections. Blood- and injection phobia could therefore from an evolutionary approach protect individuals from dangerous situations and thus lead to a safer way of life and a better chance of survival (Marks & Nesse 1994). Another early interpretation was presented by Freud who considered phobias to be a defense against internal anxiety. By transforming the internal anxiety to an external one, the anxiety could be avoided. The content of the phobias was considered to have a symbolic meaning related to unconscious anxiety (Freud 1932).

Page formulated a theory that explains blood- and injection phobia as a product of two separate but related etiologies; the first is an underlying fearful avoidance that may involve elevated trait anxiety, the second fainting, that may involve elevated disgust sensitivity. It has been suggested that the anxiety in blood- and injection phobia is related to disgust to a greater degree than to fear (Page 1994). Disgust is a fundamental emotion defined as “revulsion at the prospect of (oral) incorporation of an offensive object”.

Blood and injections can elicit both fear and disgust and it seems that disgust increases with greater distance from the body. Discomfort on seeing one’s own menstrual blood or handling red meat has not been reported in the blood- and injection phobia literature (Marks 1988). Page found that self-reported faintness in response to injection stimuli experienced by individuals afraid of needles was only evident among those who display a high level of disgust.

Physiologically, disgust is typically associated with parasympathetic activity and reduction in diastolic blood pressure leading to fainting sensations (Page 2003). It has been shown that individuals with high disgust are more resistant to exposure therapy than those patients with low in disgust (Olatunji et al. 2007 a).

In a classic study by Hebb in 1946, a realistic plaster replica of a severed chimpanzee head was placed in a cage of live chimpanzees. The animals were observed to go into paroxysms of terror

despite their lack of prior experience with such a stimulus. From these results Hebb suggested that there is a heritable component in blood phobia (Hebb 1946). Sixty-one percent of the blood- and injection phobic's report that one of their first degree relatives also has the same phobia (Öst 1992a) and both the vasovagal reflex and the blood- and injection phobia strongly tend to run in the family (Hamilton 1995).

The tendency to faint could be more highly heritable than the tendency to become afraid or feel disgust. This could produce higher heritability for blood- and injection phobia with a history of fainting than for other phobias in general.

Twin studies are one way to study the contribution of genetic and environmental factors for developing a condition. If it is observed that monozygotic (MZ) twins are more similar than dizygotic (DZ) twins with regard to a specific condition it is usually considered to be evidence of a hereditary background for the condition concerned. There is an extensive literature including several landmark twin studies which supports the theory that the familial resemblance is genetic (Torgersen 1979, Rose & Ditto 1983, Kendler et al. 1992, Neale et al. 1994, Kendler et al. 1999, Kendler et al. 2001). First-degree relatives of persons with specific phobias also generally report a threefold increase in incidence when compared to the general populations (Villafuerte & Burmeister 2003).

In 1968, *Rachman* described the conditioning theory of fear and avoidance. The theory states that anxiety is a conditioned response (CR) that is elicited in the presence of a conditioned stimulus (CS). When elicited the CR influence behavior that avoids or escapes the situation. This behavior reinforces through the fact that the anxiety disappears because of that behavior. In 1977, *Rachman* proposed that there are at least three different pathways of acquisition to the phobia for blood- and injections;

- A. Direct learning or conditioning (emergency treatment or forced treatment in childhood)
- B. Observational learning (watching others showing signs of fear in a particular situation)

C. Informational learning (hearing or reading that the situation is dangerous) (Rachman 1977). One study reports that 46% had conditioning experiences, 32% observational learning and 9% informational learning of how individuals with blood- and injection phobia had acquired their illness (Öst 1985). In another study by Öst the majority (52%) of the patients with blood- and injection phobia attributed their onset to conditioning experiences, while 24% recalled observational learning, 7% information learning and 17% could not remember any specific onset circumstances (Öst 1991a). The corresponding figures from another report are 76% with conditioning experiences, 20% recalled observational learning and 3% information learning as being primary in their fear onset (Kleinknecht 1994). The results are based on memories reported by the study population and these memories indicate that traumatic conditioning-like experiences are the predominant pathway to developing blood- and injection phobia in those populations. The foremost problem with this strategy is the obvious risk of memory distortion that can take place since the onset took place years earlier. It is not known why some individuals that have been exposed to danger or unpleasant situations develop a phobia while others do not, despite having had the same experiences. Another question to be answered is why some individuals develop a phobia at a certain point in time, after experiencing a traumatic event or not, but did not develop it earlier after events that were as traumatic as, or even more traumatic than the current one.

It has been speculated that the most serious form of blood- and injection phobia might be acquired through conditioning. But in two studies no relationship between ways of acquisition and anxiety components was found, nor did conditioning and indirectly acquired phobias differ in severity (Öst 1991a, Kleinknecht 1994).

## *Symptoms*

When individuals with blood- and injection phobia do agree to undergo for example a needle procedure, they experience anxiety and sometimes panic attacks. Some individuals are more afraid of the physiological reaction that happens in their bodies than of the stimulus itself.

Individuals may report feelings of heat, dizziness, confusion, nausea and epigastria discomfort.

Respiration becomes slow and deep and sweating is almost inevitable (Fernandes 2003). In

blood- and injection phobia following brief sympathetic activity, parasympathetic activity

predominates, leading to vasovagal syncope and causing the person to faint. During the acute

phobia state, brain function and chemistry are deranged and the circulating levels of more than

11 stress hormones increase (van Lieshout et al. 1991, Fredrikson et al. 1997, Wik et al. 1997).

Naturally, these symptoms usually cause great concern among staff and family members (Marks 1988, Hamilton 1995).

In a pregnant woman suffering from blood- and injection phobia the symptoms of anxiety and panic attacks is likely to bother the woman frequently. To be pregnant is a daily reminder of

what's planned for in the future with visits to the midwife and the upcoming delivery. It is very

likely that the phobic symptoms are present much more during pregnancy than in a non-

pregnant state. The feared situation is no longer avoidable and one can assume that the stress

and anxiety symptoms would be enough to have impact on the HPA-axis with increased levels

of stress hormones (de Weerth et al. 2003, Diego et al. 2006).

## *Emotional fainting*

It is a common phenomenon to experience a drop in blood pressure when exposed to needles,

injections or surgery, but not to the degree that a phobic person experiences. Fainting in the

presence of blood- and injection stimuli is relatively common among late adolescents; 13-19%

(Page 1994), while fainting is observed in 8.0% of high school students and 2.6% of adults who

donate blood (Newman 2003). Not all of these individuals will meet the criteria for blood- and injection phobia, fear is neither necessary nor sufficient for fainting to occur.

Blood- and injection phobia is the only phobia associated with fainting in the feared situation.

Around 70-80% of the persons with blood- and injection phobia faint when exposed to the phobic stimuli (Öst et al. 1984, Thyer et al. 1985, Öst 1992a, Olatunji et al. 2006). Persons with blood- and injection phobia with a history of fainting experience generally report higher overall levels of fear than those without fainting history (Kleinknecht 1987, Kleinknecht 1988).

The fainting reaction is a vasovagal syncope and has been described as a two-phase (biphasic, diphasic) response to a blood and injection phobia stimuli. Various explanations exist regarding the trigger mechanisms. It has been suggested that the first phase is a preparation for a flight-fight reaction but that the social context does not make that possible. The second phase, in individual's suffering from blood- and injection phobia, is an over activation of the parasympathetic nervous system which is trying to compensate for the first phase. Disgust can also activate the parasympathetic nervous system and make the response to the sympathetic nervous system even stronger. Both reactions are active strategies for coping with stress.

The initial phase involves an increase in heart rate, blood pressure and skin conductance. The second phase involves bradycardia and hypotension leading to reduced cerebral blood flow and ultimately fainting. The redirection of blood toward skeletal musculature is made evident by an increase in facial pallor.

Several case reports describe patients with blood- and injection phobia in which the drop in blood pressure and heart rate results in asystole during various medical procedures (Lipton & Forstater 1993, Cho et al. 2000, Newman & Moss 2001, Singh et al. 2008). The duration of asystole varies between 8-33 seconds. All cases are men suggesting that they react more strongly than females in this respect. Fainting in this situation can cause fall and the individual

can sustain trauma. Convulsions with loss of bowel and bladder control have also been associated with seizures from vasovagal reactions (Marks 1988).

The vasovagal reflex usually appears 5 to 30 minutes after the exposure to the phobic stimuli but it can take several hours before the reaction comes. Unconsciousness usually lasts for only a few seconds but it can last from 10 minutes to 2 hours. The blood pressure returns to normal within 2 hours. Recovery is rather slow leaving the persons weak, but most of those how faint can resume normal activity within several hours. Others can have anxiety, malaise and weakness for 1-2 days.

### ***Comorbidity***

According to the DSM IV criteria 14.1% of 1734 pregnant women had a psychiatric disorder (specific phobias excluded) during the second trimester of pregnancy (Andersson et al. 2003). Similar figures (18.1%) were found in a study using the structured clinical interview for DSM-IV on 428 women 6-week postpartum (Navarro et al. 2008).

The prevalence of antenatal anxiety during the third trimester is reported to be between 10% and 24% and it also overlaps with depression and increases the risk of postnatal depression (Sutter-Dally et al. 2004, Heron et al. 2004).

In a study by Wisner it was observed that panic attacks and depression severity at the beginning of pregnancy typically persisted and were unaffected by pregnancy or the postpartum period (Wisner et al. 1996). A review of eight studies showed no overall effect of pregnancy on anxiety disorders: in 41% pregnancy brought an improvement, but in 44% there was an exacerbation in the postpartum period and in 10% new onset in puerperium (Hertzberg & Wahlbeck 1999), the natural course of these mental illnesses is not yet determined. Anxiety symptoms during pregnancy are associated with depressive symptoms, stress and low self – esteem (Littleton et al. 2007).

Comorbidity between specific phobia and other psychiatric disorders is relatively high and tend to co-occur with generalized anxiety (Brawman-Mintzer et al. 1993, Magee et al. 1996), posttraumatic stress disorder (Goisman et al. 1998) and with other anxiety disorders (Kessler et al. 1994). Borkovec et al. (1995) found a specific phobia in 40% of patients with generalized anxiety.

In addition, individuals frequently experience more than one specific phobia (Curtis et al. 1998). Multiple phobias were reported by 5.4% of the females and 1.5% of the males in a study with 704 persons between the ages of 8-70 years (Fredriksson et al. 1996). In the study by Bienvenu the individuals with blood- and injection phobia had higher than expected lifetime prevalence of other psychiatric conditions, including marijuana abuse/dependence, major depression, obsessive-compulsive disorder, panic disorder, agoraphobia, social phobia and other simple phobias (Bienvenu & Eaton 1998). These findings are similar to what Neale et al detected in a population-based study of female twins (Neale et al.1994). In a study by Becker et al. the only mental disorder associated with blood- and injection phobia was anxiety disorders with an odds ratio (OR) of 5.24 confidence interval (CI) 2.59-10.60 (Becker et al. 2007). Large-scale epidemiological studies have found a positive association between the presence of anxiety disorders and presence of physical disorders. In the study by Sareen et al the relationship between past-year anxiety disorder diagnosis and past-year chronic physical disorder was examined among 5877 individuals. A strong association between anxiety disorders and physical disorders even after adjusting for mood disorders, substance-use disorders and sociodemographics was found. It is possible that particular physical disorders (e.g. respiratory disease, gastrointestinal disease, cardiovascular disease) might be more likely to be associated with anxiety disorders (Sareen et al. 2005). Another examination of the relationship between simple phobia and physical disorder showed that there was an increased risk for respiratory diseases (Goodwin et al. 2003).

### ***Neuroimaging***

There is considerable neurophysiologic evidence showing that the central nervous system is disorganized in the phobia state. Positron emission tomographic brain studies suggests that areas of the brain that performs emotional, cognitive, subconscious and cerebral association functions, such as parts of the paralimbic, subcortical nuclei, right amygdale, right orbito-frontal cortex, anterior temporal cortex and anterior cingulated areas of the brain mediate symptoms in phobia and different anxiety disorders (Rauch et al. 1997, Fredrikson & Furmark 2003).

Regional cerebral flow is also deranged or decreased in these areas of the brain during phobic provocation (Rauch et al. 1997, Fredrikson et al. 1997, Fredrikson & Furmark 2003).

One magnetic resonance imaging study has examined the effects of symptom induction on neural activation in the brain in persons with blood- and injection phobia. Diminished medial prefrontal cortex (MPFC) activity was observed. The MPFC has been shown to be critically involved in the automatic and effortful cognitive regulation of motions. These results could therefore reflect reduced cognitive control of emotions in persons with blood- and injection phobia (Hermann et al. 2007).

### ***Impairment and Consequences***

Having blood- and injection phobia is surely a health care problem and many individuals first become aware of blood- and injection phobia after a negative experience in the health care environment. This lesson learned often becomes generalized and may then include all situations and objects associated with the first fear (Hamilton 1995).

People suffering from blood- and injection phobia possess a heightened risk of morbidity and mortality simply because they avoid health care, sometimes for many years (Kleinknecht & Lenz 1989, Ellinwood & Hamilton 1991). Most likely there is a minor fraction (<1%) of the individuals with blood- and injection that never visits a hospitals (Agras et al. 1969).

Blood- and injection phobia can delay prenatal care including laboratory procedures (Dennis 1994, Langslow 1998) and could therefore have serious implications. The blood- and injection phobic person will be an expert of avoiding treatments and hospitals. A development of so called “safety behaviors” (e.g. avoid getting pregnant, being vaccinated or operated on) which can help to maintain the fear. People with blood- and injection phobia tend to interpret situations in such a way as to maintain or increase their anxiety for blood and injection.

In a sample of 111 persons with blood- and injection phobia, 32% said that the phobia had negative consequences concerning their career choice, work and education, 9% said that they would not be able to help other people if they got injured (especially their children), 8% completely avoided visiting hospitals and getting medical check-ups, 8% did not go to the movies, 7% said that they were generally worried and avoided various situations and 2% did not dare to become pregnant. Thirty-three percent stated no direct negative consequences, even if they were distressed by their phobia (Marks 1988, Magee et al. 1996, Davey 1997). Therefore, blood- and injection phobia may cause major social difficulties in life. A fear of blood testing or immunization can interfere with or even destroy plans for travel, education, immigration or employment. Students with blood- and injection phobia may not choose careers in nursing or medical areas.

Blood- and injection phobia can also be fatal. There are reported deaths ascribed solely to the phobia and its vasovagal reflex during needle procedures such as venipuncture, blood donation, arterial puncture, pleural tap, and intramuscular and subcutaneous injections (Hamilton 1995). Enquiries into the causes of maternal deaths in the United Kingdom indicate that women with injection phobia are at risk when exposed to anesthesia (Lum Hee & Metias 2001, Copper & McClure 2005).

Bienvenu found in his study from 1998 that the individuals with blood- and injection phobia did not differ with regard to regular care for specific medical conditions, number of out patients’

visits or hospitalizations or live births (Bienvenu & Eaton 1998). But there is no comment in the study if the medical care differed between the groups in the number of diagnostic procedures or operations. However, diabetic patients suffering from blood- and injection phobia had higher than expected rates of macrovascular complications. Other studies have also shown that diabetic patients with blood- and injection phobia had less frequently performed self-monitoring of blood glucose (Metsch et al. 1995) and had poorer glycaemic control (Marks 1988, Page 1994, Berlin et al. 1997).

Complications during pregnancy, labor or the postpartum period may necessitate needles. The threat of having a procedure involving a needle at a time when the individual already is in pain, anxious and tired may be overwhelming to a woman with blood- and injection phobia (Searing et al. 2006). In a study of one versus five sessions of exposure in the treatment of injection phobia 8 of the 35 female patients said that a major reason for their applying for treatment was a wish to become pregnant and give birth to a child. However, their injection phobia stopped them from doing this since the pregnancy period means a lot of vein punctures for various tests, and childbirth usually implies anesthetic injections. At follow-up after treatment 6 of these 8 patients had become pregnant, and 2 had already given birth, without any phobic problems.

## **The hypothalamic-pituitary-adrenal (HPA) axis in pregnancy**

Upon exposure to a stressor, the human stress system is activated and elicits a stress response involving both behavioral as well as physiological adaptation. The HPA axis and the sympathetic-adrenomedullary system comprise the main physiological response but also rennin-angiotensin, prolactin and oxytocin are released during stress-response. The sympathetic system responds quickly in seconds and the HPA axis takes 10-20 minutes for significant elevations in cortisol to occur.

### ***Corticotrophin-releasing hormone (CRH)***

There are two principal afferent pathways capable of eliciting the stress response in human. The “reactive response” pathway is not dependent on cortical involvement and is activated by stressors directly threatening homeostasis. Through ascending neuronal pathways in the brainstem, information from autonomic receptors (e.g. baroreceptors) reaches the paraventricular nucleus (PVN) of the hypothalamus and elicits CRH and arginine vasopressin. The second pathway is activated by more complex threats and involves an integration of polysensory information and previous experience. The hippocampus, amygdala and prefrontal cortex are involved and the net stress response is determined by the context-dependent summation of all relevant stimuli (Herman & Cullinan 1997). The input from these brain regions on PVN determines the CRH secretion. Upon the onset of a stressor, CRH is secreted within seconds.

CRH is also produced in trophoblasts, the fetal membranes and decidua. Placental CRH has shown to be identical to hypothalamic CRH in structure, immunoreactivity and bioactivity but differs in regulation. During pregnancy, CRH is released in an exponentially increasing amount over the course of gestation into maternal and fetal compartments.

CRH from the placenta is stress sensitive and is modulated in a positive, dose-dependent manner by all the major biological effectors of stress, including cortisol, norepinephrine, oxytocin, angiotensin II, both forms of interleukin-1 and hypoxia (Petraglia et al. 2001, Federenko & Wadhwa 2004). Maternal adrenocorticotrophic hormone (ACTH) and cortisol stimulate placental CRH secretion which in turn further activates the maternal HPA axis, establishing a positive feedback loop that results in elevated levels of CRH, ACTH and cortisol during the course of gestation.

CRH has a central role in coordinating fetal and maternal endocrine events involved in parturition. CRH's biological activity is curtailed by a binding protein; corticotrophin-releasing hormone binding protein (CRH-BP) in plasma and amniotic fluid. CRH-BP is produced in the liver and also in the trophoblasts and intrauterine tissues during pregnancy, it binds to circulating CRH and reduces its biological action. When labor starts, the levels of CRH-BP falls by about 60%, thereby releasing free CRH (Weinstock 2001, Weinstock 2006). The highest maternal levels of CRH are therefore found at labor and delivery.

Placenta CRH stimulates dehydroepiandrosterone sulphate (DHEAS) secretion from human fetal adrenal cortical cells. DHEAS is used as a precursor in the placenta to synthesize estrogens as an important factor to promote labor (Smith 1998). Placenta CRH exerts actions on the uterus and cervix to augment changes produced by estrogens on these tissues. CRH stimulates the release of prostaglandins from the placenta and fetal membranes and potentiating effects for the actions of oxytocin that mediates stimulation and maintenance of myometrial contractility at term and during labor (Challis et al. 1995).

Increased CRH and decreased CRH-BP have been measured in women with preterm labor and in women with threatened preterm labor who subsequently deliver within 24 hours. An increased level of CRH is therefore associated with the initiation of preterm labor (McLean et al. 1995, Berkowitz et al.1996, Wadhwa et al. 1998, McGrath & Smith 2002a). In a sample of

232 women elevated CRH levels at 33 weeks 'gestation were associated with a 3.3-fold increase for spontaneous preterm birth and with a 3.6-fold increase for fetal growth restriction (Wadhwa et al.2004). In 1999 Hobel et al. showed that maternal plasma CRH was associated with stress at 20 weeks 'gestation in pregnancies that ended in preterm delivery (Hobel et al. 1999).

Studies that conducted serial assessments of CRH over the course of gestation found that compared to term deliveries, women delivering preterm had not only significantly elevated CRH levels but also an accelerated rate of CRH increase over the course of their gestation (McLean et al. 1995, McGrath et al. 2002b).

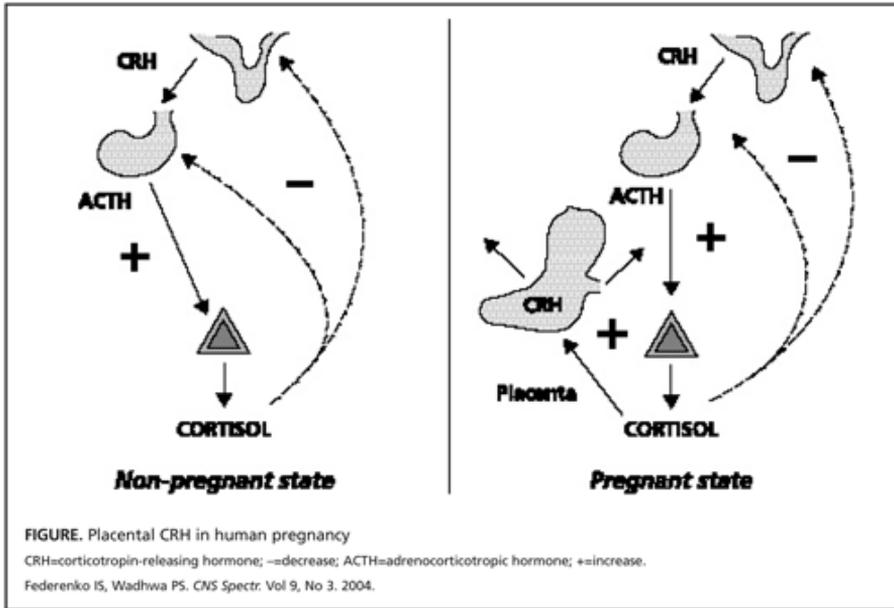
The fetal HPA axis is operative from mid-pregnancy on and CRH can be detected in the fetal hypothalamus from the 12th week of gestation. Gitau et al. have shown that the fetus is capable of responding to the stress of blood sampling independently of the mother in mid-gestation (Gitau et al. 2001).

A correlation between maternal and cord corticotrophin releasing hormone (CRH) levels has been found (Goland et al. 1988). Fetal CRH concentrations are approximately a tenth of those in the mother; however there is an arterio-venous difference in cord CRH levels suggesting a placental contribution to the fetus (Sasaki et al. 1987, Goland et al. 1988).

CRH levels during gestation or at delivery have also been found to be increased in maternal and cord plasma and in the placenta in pregnancies complicated by pregnancy-induced hypertension, preeclampsia, fetal asphyxia, fetal growth restriction and multiple gestations (Wadhwa et al.1998).

A study examining the association between CRH levels and fetal reactivity in human fetus in gestational week 31-32 suggested that elevated maternal CRH levels may influence the fetal neurologic development. In the study they observed impaired fetal responses to novel vibro-acoustic stimuli and increased arousal in response to a series of vibro-acoustic stimuli in those fetuses of mothers with elevated CRH (Sandman et al.1999).

**Figure 1 Placental CRH in human pregnancy**



***Adrenocorticotrophic hormone (ACTH)***

CRH reaches the pituitary through the pituitary portal circulation and induces secretion of ACTH from the anterior pituitary within 5-10 seconds.

ACTH stimulates the cortisol secretion from the zona fasciculata of the adrenal cortex within minutes and peaks at about 30 minutes after onset. ACTH secretion and plasma ACTH levels rise during pregnancy, though remaining within normal limits, paralleling the rise of plasma cortisol levels (Mastorakos & Ilias 2003).

## *Cortisol*

Cortisol is synthesized from cholesterol through several enzymatic steps and is a lipophilic molecule and the main glucocorticoid in the body. The normal diurnal rhythm of cortisol is with peak level in the morning as a response to awakening, decline during the day and reaches the nadir in the evening. In the early morning the HPA activity slowly increases before the cortisol awakening response (CAR) appears.

CAR is superimposed on the basal cortisol rhythm and seems to be independent of the underlying diurnal rhythm and of the cortisol response to stressors (Fries et al. 2009).

Circulating cortisol interacts with the receptors in various target organs such as the liver and muscle tissue as well as the brain and even the HPA axis itself. Cortisol acts on the hippocampus to regulate the basal HPA tone and at the hippocampal, hypothalamic and pituitary levels to regulate stress-induced levels. One peripheral regulator of cortisol is the corticosteroid binding globulin (CBG). CBG is a plasma protein that binds 95% of the cortisol and its synthesis is induced by estrogens and inhibited by cortisol and stress (de Kloet et al. 1998). Cortisol is secreted in response to a stressor but other factors can cause a transient cortisol elevation such as caffeine, smoking, physical activity, the person's posture and food intake (Wilkins et al. 1982, Pincomb et al. 1987, Lane et al.1990).

Corticosteroids act on the neurons in the brain either as a result of binding to two categories of cytoplasmic steroid receptors or by interaction with membrane-bound receptors that mediate actions of neurotransmitters such as gamma-aminobutyric acid or glutamate.

The two cytoplasmic receptors are called mineralcorticoid (MR) and glucocorticoid (GR) receptors and have different distribution and affinity for cortisol. MRs are found in high concentrations in the hippocampus, GRs are present in several brain regions including the hippocampus, hypothalamus, pituitary, cingulate cortex and amygdala. The use of transgenic mouse models has identified that variation in the level of GR alters stress responses and activity

of the HPA axis. A 30-50% reduction in GR is associated with exaggerated HPA responses to stress (Pepin et al. 1992, Michailidou et al. 2008).

The individual rhythm of cortisol is normally maintained during pregnancy (deWeerth & Buitelaar 2005) and bioavailable cortisol remains at non-pregnant levels until around 25th week of gestation (Allolio et al. 1990). Later in pregnancy there is an increased stimulation of cortisol output due to the production of CRH and the levels of cortisol during pregnancy are approximately 1.5 times higher than cortisol levels in non-pregnant women. After delivery a rapid return to non-pregnant levels occurs but normalization of the functions of the HPA axis can sometimes take weeks (Mastorakos & Ilias 2003).

Studies have shown that the maternal HPA-axis becomes hypo-responsive to stress as gestation increases (Schulte et al. 1990, Kammerer et al. 2002, Glover & O'Connor 2006). The HPA axis activity differs by parity status; higher midday total cortisol levels have been observed in nullipara compared to multiparous women (Vleugels et al. 1986, Rasheed 1993) and in a study by Jones lower waking cortisol levels have been found among nullipara compared with levels in multiparous women (Jones et al. 2006). Elevated maternal cortisol in humans is associated with lowered birth weight and premature birth (Diego et al. 2006, Field et al. 2006, Sandman et al. 2006). In a study of 131 women recruited at an antenatal ultrasound clinic between 20 and 28 weeks gestation prenatal cortisol in urine was a predictor of fetal weight (Field et al. 2005).

Cortisol concentration is about 10 times higher in the mother than in the fetus and crosses the placenta from the maternal blood, about 80% is metabolized to the inactive metabolite cortisone by the placental  $11\beta$ -hydroxysteroid dehydrogenase ( $11\beta$ -HSD) type 2. This enzyme serves as a functional barrier to protect the fetus from excessive exposure to high levels of maternal cortisol. Despite this the correlation between maternal and fetal cortisol levels has been found to be strong and maternal cortisol may account for about 40% of the variance in fetal concentrations. Contributions of 10-20% of cortisol from the mother can double cortisol

concentration in the fetal blood and influence brain development and plasticity (Gitau et al. 1998, Glover 1999, Weinstock 2006). Rodent studies have shown that maternal prenatal stress can affect the function of the placenta, including the expression and activity of 11 $\beta$ -HSD2 (Welberg et al. 2005, Mairesse et al. 2007) and low levels of 11 $\beta$ -HSD2 in the placenta have been associated with intrauterine growth restriction, possibly due to increased fetal exposure to cortisol (Mc Ternan et al. 2001, Kajantie et al. 2003, Dy et al. 2008). Reduced placental 11 $\beta$ -HSD2 function has also been associated with low relative birth weight and severe fetal distress (Kajantie et al. 2003). Recently an animal study revealed that in response to repeated maternal stress throughout pregnancy 11 $\beta$ -HSD2 activity was reduced in the placenta of the offspring to rats' exhibit high levels of stress (Lucassen et al. 2009). In a study of 262 women with normal pregnancies who completed Spielberger State and Trait anxiety scales and after that underwent an amniocentesis an association between maternal and amniotic fluid cortisol was found among anxious women, this implicates that maternal emotional state can affect the function of the placenta (Glover et al. 2009b).

Studies in rat indicate that the fetal brain is protected from glucocorticoids by 11 $\beta$ -HSD2 which is highly expressed in all areas of the brain in mid-pregnancy. However the expression of 11 $\beta$ -HSD2 is dramatically reduced in the last period of pregnancy which allows glucocorticoids to interact with their receptor systems and influence brain development (Diaz et al. 1998). There is support in the literature for believing that excess glucocorticoids during development have multiple adverse effects. Glucocorticoids are critical in promoting neuronal and glial maturational events under normal circumstances but are neurotoxic in high concentrations in the primate brain (Uno et al. 1994). Salaria et al showed in an in vitro model using microarray analysis on fetal brain aggregates that increased cortisol exposure affects the expression of over a thousand genes (Salaria et al. 2006).

Excess glucocorticoids during development can therefore cause malformation of parts of the brain (e.g. the cerebellum), increased activity of the HPA axis in adult life, and increased likelihood of corticoidsensitive disorders such as hypertension, increased anxiety and exaggerated stress responses (Herbert et al. 2006, Emack et al. 2008). It has been shown that the infants of mothers who had relatively high salivary cortisol displayed a greater incidence of crying, fussing and negative facial expressions than those with low levels but the difference between infants had disappeared by the age of 4 months. A negative correlation was also found between maternal salivary cortisol and mental and motor development at 3 months, which suggests that perceived maternal stress could influence temperament in the infants (de Weerth et al. 2003). Huizink et al found that early morning values of cortisol in late pregnancy were negatively related to both mental and motor development in infants at 3 months and motor development at 8 months (Huizink et al. 2003).

### ***Salivary cortisol***

Cortisol is present in saliva mainly in non-protein form, representing the free, biologically active fraction (5-10%) of the total plasma cortisol concentration. About 75% of the total cortisol is bound to CBG with high affinity but with a limited capacity at a serum cortisol concentration of approximately 450 nmol/L. The remaining part, about 15% of the total cortisol, is bound to albumin, which has a lower affinity for cortisol but almost unlimited binding capacity. During pregnancy the levels of corticosteroid binding globulin increase up to more than two-fold, resulting in a considerable increase in total cortisol levels in plasma (Meulenberg & Hofman 1990).

In 1964 Katz and Shannon showed the presence of the enzyme 11 $\beta$ -HSD converting cortisol into cortisone in the salivary gland but not in saliva (Katz & Shannon 1964). Because of this cortisol metabolism during the passage through the salivary gland, the salivary cortisol concentration represents approximately 70% of the free plasma cortisol concentration. Despite

this fact the salivary cortisol concentration does reflect the free fraction of circulating cortisol well. The transfer of cortisol from blood to saliva has been shown to be rapid; an increase of cortisol in blood is reflected in saliva within 60 seconds and a state of equilibrium is reached within five minutes (Walker et al. 1984).

It has been suggested that the concentration of salivary cortisol provides a better assessment of the HPA function than serum cortisol since the concentration of cortisol in the saliva gives a more accurate measure of the biologically active hormone (Kirschbaum et al. 1989, Meulenberg & Hofman 1990, Kirschbaum & Hellhammer 1994). Fleschner et al. suggested in their study that stress decreases the CBG levels resulting in increased levels of unbound cortisol and it is therefore important to measure cortisol in saliva and not in serum (Fleschner et al. 1995).

## **The HPA axis and mood disorders**

Different patterns of derangement of the HPA axis regulation have been shown during situations of chronic or prolonged stress and have also been associated with different psychopathologies. Melancholic depression is associated with raised cortisol and atypical depression with reduced cortisol output (Gold & Chrousos 2002). Both posttraumatic stress disorder (PTSD) and chronic fatigue syndrome have been reported to show a blunted CAR (Roberts et al. 2004, Wessa et al. 2006, Nater et al. 2008). A study examining 774 individuals with current anxiety disorder found a higher 1-hour cortisol awakening response compared to healthy controls (Vreeburg et al. 2010).

Postnatal depressive symptoms are associated with the major changes in the function of the HPA axis after delivery and have been shown to be associated with higher cortisol levels at waking and no increase at +30 min compared with controls (Kammerer et al. 2006, Taylor et al. 2009). Obel et al. observed that evening but not morning saliva cortisol was raised in women with high perceived life stress at 30 weeks but not at 16 weeks of gestation (Obel et al. 2005). Some associations between maternal antenatal anxiety and maternal cortisol have been reported (Diego et al. 2006, Sarkar et al. 2006, Kivlighan et al. 2008). In a study of 180 women at approximately 36 weeks gestation showed that having an anxiety disorder during pregnancy had an association with elevated cortisol but only in subjects with comorbidity of depression (Evans et al. 2008).

## **The use of Self-report questionnaires**

### ***Reliability and validity***

Psychiatric self-report questionnaires are frequently used in studying mental illness among childbearing women. Two advantages of using self-report questionnaires are that procedure is less time-consuming than other alternatives, and also makes it possible to study large samples. In some studies the diagnosis is interview-based, that require interviewers specially trained in psychiatry, is time-consuming and often generates a smaller study population.

The limitations in using self-report questionnaires are that different people respond in quite different fashion; responders are said to display different “styles”. Style in this context refers to specific ability of an individual to understand and interpret the questions adequately, and the degree to which each individual might show a tendency to routinely answer the questions without fully considering the content (Tsuang et al. 1995).

Reliability refers to the extent to which the instruments (questionnaires) are accurate and precise and also to the stability and predictability of the method. Test-retest correlations are used to evaluate the reliability; they can be somewhat problematic to use in the measurement of psychiatric symptoms as the test-retest correlations have a tendency to change over time. The prevalence of blood- and injection phobia, for example, decreases during a lifetime but is stable over shorter periods.

Internal consistency measures the homogeneity of items found in the questionnaires by measuring whether several items that are intended to measure the same general construct produce similar scores. The goal in designing a reliable instrument is for scores on similar items to be related (internally consistent), but for each to contribute some unique information as well.

Internal consistency is usually measured with Cronbach's alpha, statistic calculated from the pair wise correlations between items. Cronbach's alpha ranges between zero and one. A

commonly-accepted rule of thumb is that a value of  $\alpha$  of 0.6-0.7 indicates acceptable reliability, and 0.8 or higher indicates good reliability. High alpha values (0.95 or higher) are not necessarily desirable, as they may indicate that the items may be entirely redundant.

Validity of a test is a measure of whether an instrument measures what it is supposed to measure or not (Kerlinger 1986). Different aspects of validity are content validity; the idea that a test should sample the range of responses or criterion validity; the idea that a test should correlate with other measures of the same theoretical construct. Regarding the validity of self-rating scales, numerous studies have been reported with promising results on comparing the empirical clustering of symptoms with clinical syndromes (Tsuang et al. 1995).

### ***Sensitivity and specificity***

A screening instrument requires high sensitivity and specificity. Sensitivity measures the proportion of actual positives that are correctly identified as such, and specificity measures the proportion of negatives which are correctly identified. Sensitivity is the more important, because a screening instrument must not miss cases. Once a possible case has been identified, an interview can eliminate the false positives.

The positive predictive value is the proportion of patients with positive test results who are correctly diagnosed. It is the most important measure of a diagnostic method as it reflects the probability that a positive test reflects the underlying condition being tested for. Its value does however depend on the prevalence of the disease, which may vary.

The following questionnaires have been used in this thesis:

### ***Injection Phobia Scale-Anxiety***

In the screening of symptoms for blood- and injection phobia the “Injection Phobia Scale-Anxiety” (IPSA) was used in this thesis. IPSA consists of 18 items describing various anxiety provoking situations (Öst et al. 1992b). The woman rates the degree of anxiety in situations involving injections from 0-4 (scale range 0-72). The items are as follow (translated into english by CL for this thesis): “Giving a blood sample by having a finger pricked”(1), “Having a shot in the upper arm” (2), “Look at a picture of a syringe with a needle” (3), “Feel a smell of hospital” (4), “Receive a shot by the dentist” (5), “Having blood drawn from a vein” (6), “Looking when another person is having blood drawn from a vein” (7), “Receiving a shot in the buttock” (8), “Look at a picture of a person receiving a shot” (9), “Listen to someone talking about injections” (10), “Look at and touch veins in the bend of the arm” (11), “Look at a movie of a person receiving a shot” (12), “Look at a person receiving a shot” (13), “Look at a person dressed as a nurse” (14), “Having the ears pierced”(15), “Receive a vaccination” (16), “Receive an injection in a vein” (17), “ Look at another person giving blood” (18). See Appendix 1.

Öst et al. provided initial data on the internal consistency (Cronbachs alpha 0.86) of the IPSA in a sample of 59 patients, noting its positive association with phobic-relevant avoidance and its reactivity to changes in behavioral treatment (Öst et al. 1992b). Additional studies have shown that the IPSA discriminates blood- and injection phobia from spider phobia (Sawchuk et al. 2000) and is positively associated with other measures of disgust (Olatunji et al. 2007b) and contamination fear (Sawchuk et al. 2002) suggesting adequate validity. A resent study by Olatunji has examined the factor structure, reliability, validity and clinical specificity of the IPSA. They found that the IPSA were found to be internally consistent, with all items having moderate to high correlations with the total score. Additional examination of the psychometric properties found that the IPSA may be composed of two lower order factors assessing distal

fears of injections and contact fear of injections. The two factor scores demonstrated good internal consistency and were highly correlated with each other and the IPSA total score. The IPSA total scores were mildly correlated with age in the study and were significantly higher among women than among men  $p < 0.001$ . A 12-week test-retest reliability study was carried out with an intraclass correlation coefficient of 0.88 indicating that the total score on the IPSA during a single assessment are likely to be representative of an individual's injection phobia level on other occasions. The reliability coefficients were generally stronger among women than among men.

When testing for the predictive validity the results showed that the IPSA scores were highest among those with a fainting and avoidance history suggesting that the IPSA have some utility as a screening tool in the applied medical setting. When examining the clinical specificity, the phobic group ( $n=39$   $M= 44.84$   $SD 8.86$ ) diagnosed according to DSM-IV scored higher than did nonphobic controls ( $n=43$   $M= 9.20$   $SD 11.40$ ) on the IPSA. Altogether the study concluded that these findings provide supportive evidence for the clinical use of the IPSA (Olatunji et al. 2010).

### ***Injection Phobia Scale-Avoidance***

The Injection Phobia scale- avoidance (IPSAV) consists of the same situations as on the IPSA. The situations are rated for avoidance on a 0-2 scale (range 0-36). The internal consistency of the scale is 0.8 (Cronbachs alpha) (Öst et al. 1992b).

The anxiety and avoidance scales are correlated significantly ( $r = 0.44$ ;  $p < .005$ ) and in both scales, IPSA and IPSAV, the concurrent validity (the degree to which scores on an instrument are correlated with an external criterion measured at the same time) seems to be adequate. The scales are also sensitive to change after treatment (Öst et al. 1984, Öst et al. 1989a, Öst et al. 1991b, Hellström 1996). See Appendix 2.

### ***The Edinburgh Postnatal Depression Scale***

The Edinburgh Postnatal Depression Scale (EPDS) is a 10-item self-report scale specifically designed to screen for postnatal depression in community samples and was developed by Cox and colleagues (Cox et al. 1987). The EPDS can also be used as a valid measure of dysphoria through the various stages of pregnancy and puerperium (Cox et al. 1987, Green & Murray 1994).

Each item is scored on a 4 point scale (0 to 3), the minimum and maximum total score ranging from 0 to 30 respectively. The scale rates the intensity of depressive symptoms present within the previous 7 days. Five of the items are concerned with dysphoric mood itself, two with anxiety, and one each with guilt, suicidal ideas and “not coping”. The EPDS is widely used in the world and has been translated into at least 11 languages, including Swedish (Lund & Gyllang 1993).

The EPDS is to be considered as a screening tool and not a diagnostic instrument. When using  $>12$  as a cut-off level Cox et al. showed a sensitivity of 86%, a specificity of 78% and a positive predictive value of 73% for major depressive illness (Cox et al. 1987). Another validation of the EPDS by Murray who also used a cut-off level of  $>12$  showed a sensitivity of 68%, a specificity of 96% and a positive predictive value of 67% for both major and minor depressive illness (Murray & Carothers 1990). When using  $\geq 10$  as a cut-off level the sensitivity for the detection of major depression increased to almost 100% and the specificity to 93% (Harris et al. 1989). Validation of the Swedish version of the EPDS has been tested and the findings were identical with, or similar to, those from earlier studies (Wickberg & Hwang 1996).

### ***The Beck Anxiety Inventory***

The Beck Anxiety Inventory (BAI) is a 21-items self-report inventory for measuring the severity of anxiety (Beck et al. 1988). Symptoms of anxiety and depression are similar and it seems to be a delicate task to distinguish between affective, somatic and behavioral symptoms. But BAI is able to discriminate anxious groups from non-anxious groups (e.g. major depression) and is constructed to avoid confounding with depression (Beck et al. 1988, Creamer et al. 1995).

Each item is scored on a 4 point scale (0 to 3), the minimum and maximum total score ranging from 0 to 63 respectively. The respondent is asked to rate each item experienced during the preceding week. Score of 0-7 reflect minimal anxiety; 8-15 mild anxiety, 16-25 moderate anxiety and score 26-63 indicate severe anxiety (Beck 2005). The items are as follow:

Numbness or tingling (1), feeling hot (2), wobbliness in legs(3), unable to relax (4), fear of the worst happening (5), dizzy lightheaded (6), heart pounding or racing(7), unsteady (8), terrified (9), nervous (10), feelings of shocking (11), hand trembling (12), shaky (13), fear of losing control (14), difficulty breathing (15), fear of dying (16), scared (17), indigestion or discomfort in abdomen (18), faint (19), face flushed (20), and sweating (not due to heat) (21).

## **Treatment and phobia**

Specific phobias are the most readily treatable of anxiety disorders. The treatment of choice for these phobias is a type of cognitive-behavioral therapy also called systematic desensitization or exposure therapy (Chambless 1990, von Knorring et al. 2005). This treatment is very effective. According to the US National Institute of Mental Health, about 75% of people are able to overcome their phobias through cognitive-behavioral therapy.

### ***Cognitive behavioral therapy (CBT)***

Exposure is a standard intervention technique in the behavioral treatment of anxiety disorders (Barlow 2002, Patel et al. 2005). Hierarchical or massed exposure to the feared object or situation in a safe and controlled way is given in a number of sessions.

CBT using exposure therapy employs techniques designed to expose the patient to the anxiety provoking stimuli. The therapy can be conducted by “in vitro” methods (imagination) or “in vivo” methods (direct exposure). The good effects of exposure and restructuring of cognitions are explained by the observational evidence that the person has become able to stop avoiding behavior and reduction of dysfunctional behavior.

Before treatment starts, an assessment of the patient’s avoidance and cognitions is carried out. The nature of the phobia and the suitability for treatment are decided upon. The etiology of the individual’s phobia is discussed, an explanation of the way that exposure works in CBT is presented, and the patient receives preliminary education in the use of relaxation techniques. The individual’s anxiety level is evaluated and finally a goal for the treatment is determined. The review by Choy reports that in vivo exposure results in good treatment outcomes for most types of specific phobias, provided the exposure time is of sufficient length, which has been estimated to be between 2 to 4 hours (Choy et al. 2007). Several studies report a response rate of specific phobia to the in vivo exposure of 80-90% (Choy et al. 2007) but one study by Öst et

al. with only in vivo exposure for treatment of blood- and injection phobia, found that only 40% of the patients were clinically improved at the end of treatment and only 50% of them were still considered to have maintained this improvement after one year (Öst et al. 1991b).

### ***Applied Tension (AT)***

The AT method for the treatment of blood- and injection phobia was developed by Öst & Stener (1987). This method takes advantage of the unique characteristic of a biphasic physiological response when an individual with blood- and injection phobia is exposed to phobia-provoking stimuli. The individual first learns to recognize the early signs of a decrease in blood pressure and then is taught to practice exerting muscle tension. The tension technique utilizes repeated tense (10-15 s) and release (20-30 s) sequences – release is not synonymous with relaxation- of the skeletal muscles in the arms, legs and thorax to counteract cardiovascular and autonomic changes associated with the blood- and injection associated syncope. An increase in blood pressure and heart rate promotes an increased blood flow to the heart and brain that prevents the fainting response. In a study by Hellström 30 individuals with blood- and injection phobia took part in one or five sessions with AT, they all managed to rise the systolic and diastolic blood pressure 11-26 mmHg and all except three persons were improved (Hellström et al.1996).

The tension technique is often combined with a gradual exposure to blood- and injection phobic stimuli (Peterson & Cigrang 2003, Choy et al. 2007). Two follow-up studies of subjects with blood- and injection phobia treated with AT after 12 months reported that between 70-80% were found to be clinically improved (Ayala et al. 2009).

Since one of the greatest fear experienced by a person suffering from blood- and injection phobia is the probability of fainting it seems important to get control over the physical reaction in the body and AT is one method providing that.

### *EMLA® (Eutectic Mixture of Local Anesthetics)*

EMLA is a unique topical anesthetic cream that is available in drugstores. EMLA is a eutectic mixture of lidocaine and prilocaine that is liquid at room temperature, even though both lidocaine and prilocaine are room-temperature solids. The term eutectic refers to the fact that the melting temperature of the mixture is lower than the melting point of either pure compound. EMLA must be applied at least one hour before the needle procedure is implemented. The effectiveness of EMLA cream varies greatly from individual to individual. EMLA works quite well for most people whose blood- and injection phobia is triggered by the sensation of the needle penetrating the skin and vein. EMLA can be helpful in clinical practice but use of EMLA does not completely solve the problems faced.

### *Drug treatment*

Drugs are not recognized as a standard treatment for specific phobia and there are only a few studies to be found in which drug use has been studied. The general view is that medication has little benefit in reducing a specific phobia (Choy et al. 2007). Benzodiazepines have been used on dental patients not only to reduce anxiety but to enable the patient to cooperate better; no long-term effect has been shown (Thom et al. 2000). In a preoperative management of patients with needle phobia midazolam is the most preferred benzodiazepine for anxiolysis because of its rapid onset and short duration of action (Bamgbade 2007).

Nitrous oxide sedation during dental treatment has been shown to lower anxiety with the same result as cognitive or behavioral therapy with a follow up for a period of 10 weeks (Willumsen et al. 2001).

Alamy et al reported results from a pilot study with only 12 subjects, that escitalopram may hold promise as a treatment for specific phobia but that larger randomized controlled trials are needed since the pilot study was underpowered (Alamy et al. 2008). Benjamin et al found in a study of 11 subjects that paroxetine appeared to be significantly superior to a placebo, which led

them to conclude that this therapeutic option deserves further examination in a larger trial (Benjamin et al. 2000).

#### *Others*

The effect of Self-Injection Anxiety Therapy has been studied on patients so afraid of blood and injections that they can't inject themselves with medications they need. With a combination of CBT and learning to self-inject the results is promising (Mohr et al. 2005).

The use of stress-reducing medical devices e.g. decorated syringes (flowers, musical notes) can effectively and significantly reduce aversion, anxiety, fear and overall stress among both children and adults (Kettwich et al. 2007).



## **Aims of the present thesis**

To examine the prevalence of blood- and injection phobia in a pregnant population

To investigate if group CBT is effective in treating pregnant women's blood- and injection phobia and examine if that treatment has any impact on anxiety and depressive symptoms during pregnancy and postpartum

To investigate if pregnant women with blood- and injection phobia have an adverse obstetric and neonatal outcome

To investigate if pregnant women suffering from blood- and injection phobia have raised cortisol levels or are characterized by unusual diurnal salivary cortisol profiles and to examine the levels of CRH, ACTH and cortisol in serum

## Participants in the study I-IV

Figure 2a. The pregnant women with blood- and injection phobia

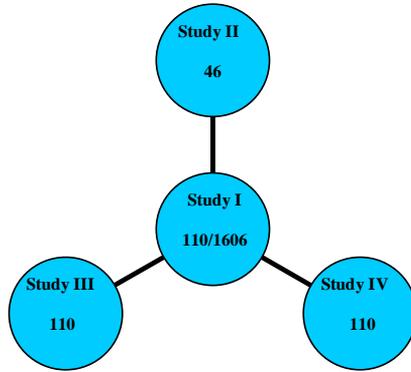
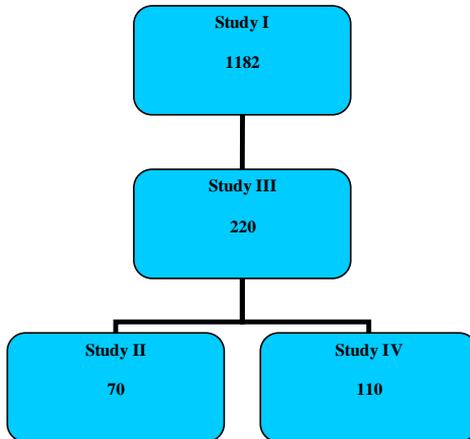


Figure 2b. The pregnant women without blood- and injection phobia



## Subjects and methods

### Study I

Study I was designed as a cross-sectional study to determine the prevalence of blood- and injection phobia in a pregnant population. The sample comprises the population of pregnant women consecutively registered at the antenatal care clinics (ACC) in two counties in the south east region of Sweden. Enrolment took place during 2005; the study was stopped the 31st of January 2006 because other research studies waited to start recruiting patients. The only exclusion criterion was inability to understand the Swedish language. A total of 1606 women attending their first antenatal care visit with a midwife were approached.

The participating women were asked to complete the questionnaire “Injection Phobia Scale-Anxiety” (IPSA) at the ACC in gestational week 10-12. In this study the cut-off level of  $\geq 20$  was used as criterion for the woman to be telephone-interviewed. Earlier studies that had used the IPSA showed that patients with blood- and injection phobia scored at a mean above 40 (43.8 SD 10.9 and 48.3 SD 5.9) on the IPSA (Öst et al.1992b). The cut-off of 20 was therefore considered safe, in that using it would insure that no case of blood- and injection phobia was missed.

In total, 347 women scored  $\geq 20$  and were thereby diagnosed or dismissed according to the DSM-IV criteria for blood- and injection phobia. All interviews were done by the same psychotherapist (GS) how was not aware of the woman’s score on the IPSA when conducting the interview. The main reason for doing a telephone interview and not a face-to-face interview was because of practical reasons, mostly due to the large study area.

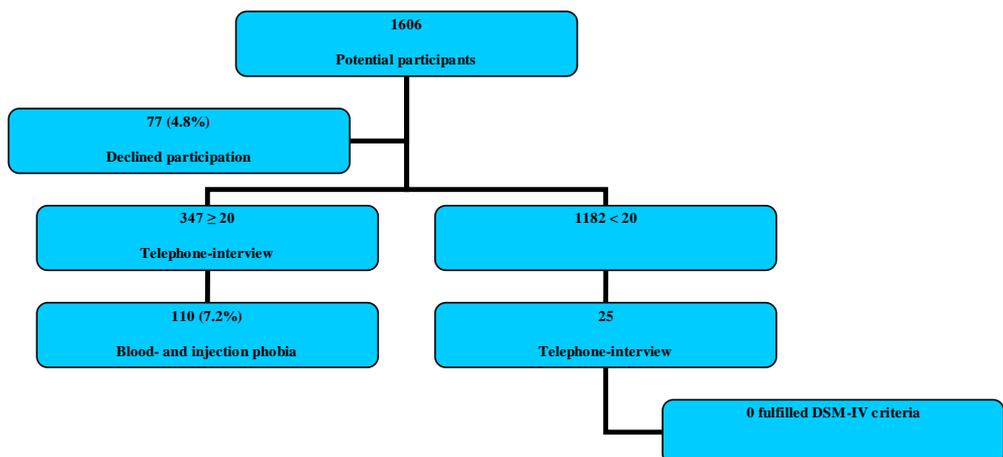
The specific questions asked in the diagnostic interview were questions about the woman’s fear and avoidance regarding for example blood seen after a minor cut, having blood drawn and receiving injections. The questions were asked regarding the individual’s own experiences and about witnessing others in the same situations. Subsequent questions were when and how the

fear begun causing problems for the person, to what extent the fear interferes with the individual's life, if the individual experiences anxiety when entering the feared situation and what the person believes will happen in the situation. All women were asked about the somatic reactions such as dizziness, sweating, and feeling faint, fainting or almost fainting, experienced when they was confronted with these types of stimuli. If the woman was under age 18 the symptoms had lasted at least 6 months for receiving the diagnosis. An assessment was done concerning that the anxiety, panic attacks or phobic avoidance with the specific object or situation was not better accounted by another mental disorder. It was also made clear that the woman recognized that the fear was excessive or unreasonable.

Page studied a population that consisted of 308 patients who had responded to a questionnaire about fear of blood and injections (Page 1996). He suggested that if doctors were routinely to ask "are you overly fearful of blood, injury and injections?" they could be reasonably confident of identifying patients with blood- and injection phobia.

In order to further test the content validity of the IPSA, 25 pregnant women who had scored < 20 on the IPSA were interviewed. They were randomly chosen and added to the list of woman to interview (see figure 3).

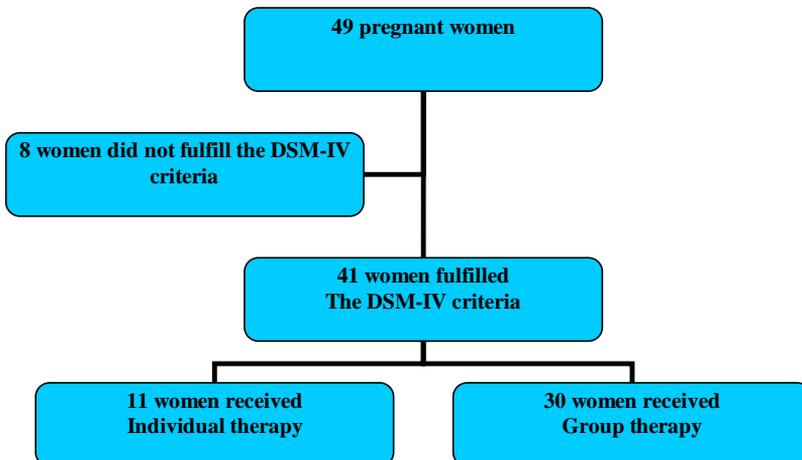
**Figure 3. Participants in study I**



## Study II

Study II is an open case control study with a treatment intervention. In 2005, 49 women in early pregnancy were referred to the unit of Psychosocial Obstetrics & Gynecology due to symptoms of blood- and injection phobia. First each woman had an individual visit with a psychotherapist (GS). The therapist made an assessment of the patient's condition and formulated a diagnosis according to the criteria in DSM-IV for blood-and injection phobia. Forty-one women fulfilled the criteria for blood- and injection phobia and were invited to take part in a two-session group therapy. Eight out of the 49 referred pregnant women did not fulfill the diagnostic criteria for blood- and injection phobia and received counseling by their midwives at the ACC. Eleven out of the 49 women wanted to be treated individually because they could not handle a group situation. In total, 30 pregnant women received a two-session group CBT (see figure 4). None of the women received any other psychological or pharmacological treatment during this period.

**Figure 4. Participants referred for CBT in study II**



The women acted as their own controls when evaluating the effect of the two session group CBT in this study, but since little was known about blood- and injection phobia during pregnancy or how the symptoms change over time two comparison groups were included in the study. From Study I conducted during the same time period and in the same geographic area as Study II, 46 women diagnosed with interviews according to DSM-IV for blood- and injection phobia by the same psychotherapist served as a comparison group together with 70 pregnant women without blood- and injection phobia. None of the women received any psychological or pharmacological treatment during this period other than regular antenatal health care.

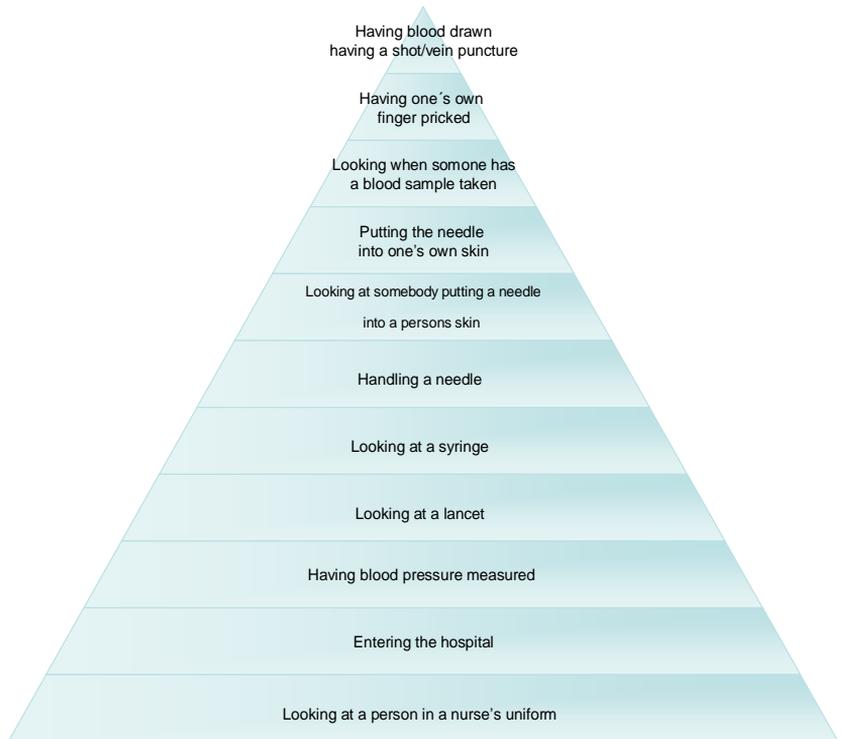
The reason for employing group therapy instead of individual therapy was that the latter is time-consuming, expensive and difficult to manage in an ACC-setting. It also became clear that the group members would gain from seeing others being exposed to therapy and would therefore be less likely to feel alone about their phobia.

The group CBT sessions were conducted using a two-session design. The reason for a two-session design was that it would not be possible to manage all the different steps in the therapy in one session to achieve enough exposure to all the stages of therapy. Each treatment group consisted of 4-6 women who met with an authorized CBT psychotherapist (GS) and a midwife who had been specially trained for work with such a group. The two group therapy sessions were scheduled for two afternoons four weeks apart. The treatment was based on a model described by Öst (Öst et al. 1992b).

All women were informed beforehand that the therapist and the midwife would not do any kind of intervention without having first received full consent from each participant.

Before treatment could start, each woman was asked to create her own anxiety hierarchy list by recording, in order of decreasing level of anxiety, all the situations in which she felt anxiety (Figure 5).

**Figure 5. Example Hierarchy**



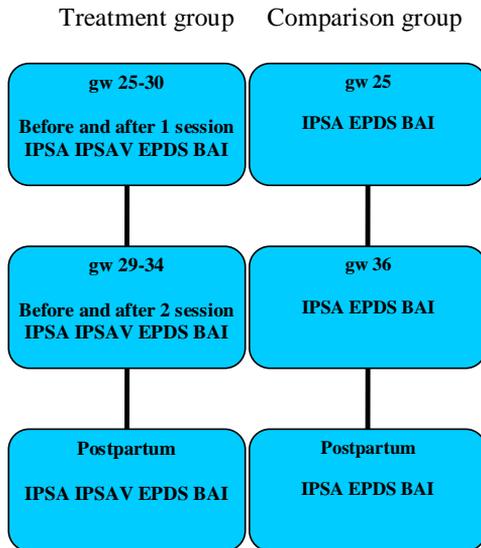
*Session one*, which took place around gestational week 25-30, consisted of an intensive and prolonged exposure to lancets, syringes, injection needles and intravenous catheters as well as instruction about the different functions of these devices. The midwife also explained what utensils were to be used in a delivery situation and the women got a chance to ask questions and to be challenged about their beliefs and interpretations about, for example, lancets and injection needles. All women were asked to measure their anxiety and the therapist did not continue with new tasks until all the participants in the group were ready and had reached a low anxiety level of 1-2 (verbally estimated from 1-10 where 10 is maximum anxiety). In this session the midwife performed a vein puncture and gave a subcutaneous injection of saline in the arm of the therapist. All participants were then given lancets, syringes, and injection needles to touch

and look at for training purposes and as homework. A relaxation session lasting five minutes closed the first session.

The *second session* started with a discussion on how the four weeks had been experienced by the women, and all participants were given the opportunity to ask questions and report on their homework. This session consisted of a prolonged intensive exposure to the most phobic situations; pricking a finger, subcutaneous injection in the arm, vein puncture and insertion of an intravenous catheter.

The anxiety-inducing order of these components was discussed and almost all participants considered the order given above to match their individual phobia hierarchy. Although, the anxiety level associated with pricking a finger or having a subcutaneous injection in the arm could vary, all women rated vein puncture and insertion of an intravenous catheter as the most anxiety-provoking situation. During the session each of the exercise steps was done on each participant at least once. After the second session, each woman was given a maintenance program (Öst et al. 1989b) that encouraged her to do one of the above things at each routine visit to the ACC. A relaxation session of 5 minutes closed the second therapy session as well. The 30 women with blood-and injection phobia in the CBT treatment group were assessed with questionnaires on 5 occasions: before and after each group therapy session and 3 months after delivery. In order to assess the women's self reported degree of phobia, the IPSA and the IPSAV were used (Öst et al.1992b). To assess depressive symptoms the EPDS (Cox et al. 1987) was used and to assess anxiety symptoms the BAI (Beck et al. 1988) was used. The two comparison groups answered the IPSA, EPDS and BAI at gestational weeks 25, 36 and 6-8 weeks postpartum (see figure 6).

**Figure 6. Flow-chart of participants in study II**



### Study III

From a population-based prospectively collected cohort the 110 women identified with blood- and injection phobia during pregnancy in study I was examined regarding obstetric and neonatal outcome.

Among the 1182 women scoring < 20 on the IPSA in study I, 220 women were randomly stratified for age and parity as a control group for the index women. The randomization was done by a research assistant who, from the data sheet, randomly picked one control woman for each index woman among the feasible group of women considering age and parity. The Swedish antenatal health care system reaches almost 100 % of all pregnant women (The National Board of Health and Welfare 2010). The same percentage is valid for deliveries as there are no private maternity hospitals in the study area and home deliveries are rare. The ACC provide regular check-ups on the physical and psychological health during pregnancy and puerperium.

At the ACC healthy pregnant women are advised to attend the regular antenatal program with seven to nine visits to a midwife and, if needed, extra appointments with an obstetrician and/or with the midwife. The first visit generally takes place around gestational week 10 –12.

All data related to the pregnancy, delivery, and the puerperium was registered in the standardized Swedish antenatal, delivery and neonatal records.

The data were manually extracted from the records by CL, and are thus prospectively collected.

The following data were collected: age, parity, marital status, occupation, Body Mass Index, smoking, drug abuse, number of induced abortions, miscarriages, or extrauterine pregnancies.

Any history of psychiatric disorder (depression, anxiety disorders except blood- and injection phobia, eating disorder, psychotic disease), fear of childbirth or obstetric complications, actual chronic medical diseases (e.g. asthma with continuous need of pharmacological treatment , epilepsy, hypertension, rheumatic arthritis, inflammatory bowel disease, diabetes),

pharmacological treatment, number of visits at the antenatal care clinics before delivery

(midwife and obstetrician), pregnancy complications (preeclampsia, hyperemesis, back pain,

vaginal bleeding, premature contractions), sick leave during pregnancy, and perinatal events

including all relevant delivery data were obtained. All women in the study had a routine

ultrasound in the beginning of their pregnancy to determine the gestational week and expected

date of delivery. The frequency of postnatal hospital stay exceeding 48 hours for the index

women was compared with that of the control women. Neonatal morbidity was defined as a

condition that generated a diagnosis on the baby and demanded a pediatrician's attention more

often than simply at the time of the routine examination of the newborn for example jaundice, fever or hypoglycemia.

Small for gestational age (SGA) was defined as a birth weight less than two standard deviations below the mean weight for gestational length according to the Swedish standard (Marsal et al.

1996). Nulliparas and multiparas were analyzed separately because of their differences as groups concerning the medical-, obstetric-, and gynecologic histories.

To assess the women's degree of anxiety the Beck Anxiety Inventory (BAI) was used in gestational week 25.

#### **Study IV**

All the 110 pregnant women with blood- and injection phobia identified in Study I and 110 out of the total 220 pregnant women that were randomized as a control group in Study III were asked to provide morning and evening samples for measurement of salivary-cortisol in pregnancy week 25 and 36. The study was supervised by each woman's midwife at the antenatal care clinic, who administered the instructions for home saliva collection together with the material to the woman in the designated gestational week.

Samples were collected immediately upon awakening and in the evening before going to bed. They were instructed not to brush their teeth, nor eat, nor drink for at least 30 min before collecting the samples. Sample collection was preferably done on ordinary days avoid of extra psychological or physical stress. In week 25 when the mandatory blood sample for blood testing was taken, a sample for serum cortisol was collected. In addition blood was drawn for analysis of CRH and ACTH in women living close to the laboratory (n=38 women with blood- and injection phobia n=28 control women).

The samples were handled according to written instructions by the laboratory personal and stored at a correct and constant temperature in the freezer in the lab. Of the above mentioned population 73 pregnant women with blood- and injection phobia and 53 pregnant healthy controls managed to leave at least one sample.

The Salivette® test tube (Sarstedt, Nuembrecht, Germany) method for salivary sampling was used. The Salivette® is a plastic centrifuge vessel equipped with a suspended insert containing a

cotton wool swab. The use of filter strips for saliva collection and their validation have been described in detail by Neu (Neu et al. 2007). The cotton wool swab was removed from the suspended insert and soaked in saliva by being rotated in the mouth for 60 seconds yielding about 0.5 mL of saliva. Afterwards the cotton wool swab was put back into the suspended insert and the tube was closed with the stopper. The saliva samples were stored at room temperature during transport to the laboratory; on arrival they were centrifuged for 15 minutes at 1900 g, and then frozen at -20° C until they could be assayed. A commercial enzyme immunoassay (Salimetrics, <http://www.salimetrics.com>) designed for the analysis of *salivary cortisol* was used. The lowest concentration of cortisol that can be distinguished from 0 was < 0.083 nmol/L. *Cortisol* was measured using a chemoluminescence kit from Siemens Medical Solutions Diagnostics on an Advia Centaur XP. The lowest detectable concentration was 5.5 nmol/L. *ACTH* was measured using a chemoluminescence kit from Siemens Medical Solutions Diagnostics on an Immunlite 2500 Immuno Chemistry System. The lowest detectable concentration was 5 ng/L. *CRH* was measured using a competitive radioimmunoassay in plasma extracted on C18-reverse phase columns. CRH antiserum B3-23 against human CRH (<http://www.eurodiagnostica.com>) and 125I-CRH-Tyro-CRH (<http://www.eurodiagnostica.com>) was used as antiserum and radioligand, respectively. Human CRH SC060 (<http://www.neomps.com>) was used as calibrator. The lowest detectable concentration was 5 pmol/L.

## **Ethical considerations**

The study was approved by the Regional Ethics Committee for Human Research of the Faculty of Health Sciences, Linköping University, No.M 192-04 in 2004. In connection with preparing the study, ethical questions and dilemmas were taken into consideration. There is always a possibility that questions concerning mental health may create anxiety and increase stress for women with a specific phobia such as blood- and injection phobia. However the positive effects of paying attention to this problem and making the women aware of an interest in this matter could outweigh some of the negative effects. All information was given to the participants both orally and in writing. Individual informed consent was obtained from all women and a note to the midwife in a reminder box showed up when the women's computerized medical records were opened.

In *study I*, all women were informed of the purpose of the study by the midwife at the ACC and in a letter from the authors before the woman were asked to answer the IPSA questionnaire. The information about participation also included information stating that participation was voluntary and that there was a possibility of withdrawing from participation at any time without affecting on-going care or future contact with the ACC. The women were informed that there was a possibility that they could receive a telephone call later on and that this telephone call was a diagnostic interview. If the woman was diagnosed with blood- and injection phobia during the interview the therapist made a note to that woman's midwife at the antenatal care clinic. These women were asked during the next visit with the midwife if they would be willing to answer questionnaires on three future occasions - gestational week 25, 36 and postpartum - and at those times to also leave blood and saliva samples.

The comparison/control groups in *study II, III and IV* were informed by the midwife that they had been chosen to participate in the rest of the study and they were asked to complete questionnaires in week 25, 36, and postpartum and also to leave blood and saliva samples.

All women were given the opportunity to contact the authors or a research midwife for further information if necessary. The women were reminded once by the midwife if they had not yet sent in the questionnaires by post.

In *study II* the women who received CBT were individually informed about the study by the therapist when the women were agreeing to be in the group to be given CBT. CBT for blood- and injection phobia might cause anxiety and stress and there is a risk that a pregnant women before, after and/or during a treatment session can experience a great deal of discomfort. There was also a possibility that this could affect the unborn child because of raised cortisol levels. Unfortunately no collection of saliva for cortisol analyses in connection with therapy was carried out. The goal of CBT is worthwhile and if the goals are met, then this would mean that the levels of anxiety and stress were reduced in the treated women during the rest of the pregnancy.

Given our knowledge about stress and anxiety during pregnancy and the effects they may have on obstetric and neonatal outcomes, it is ethically difficult to randomize pregnant women with blood- and injection phobia to receive treatment or be on a waiting-list. The comparison group in study II received only the ordinary treatment routinely offered at the ACC and was never offered the chance of participating in a study in which CBT could be an option.

In *study IV* when blood was drawn for the almost compulsory blood group testing in gestational week 25, extra blood was taken for additional analyses. In that way no extra expose to one of the very thing – drawing blood - that they fear most was carried out. Being subjected to the salivary cortisol test can be uncomfortable but this probably is not a common phobia- provoking stimulus.

The lab results of each test on patients and controls were evaluated according to the reference list and an endocrinologist was to be consulted to take care of further investigation if necessary.

All women were guaranteed and treated with confidentiality. Thus each woman was assigned a code number, designed to make it possible to identify her data in the medical records and in the answer sheets to the questionnaires. All results are presented at group level and it is not possible to identify any individual.

## **Statistics**

The statistical analyses were done using the statistical programs SPSS (version 14, 16,17, Chicago, Illinois, USA)

All statistical tests were two-sided and the rejection of the null-hypothesis was set to  $\alpha=0.05$  in every statistical analysis.

-Student t-test was used to test differences between quantitative variables with approximately normal distribution (Study III)

-The Chi-square ( $\chi^2$ ) test was applied for testing differences in frequencies between categories (Study I, III).

-A power calculation was performed in study II.

-The sensitivity, specificity and positive predictive value of the IPISA were calculated (Study I).

-The relationship between the sensitivity and 1-specificity was illustrated in a receiver operating characteristic (ROC) curve (Study I).

-The Wilcoxon's test /Mann-Whitney test was used to test differences between non-parametric data (study III, IV).

-The possible effects of independent factors on dependent factors in study III were estimated through multiple logistic regression analyses and the OR was presented with a 95% CI (Study III).

-Univariate analyses of variance (ANOVA) were performed to test differences between groups on different occasions (Study II, III.)

-The analysis of variance (ANOVA) for repeated measures was applied for testing differences between groups over occasions (Study II, IV).

-Pearson's correlation was used to explore the magnitude and direction of the linear relationship (Study IV).

-The raw salivary cortisol values in nmol/L are presented in paper IV. In addition the raw values were transformed to the natural logarithm ( $\ln(1+x)$ ) in order to achieve normal distributions for statistical analyses. Median values, 25<sup>th</sup> and 75<sup>th</sup> percentile are presented in the tables and means and standard deviations in the text (Study IV).

-Normality was tested using the Kolmogorov-Smirnov's test (Study IV).

-Dixon test for outliers (Study IV).

## **Result and Discussion**

### **Prevalence of blood- and injection phobia among pregnant women (Study I)**

The mean age of the 347 women that scored  $\geq 20$  on the IPSA was 29.1 years (range 17-45 years SD 4.91). There was an equal distribution between nulliparas and multiparas.

One hundred ten of the 347 women fulfilled the DSM-IV criteria of blood- and injection phobia during the interview, giving prevalence in the study population of 7.2% (110/1529).

The 110 pregnant women with blood- and injection phobia (mean age 30.9 years range 19-43 years SD 4.53) scored  $\bar{x} = 44,7$  SD= 8.63 on the IPSA which is similar to other studies using the IPSA (Öst et al.1992b, Olatunji et al. 2010).

In order to further test the content validity of the scale, 25 pregnant women who had scored < 20 on the IPSA were interviewed; none of them fulfilled the DSM-IV criteria for blood- and injection phobia.

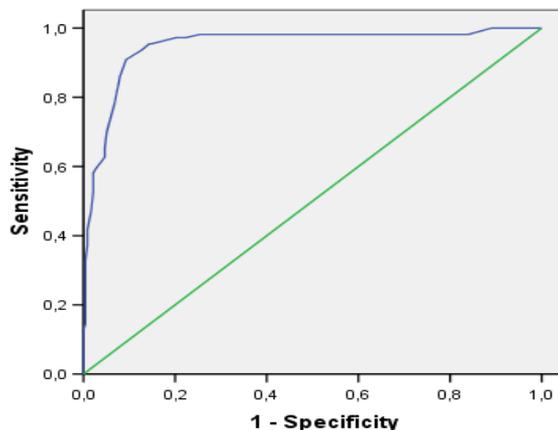
The prevalence in this study is higher than what has previously been reported from a non-pregnant female population and should be seen in relation to the mean age observed in our group (29 years), but also to the fact that the women in the study population is pregnant and no longer can avoid the things connected with their phobia. Other studies have shown that the prevalence of blood- and injection phobia decreases during the life span (Agars et al. 1969, Costello 1982). It would therefore have been reasonable to believe that the prevalence in the youngest age group  $\leq 24$  years (n=56) would be higher comparing to the rest of the group, but no differences were found among the age groups studied. The prevalence of blood- and injection phobia did not differ either between nulliparas and multiparas.

Seventy-seven patients (4.8%) declined participation. The reason for this as noted by the midwife was that they did not have time, the patient was already taking part in another study or that they chose to give no reason at all.

This study shows that blood- and injection phobia in pregnant women is a fairly common phenomenon. The IPSA appeared to be fully acceptable to the large majority of pregnant women. As a diagnostic aid for blood- and injection phobia a threshold of 35 (sensitivity 94%) or more is needed. However, in some clinical or research settings it might be important not to miss any cases of blood- and injection phobia, and under these circumstances a threshold of 30 (sensitivity 98%) might be reasonable.

To illustrate the relationship between sensitivity and specificity a receiver operating characteristic (ROC) curve was constructed. A ROC curve (see figure 7) illustrates the use of IPSA to distinguish a diagnosis of blood-and injection phobia and a non diagnosis. The x-axis represents the false positive fraction or 1-specificity and the y-axis represents the true positive fraction or the sensitivity. The area under the curve tells us how good the test is; the closer to 1, the better the test. The area under the ROC curve for IPSA in this study was 0.95.

**Figure 7. The Receiver operating characteristic curve**



## **An open trial with cognitive behavioral therapy for blood- and injection phobia in pregnant women - A group intervention program (Study II)**

All 30 women who received CBT group treatment attended both sessions in full and also participated at the follow-up evaluation, which took place 3 months after delivery.

The mean age was 28.5 years (SD = 5.03) and 21 (70%) were first-time mothers while nine women had given birth to one or two previous children. At the follow-up all but two women had normal vaginal deliveries (93%).

Of the 46 untreated women with blood-and injection phobia, 44 answered all the questionnaires without any missing data. The mean age was 30.5 years (SD= 4.09) and 25 (54.3 %) were nulliparas. Thirty-five (76.1%) of the 46 untreated women had normal vaginal deliveries, seven (15.2%) a caesarean section and four women (8.7%) were delivered with a vacuum extraction.

In the group without blood- and injection phobia the mean age was 30.7 years (SD = 4.22). Of these 70 women, 42 (60.0%) were nulliparas and 56 (80%) had vaginal deliveries, seven (10.0 %) a caesarean section and eight (11.4%) were delivered with a vacuum extraction. One woman had a vacuum extraction that failed and she was thereafter delivered with a caesarean.

The scores of the treatment group on the IPSA and the IPSAV were reduced both over the whole study period ( $p < 0.001$  and  $p < 0.001$ ) as well as when the scores before and after the two treatment sessions were compared, even though some women still scored relatively high.

Adjusting for parity and age did not change the results. The scores were also reduced at the follow-up 3 months postpartum, as compared to both the first and second occasions ( $p < 0.001$  and  $p < 0.001$ ). During the first session, 29 out of 30 participants scored lower on the IPSA after the treatment was completed, compared with before the treatment, while one woman had the same score before and after. The corresponding numbers for the IPSAV during the first session were that 20 out of 30 participants scored lower, nine participants had the same score

before and after and one woman scored one point higher after the treatment session than before. During the second session the treatment effect was more marked; all women scored lower after the second treatment session, on both the phobia scales than they had before. Both within the group with untreated blood- and injection phobia and within the group of women without blood- and injection phobia there was a tendency towards a reduction of scores on the IPSA over time ( $p = 0.04$  and  $p = 0.067$ ). In comparisons of the three groups of women on the three different occasions, the CBT treated women had significantly higher scores for phobic symptoms before the first treatment session ( $p < 0.001$ ) than both untreated women and controls without blood- and injection phobia, however, at the postpartum follow-up, the CBT treated women scored significantly lower than the untreated women, but higher than the controls without blood- and injection phobia ( $p < 0.001$ ), see Table 2.

**Table 2. The women’s scores on the “Injection Phobia Scale-Anxiety” before and after treatment sessions as well as during the postpartum follow-up**

	Treated women (n=30)			Untreated women (n=44)		Controls (n=70)	
	Mean	SD	p*	Mean	SD	Mean	SD
<b>First treatment</b>							
Before session	52.8	6.52	<	44.8	11.24	3.9	5.39
After session	45.0	6.26	0.001				
<b>Second treatment</b>							
Before session	42.0	6.54	<	43.5	12.27	3.1	5.53
After session	25.0	6.23	0.001				
Post partum follow-up	18.6	5.12		40.3	12.19	2.5	5.06

\* p-value for the difference before and after each treatment session.

All of the women in the CBT treatment group scored higher than or equal to 10 (i.e. had clinical symptoms of anxiety) on BAI before the first treatment session, compared with 80% (24/30) before the second session and 41% (12/29) at the postpartum follow-up.

In the untreated group with blood- and injection phobia, 19% scored higher than or equal to 10 at gestational week 25 compared to 52.2% at gestational week 36 and 28.3% at the postpartum assessments. In the other control group all women scored less than 10.

In all the three groups the score on the BAI scale was significantly reduced over time, in the untreated blood- and injection phobic group ( $p=0.006$ ) and in the control group without blood- and injection phobia ( $p=0.001$ ) with the most dramatic change in the CBT treatment group ( $p<0.001$ ), even after adjustments for parity and age, see Table 3. In the control group without blood- and injection phobia the reduction of anxiety levels among nulliparas ( $p<0.001$ ) was stronger compared to multiparas ( $p=0.038$ ). The BAI scores were higher among the treated women, as compared to the other two groups of women, during both treatment sessions

( $p < 0.001$ ). However, no significant differences were evident between the two groups of phobic women at the post partum check-up.

Twenty of the 30 women in the CBT treatment group (67%) showed depressive symptoms (i.e. scored higher than or equal to 10 on the EPDS) before the first treatment, compared with 7 women (23%) before the second session and 3 women (10%) at the postpartum follow-up.

In the untreated group of women with blood- and injection phobia 17% scored higher than or equal to 10 at gestational week 25 on the EPDS compared with 46% at gestational week 36 and 17% at the postpartum assessments. In the other control group all women scored less than 10 on all occasions. In the CBT treatment group a reduction in the EPDS score was observed over time ( $p<0.001$ ), especially among nulliparas, even after adjustments for age. No change was found in the untreated group of women with blood- and injection phobia ( $p=0.408$ ) or in the other control group ( $p=0.606$ ) see table 3. The EPDS scores were higher among the treated women, as compared to the other two groups of women, during the first treatment

session ( $p < 0.001$ ). However, no significant differences were evident between the two groups of phobic women at the second treatment session or at the postpartum check-up.

**Table 3. BAI and EPDS scores on the three different occasions for each group of women, respectively**

	First treatment session		Second treatment session		Post partum follow-up	
	Mean	SD	Mean	SD	Mean	SD
<b>Score on the BAI</b>						
Treated (n = 29)	22.2	6.41	16.3	6.10	9.9	4.60
Untreated (n = 44)	10.6	7.29	12.1	9.39	8.7	9.22
Controls (n = 70)	2.9	3.37	4.5	5.59	2.5	3.35
<b>Score on the EPDS</b>						
Treated (n = 30)	10.3	3.13	7.8	2.61	7.2	2.21
Untreated (n = 44)	8.4	5.10	9.1	5.85	7.5	5.57
Controls (n = 70)	3.9	3.01	3.8	3.70	3.6	3.65

The repeated measures ANOVA with baseline measurements of IPSA to account for regression to the mean did not change any of the presented results. The analyses were performed for the two groups, treated and untreated women, as well as for all three groups. In both cases, the group assignment (i.e. CBT treated, untreated, and controls) was found to have a significant effect as well as the interaction between time of assessment and group.

The reason for significantly higher scores on the IPSA and EPDS in the CBT treatment group compared with the untreated phobic women at the first assessment could partly be explained by the fact that the CBT treatment group knew that they were soon to be exposed to a phobic situation. One could assume the same explanation for the higher score on the BAI in the CBT group compared with the untreated group at both the first and second treatment session.

However, since the participants were not randomized to a treatment/control group there might be a systematic difference between the groups that accounts for the baseline measures.

In the postpartum follow-up no difference between the CBT treatment group and the untreated phobic group was found regarding symptoms of anxiety or depression, probably because no

specific treatment for these two conditions was given. The reasons for the successful outcome of the CBT group treatment are probably four-fold: all participants in the group were highly motivated, they were all pregnant with an upcoming delivery in the near future, they all had the same type of phobias, and the exposures to the phobic situations were extensive. The results show that a two-session CBT group for pregnant women with blood- and injection phobia is valuable and gives stable results up to at least 3 months after delivery. It also seems to reduce anxiety and depressive symptoms during pregnancy, which is beneficial for both mother and fetus/neonate. To minimize phobic symptoms, depression and anxiety in pregnant women with blood- and injection phobia this method could be applied.

### **Obstetric and perinatal outcomes among women with blood- and injection phobia during pregnancy (Study III)**

Women with blood- and injection phobia were over-represented in the lower socioeconomic groups ( $p < 0.001$ ) and obesity was also more common among the index women compared with the control women ( $p < 0.001$ ). Smoking in early pregnancy was more common among women with blood- and injection phobia ( $p = 0.001$ ) and this relationship was still evident after adjusting for sociodemographic variables and a history of psychiatric disorders ( $p = 0.031$ ). Multiparas with blood- and injection phobia had chronic medical diseases more often than multiparas without blood- and injection phobia ( $p = 0.019$ ). This association between having an anxiety disorder and a physical disorder has previously been reported in the literature (Sareen et al. 2005, Kose & Mandiracioglu 2007).

Fear of childbirth was significantly more frequent among women with blood- and injection phobia ( $p < 0.001$ ) and was still evident after adjustment ( $p = 0.001$ ). The multiparas with blood- and injection phobia also had a history of having had more induced abortions than the control women ( $p = 0.007$ ). This might be explained by fear of childbirth or a previous delivery experience that could have reinforced the blood- and injection phobia or even led to a

development of the phobia. The phobic women's less privileged socioeconomic background could also be of importance when they face an unwanted pregnancy.

The women with blood- and injection phobia were more often delivered with an elective caesarean section ( $p=0.032$ ). This difference remained in the multiple logistic regression analyses ( $p=0.007$ ). Among multiparas women, 15 % of those with blood- and injection phobia vs. 6 % in the control group were delivered by means of an elective cesarean section and the corresponding figures among nulliparas women were 4 % versus 2 %. The indications for the elective cesarean sections among the phobic women were registered in the medical records as "fear of childbirth" (6 out of 10), breech presentation (2 out of 10) and previous fourth-degree perineal tear (2 out of 10). In the control group, none of the women were delivered by cesarean section because of fear of childbirth. The high frequency of fear of childbirth partly explains the higher rate of elective cesarean section for the index women. Elective cesareans are more common among multiparas women compared to the women who gave birth to their first child, the reason for that difference might be due to the fact that those phobic women who already had experienced a delivery refused to go through the same procedure once more because of a negative experience; the phobia could also provoke more anxiety and even panic attacks in these women facing a second delivery.

The decision to have an elective cesarean section is based on more than medical factors alone; factors such as local traditions and women's opinions and requests might play an important role. All these considerations can limit the implications of applying these results outside of Sweden.

In a comparison of the results from the BAI conducted in gestational week 25, the women with blood- and injection phobia ( $n=74$ , mean=10.06, SD 7.2) scored higher than the control group ( $n=145$ , mean=7.32, SD 8.87),  $p<0.001$ . This finding strengthens the line of reasoning

that these women suffer from more anxiety than the women without blood- and injection phobia.

After adjusting for sociodemographic variables, smoking and a history of psychiatric disorders, complications like preeclampsia ( $p=0.008$ ), premature contractions ( $p=0.035$ ) and premature delivery ( $p=0.047$ ) were more common among the women in the index group. Children of mothers with blood- and injection phobia had a higher occurrence of neonatal morbidity ( $p=0.002$ ), were more often born SGA ( $p=0.044$ ) and had a longer postnatal hospital stay ( $p<0.001$ ). The findings of a higher rate of premature delivery and giving birth to a baby small for gestational age among the phobic women adds to previous findings that high degree of stress and anxiety during pregnancy might have an impact on gestational length and result in premature birth and low birth weight (Federenko& Wadhwa 2004, Diego et al. 2006). Crandon found that there was an association between high anxiety in the third trimester and preeclampsia (Crandon 1979) and Kurki et al. reported that anxiety in early pregnancy were associated with risk for subsequent preeclampsia (OR3.2 CI 1.7-7.4) (Kurki et al. 2000).

In study III the absolute numbers for preeclampsia, preterm deliveries and SGA babies was under 10 in both groups and in the statistical analysis these above mentioned variables comes with broad confidence intervals which makes the true clinical importance of this finding hard to interpret. Further and larger studies are therefore needed to confirm our results.

The longer postnatal hospital stay in the index group, even after controlling for the higher rate of elective cesarean section, might be explained by the higher rate of complications such as preeclampsia or neonatal morbidity.

## Salivary cortisol in pregnant women suffering from blood- and injection phobia

### (Study IV)

Of the possible 110 women with blood- and injection phobia and the 110 women acting as controls, 73 respectively 53 individuals contributed with at least one sample blood and /or saliva. The individuals in the study population who had both morning and evening cortisol values either in one or both weeks were included in the analysis of salivary cortisol, see Table 4.

**Table 4. Maternal diurnal salivary cortisol levels (08am 3.5-27 nmol/L 10 pm <6.0 nmol/L in a non pregnant population)**

	Gestational week		Pregnant women with blood- and injection phobia			Healthy pregnant controls			
	Morning (M)	Evening (E)	N	25 <sup>th</sup>	Median	75 <sup>th</sup>	N	25 <sup>th</sup>	Median
25M	65	65	9.5	12.7	16.6	37	10.3	12.6	15.4
25E	65	65	2.0	2.9	3.9	35	1.7	2.6	3.2
36M	42	42	10.8	13.8	16.9	21	9.5	13.8	16.3
36E	43	43	3.1	4.0	5.4	21	3.0	3.9	5.0

In a repeated measurement ANOVA with cortisol levels at the different occasions as within-subject and age, parity, gestational week and phobic status as between-subject the women with blood- and injection phobia had higher levels of cortisol compared to the healthy controls ( $F= 6.25$   $df=1$   $p=0.014$ ). If smoking was included as a between-subject variable, the effect remained ( $F= 6.26$   $df=1$   $p=0.013$ ). This supports previous research concerning the relationship between anxiety/stress and cortisol and has an important clinical implication as these patients are relatively common at the antenatal care clinics. Elevated levels of cortisol due to stress and anxiety tend to alter the obstetric and neonatal outcome with premature labor, shortened pregnancy length, low-birth weight and impaired fetal brain development as a consequence (Wadhwa et al. 1993, Copper et al. 1996, Weinstock 2005, Field et al. 2006).

As expected this ANOVA also showed that the cortisol levels in the whole study population in gestational week 36 (Mean=9.1 SD=5.9) were higher compared to gestational week 25 (Mean=8.3 SD=6.6)  $F= 7.27$   $df=1$   $p=0.008$ . The expected diurnal decline in salivary cortisol was observed in both groups ( $F=60.48$   $df=1$   $p<0.000$ ).

Analysis of the interaction of cortisol levels and week ( $F=0.21$   $df=1$   $p=0.65$ ), parity ( $F=0.80$   $df=1$   $p=0.37$ ) and age ( $F=2.30$   $df=2$   $p=0.10$ ) showed no differences between the women with blood- and injection phobia and the controls. Studies of samples from non-pregnant women have shown afternoon cortisol levels to be the most susceptible parameter to the influence of psychological stress (Grossi et al. 2001, Powell et al. 2002). This was not confirmed in this study indicating that pregnancy-induced resetting of the HPA axis blurs the relation between stress and cortisol levels in the evening. The pregnant woman's HPA- axis becomes hypo-responsive to stress as gestation progresses and previous research has shown that maternal psychological functions only marginally impact the diurnal rhythm of cortisol in late pregnancy (Schulte et al. 1990, Petraglia et al. 2001, Kammerer et al. 2002, Urizar et al. 2004). This was also supported in this study.

It has been suggested in some studies that nulliparas have lower waking cortisol levels compared to multiparous women and that the midday cortisol levels are higher compared to multiparous women (Vleugels et al. 1986, Rasheed 1993, Jones et al. 2006). On the other hand Goedhart et al. have shown that women with higher age and parity have lower maternal cortisol levels in the morning, but this study was performed in the first trimester (Goedhart et al. 2010). No interactions were found in this study concerning cortisol levels, age and parity. Several studies on stress and anxiety during pregnancy has described higher plasma CRH, ACTH and cortisol concentrations particular if the stress was of chronic rather than episodic nature (Demyttenaere et al. 1989, Wadhwa et al. 1996, Hobel & Culhane 1999). Gestational stress does not only activate the maternal HPA axis but can also cause an increase in the

release of CRH from the placenta by catecholamines and cortisol (Petraglia et al.1996).

Another study by Petraglia et al. found no relationship between psychosocial stress and CRH in gestational week 28 (Petraglia et al. 2001). On the other hand; Sarkar et al showed that maternal state anxiety in women awaiting amniocentesis is positively correlated with plasma cortisol independent of gestation and time of collection (Sarkar et al. 2006). One could assume that the levels of CRH, ACTH and serum cortisol would have been higher among the pregnant women with blood- and injection phobia comparing to the pregnant controls but no such a differences were found.

The mean salivary cortisol levels in the study population were similar to those reported by others for women in their 36th week of pregnancy (Allolio et al. 1990, Meulenberg & Hofman 1990, Kivlighan et al. 2008) and approximately 1.5 times higher than mean values reported for non-pregnant controls. These observations confirm that women in this sample displayed the moderate elevations in salivary cortisol normal for late pregnancy.

The support for an association between placental weight and birth weight is well-recognized in the literature (Jansson & Powell 2007) but Kivlighan et al. also reports an inverse association between morning cortisol levels, placental weight and birth weight (Kivlighan et al. 2008).

That finding could not be confirmed in the study as no correlation where found between morning salivary cortisol levels and birth weight (week 25  $r = -0.024$   $p = 0.82$  week 36  $r = -0.031$   $p = 0.81$ ), this is in line with a study by Goedhart (Goedhart et al. 2010). Earlier clinical and experimental studies have shown the detrimental effects of conditions associated with increasing cortisol concentrations in pregnancy. The finding in this study indicates that untreated blood- and injection phobia during pregnancy increases cortisol concentrations.

## Methodological considerations

*Study I* was designed to investigate the prevalence of blood- and injection phobia in a pregnant population, the study participants were selected from the antenatal care clinics in Kalmar, Västervik and Linköping. Almost 100% of the pregnant population in Sweden attends one of the antenatal care clinics, so there is a good chance of reaching the whole pregnant population.

The women invited to participate in the study were consecutively included and should therefore be a representative sample of women attending these clinics. There is always a possibility that the women were not truly consecutively registered, since it is at least theoretically possible that some women were not considered or were not asked about the study. But of all the women who were asked; very few refrained from participation (4.8%). The above design was meant to obtain a broader representation of the population and in that way increase the generalizability. One should perhaps be cautious in asserting that the prevalence is the same in all of Sweden, but it is likely that it is representative of the situation in the entire country.

There is always a possibility that cases with blood- and injection phobia is missed since the whole population of pregnant women (n=1529) were not interviewed. It was not feasible, however, to interview the whole study population, instead a high-quality measuring instrument to find women with a strong likelihood of having the diagnosis was used and a diagnostic interview was performed in selected cases ( $\geq 20$  on the IPSA).

The participants in *study II* were not randomized to a treatment/control group and there is therefore a difference between the groups. This constitutes a source of systematic bias, which makes it difficult to draw conclusions when comparing the groups. A randomized clinical trial would have been the best design but since anxiety during pregnancy is thought to be a risk

factor for poor obstetric and neonatal outcome, ethical considerations prevented randomizing of the women referred to the unit for treatment.

Women with blood- and injection phobia in the treatment group scored higher on the IPSA before the first treatment session than the group of women with blood- and injection phobia in week 25 that did not receive any treatment. This could be due to the above mentioned bias but may also have occurred because they knew that they soon would be in their most anxiety-provoking situations.

To try to confirm that the actual CBT reduces the symptoms of blood- and injection phobia, depression and anxiety, one could design a study in which results from a one-session CBT program are compared with results from a two session CBT program, and perhaps even a three session CBT program to get some kind of “dose-response curve”.

All women in the three different groups are from the same geographic area and enrolled during the same time period. The untreated women with blood- and injection phobia illustrate how symptoms of the phobia itself, anxiety and depression change over time in pregnant women with blood- and injection phobia. In a comparison of the groups it is reasonable to draw the conclusion that it is the CBT that helps the women with blood- and injection phobia to improve, as is shown by a reduction in scores on the different scales, rather than these changes simply being a result of the passage of time.

There are a fairly large number of women in all three groups (the CBT treated, the women without treatment and the healthy women). To detect a difference at the 0.05 level with a power of 80% (there is a 20% risk for a Type II error) at least 16 women were needed for treatment to determine the effect size as a reduction of 25 on the IPSA score.

To evaluate the interaction of time on the CBT, a follow up 3 months after delivery was carried out and the results were stable. One should also keep the Hawthorne effect in mind

when evaluating this study. Extra attention is provided to the participants and they are strongly encouraged to continue the therapy during the study time.

The amount of health care that each woman in *study III* received could affect the obstetric and neonatal outcomes, but the women were all routinely managed at the antenatal care clinics and despite any social disadvantage, medical or psychiatric disease, the pregnancy care and surveillance were the same in the two groups. When analyzing the data both groups of women visited their midwives and obstetricians with the same frequency. The medical records from which all information is drawn may sometimes lack information, despite standardization, but this problem exists in both groups. The data were prospectively collected and later extracted from standardized medical records and not from maternal recall, which is an advantage.

However when scrutinizing the medical records it was known if the patient had blood- and injection phobia or not, which might be a bias (subjectivity of the researcher).

There were two cases of intrauterine fetal death, one in each group. These cases were excluded when analyzing data concerning premature delivery and small for gestational age.

The reason for excluding the above mentioned cases was to reduce their impact on the results concerning anxiety/stress and premature delivery /SGA as they are potential confounders; these cases were considered to be outliers. The chronic medical diseases that were considered to be potential confounders were hypertension and inflammatory bowel disease. None of the women with these conditions delivered prematurely nor did they have a baby small for gestational age. Also the distribution of actual chronic medical diseases that could affect outcomes did not differ between the groups and was therefore not considered as an independent variable in the multiple regression analyses.

The group of pregnant women with blood- and injection phobia has other characteristics compared to the controls in our study. They are more obese, less well educated, smokers to a higher extent, and the multiparas have more chronic diseases. Interpretations of these results

should always be considered as observational findings, rather than findings from which conclusions can be drawn, since they were not included in our hypothesis and therefore not tested for. Because the two groups of women (blood- and injection phobia group and the control group) differ in some respects it is important to control for that in the statistical analyses. A stratified randomization to control for age and parity was done, but the problem is that it lies in the nature of the women with blood- and injection phobia to differ from the background population. One can always argue that the control group in study III is not representative for the background population – they are too healthy - and this would therefore result in a systematic bias. Maybe a better matching of the control group could have been carried out so that the only factor that differed would have been having blood- and injection phobia or not but that would hardly be feasible in a clinical setting. In the statistical analysis the important confounders that could be adjusted for were included as independent variables; age and parity (which also were stratified for), marital status, socioeconomic groups, BMI, smoking and a history of psychiatric disorders.

No power calculation was performed for the study of obstetric and neonatal outcome among the pregnant women with blood- and injection phobia since the control group is double the size compared to the index women.

The causal relationship between having blood- and injection phobia and a higher risk of obstetric and neonatal outcomes can be explained by a reasonably good theory, which strengthens the probability that the results in the study are true.

In *study IV* there are many missing samples at one or more collection points. These included failure to collect as directed which has its roots in the patient material and study design. The study encompassed three counties in Sweden in order to invite a sufficient number of patients, and covered all antenatal care clinics in three cities involving 60 midwives monitoring 1-2

patients each. Properly instructing and monitoring both midwives and patients proved to be an almost overwhelming task.

The drop-outs might differ at any point with the measured women. In the group of women with blood- and injection phobia one might reason that the women with the highest degree of fear/stress might even avoid leaving salivary cortisol samples. That would give the material some bias, but in that case it presumably would have been the highest levels of salivary cortisol that would have been left out. A power calculation was done with a significant criterion of  $\alpha = .05$  and the power of .80 (a 20% risk for a Type II error). With an effect size of .80, a population of 25 was needed. Although that number of individuals was not complete at all collection points in the control group, a difference in salivary cortisol levels between the women with blood- and injection phobia and the healthy controls was found. The number of sample when analyzing CRH, ACTH and S-cortisol could have been too small to detect a difference.

The methods that were used for analyzing salivary cortisol, CRH, ACTH and s-cortisol are in routine use for health-care purposes and have been validated according to laboratory standards. All samples were first collected and then analyzed during the same time period

## **Conclusions**

The prevalence of blood- and injection phobia among pregnant women in the southeast region of Sweden is 7%. Blood- and injection phobia during pregnancy is therefore a common health care problem that needs to be further addressed and recognized.

To increase the mental health for women suffering from blood- and injection phobia during pregnancy and to reduce symptoms of anxiety, depression and phobia, a two-session program providing CBT in group seems to be of value and produces stable results for at least 3 months after delivery.

Pregnant women with blood- and injection phobia are more likely to be delivered by elective cesarean section. The children of the mothers with blood- and injection phobia are more often diagnosed with a complication at birth compared to children of women not suffering from this specific phobia.

Untreated blood- and injection phobia during pregnancy increases salivary cortisol concentrations but do not seem to alter the diurnal pattern of cortisol. No differences were found concerning CRH, ACTH or S-cortisol between the women with blood- and injection phobia and the controls.

## **Clinical implications and Management of Patients with blood- and injection phobia**

The research idea for this thesis emerged from meetings with pregnant women suffering from blood- and injection phobia during work at the ACC. To have blood- and injection phobia is a common *clinical problem* of importance, both for the affected women but also because these women need a lot of extra time in the care giving situation.

The anxiety disorder blood- and injection phobia is not very well understood and the research on this field have not until now been done on pregnant women. It is important to *identify women with blood- and injection phobia* in order to provide an effective treatment to reduce stress and symptoms of anxiety during pregnancy. These women need extra support both during pregnancy and delivery.

It is important to take a proper medical history regarding anxiety and avoidance of injections and seeing blood but also to ask for fainting in the past. The use of *IPSA* as a screening tool before referral for a definitive diagnose and treatment could be useful. To take this problem seriously could help to reduce the occurrence of negative obstetric, neonatal and child events for the mother to be and her baby.

It is also important to recognize this problem early to facilitate future contacts with the health care. It is essential that all *personnel in the health care systems* have knowledge on how to manage these individuals. It is important to communicate empathy and respect for these patients by assuring them that they are not “wimps” or “oddballs”. Most patients believe that their phobia is all in their mind and that they would not be fearful if they were stronger or more mature. Giving the patient a name on the condition legitimatizes them and gives them a better chance to communicate with the health care system. Such approach helps them to accept their condition without embarrassment and makes them realize that they are not alone.

Shock and syncope are reduced among phobic patients by having them *lie supine* with legs elevated (if possible during pregnancy) and tense their muscles during needle procedures. This augments the central venous reservoir, increases stroke volume and helps maintain cerebral perfusion.

The use of nerve *gate-blocking methods* e.g. pinching or rubbing the area to distract the patient during a needle stick can be helpful. *Topical anesthesia* at the needle site can be used to prevent the vasovagal reaction. Premedication with oral or sublingual benzodiazepines and /or *NO2* before a needle procedure can be considered. *NO2* is available and easy to use in the delivery ward. Referral to a unit that can offer *cognitive behavioral therapy* with exposure for a long-lasting effect on the symptoms is to recommend.

## **Future Perspectives**

All data that has been collected during the study period has not yet been analyzed and remains to be processed. New questions and ideas have arisen and needs further planning.

- Women in the study population in study III have fulfilled the Temperament and Character Inventory (TCI) developed by R. Cloninger in order to investigate possible differences in personality between women with blood- and injection phobia and the control group. This results needs to be analyzed. One could for example assume high scores for women with blood- and injection phobia in the personality dimension harm avoidance.

- Blood samples were collected from the umbilical cord after delivery of the women participating in study III. A promoter polymorphism that decreases transcription of the serotonin transporter gene (5-HTTLPR) is associated with anxiety and a variation in the gene affects HPA axis activity. These samples will be analyzed in order to investigate if women with blood- and injection phobia and their children differ in that gene variation compared to healthy controls.

- It would be interesting to study the children of the study population in study III with regard to neurodevelopment and the activity in their HPA axis.

## **Swedish summary - Sammanfattning på svenska**

### *Bakgrund*

Idén till denna avhandling föddes på mödrahälsovården där mötet med gravida kvinnor som uttryckte en rädsla för blod och injektioner tycktes bli allt mer vanligt. Det kändes som om att problemet med rädsla för blod och injektioner var viktigt, dels ur ett rent humanitärt perspektiv eftersom den enskilda kvinnan lider av sin åkomma, men också då dessa kvinnor har behov av extra tid och stöd i kontakt med hälso- och sjukvården.

Blod- och injektionsfobi är en specifik fobi som tillhör gruppen ångestsjukdomar. Diagnosen baseras på kriterier fastställda av Amerikanska psykiatriförbundet i boken ”Diagnostic and Statistic Manual of Mental Disorders” (DSM 1994).

Det vanliga är att personer med blod- och injektionsfobi upplever stark oro, ångest och panikattacker om de utsätts för blodprovtagning, injektioner eller bevittnar någon annan i liknande situation. Dessa personer får kroppsliga symtom, blir bleka, svettiga och kan ibland svimma när de utsätts för sina största rädsor. Att undvika det man fruktar mest, blod och injektioner, blir omöjligt för en gravid kvinna med denna fobi då hon utsätts för kontroller, provtagningar och har en kommande förlossning framför sig.

Man vet idag att stress och ångest under graviditet är ogynnsamt både för den blivande mamman och för barnet hon väntar. Många studier beskriver ökad risk för förtidig födsel, tillväxthämning men också sämre utveckling hos barnet avseende motorik och beteende. Det finns flera sätt som stress och oro hos den blivande mamman kan överföras till barnet men den viktigaste mekanismen tycks vara via stresshormoner och då framförallt kortisol.

Då inga studier på gravida kvinnor med blod- och injektionsfobi hade gjorts var syftet med denna avhandling att försöka kartlägga hur vanligt det är med denna fobi i en gravid population och om man kan behandla blod- och injektionsfobi hos gravida kvinnor med kognitiv beteendeterapi i grupp. Forskningen syftade också till att undersöka utfallet i

samband med graviditet och förlossning och till sist se om kvinnor med blod- och injektionsfobi har högre kortisolnivåer jämfört med en gravid population utan blod- och injektionsfobi.

#### *Arbete I - Förekomst av blod- och injektionsfobi hos gravida kvinnor*

I en deskriptiv tvärsnittsstudie, för att undersöka förekomsten av blod- och injektionsfobi, tillfrågades 1606 gravida kvinnor från samtliga mödravårdscentraler i Linköping, Västervik och Kalmar om deltagande i studien. Rekryteringen ägde rum under 2005 vid första mödrahälsovårdsbesöket hos barnmorska. Sjuttiosju kvinnor (4.8%) tackade nej och önskade inte delta i studien. Sammanlagt 1529 kvinnor besvarade enkäten ”Injektionsfobi skala – ångest” (IPSA). IPSA är en enkel självskattningsskala som berör specifika frågor rörande blod- och injektionsfobi. Den består av 18 frågor där man graderar sin ångest från 0-4 (där 0 är ingen ångest och 4 är maximal ångest) i olika situationer t.ex. ”få en spruta i skinkan” eller ”få en injektion i en blodåder”. Alla kvinnor som skattade  $\geq 20$  (347st) på skalan blev telefonintervjuade av samma psykoterapeut och diagnostiserades enl DSM-kriterierna för blod- och injektionsfobi. Totalt uppfyllde 110 kvinnor kriterierna vilket innebär en förekomst av blod- och injektionsfobi hos gravida kvinnor på 7.2% (110/1529). IPSA verkar vara en lättillgänglig skala för den stora majoriteten av gravida kvinnor och kan användas som ett hjälpmedel vid misstanke om blod- och injektionsfobi. Ett tröskelvärde på 35 poäng eller mer indikerar att kvinnan kan lida av blod- och injektionsfobi.

#### *Arbete II - En öppen studie med kognitiv beteende terapi i grupp till gravida kvinnor med blod- och injektionsfobi*

I en öppen behandlingsstudie erhöll 30 kvinnor diagnostiserade med blod- och injektionsfobi kognitiv beteende terapi i grupp vid två tillfällen med fyra veckors mellanrum under sin graviditet. Första behandlingen ägde rum runt graviditetsvecka 25-30. Behandlingen var inriktad på att hantera de tankar och känslor som uppkom när deltagarna exponerades för

olika kanyler, sprutor och injektionssituationer. Före och efter varje behandlingstillfälle besvarades 4 enkäter; IPSA, ” Injektionsfobi skala – undvikande” (IPSAV), ”Beck Anxiety Inventory” (BAI) och ”Edinburgh Postnatal Depression Scale”( EPDS). Som uppföljning tre månader efter avslutad behandling fick kvinnorna återigen fylla i samma enkäter. Som jämförelsegrupp rekryterades 46 gravida kvinnor med blod- och injektionsfobi och 70 friska gravida kvinnor från prevalensstudien (arbete I). Dessa kvinnor erhöll ingen egentlig behandling mot sin fobi utan kontrollerades på sedvanligt sätt hos sin barnmorska på mödrahälsovården. Samtliga kvinnor i kontroll grupperna besvarade 3 enkäter; IPSA, BAI och EPDS i graviditetsvecka 25, 36 och 6-8 veckor efter sin förlossning.

I behandlingsgruppen förbättrades poängen på IPSA och IPSAV under behandlingstiden och vid uppföljningen tre månader efter förlossningen. Poängen på de båda skalorna förbättrades också om man jämförde resultaten före och efter varje behandlingstillfälle. Vid uppföljningen efter förlossningen visade resultaten att de behandlade fobikerna hade lägre poäng jämfört med de ickebehandlade fobikerna men högre jämfört med de friska kontrollerna.

Kvinnorna med blod- och injektionsfobi förbättrades också avseende symtom på depression och ångest under sin graviditet med lägre poäng på EPDS respektive BAI skalan men vid enkätuppföljningen efter förlossningen fanns ingen skillnad mellan grupperna avseende dessa symtom.

### *Arbete III - Graviditets- och förlossningsutfall hos gravida kvinnor med blod- och injektionsfobi*

De 110 gravida kvinnor som diagnostiserats med blod- och injektionsfobi i arbete I matchades mot 220 gravida kvinnor utan blod- och injektionsfobi avseende ålder och om de var förstföderskor eller ej. Syftet med studien var att ta reda på om kvinnor med blod- och injektionsfobi pga. den ångest- och stressfyllda situation som graviditeten betyder för dem, har ett sämre graviditets- och förlossningsutfall jämfört med gravida kvinnor utan denna

specifika fobi. Ur de standardiserade mödrahälsovårdsjournalerna hämtades uppgifter avseende; ålder, antal födselar, civilstånd, yrke, body mass index, rökning, drogmissbruk, antal inducerade aborter, antal missfall, antal extrauterina graviditeter, psykiatrisk sjukdom (depression, ångest, ätstörning, psykossjukdom), förlossningsrädsla, tidigare obstetrisk historia, nuvarande kronisk sjukdom (astma med kontinuerlig behandling, epilepsi, hypertention, reumatism, diabetes, inflammatorisk tarmsjukdom), läkemedelsanvändning, antal besök på mödrahälsovården hos läkare resp. barnmorska, graviditetskomplikationer (havandeskapsförgiftning, illamående, ryggvärk, vaginala blödningar, förvärrar), sjukskrivning under graviditet samt data rörande barnet och förlossningen.

I den multivariata statistiska beräkningen visade det sig att gravida kvinnor med blod- och injektionsfobi har större risk för att bli förlösta med planerat kejsarsnitt samt att barnen till kvinnorna med blod- och injektionsfobi uppvisade en större grad av sjuklighet i samband med födelsen.

#### *Arbete IV – Salivkortisol hos gravida kvinnor med blod- och injektionsfobi*

110 gravida kvinnor med blod- och injektionsfobi och 110 friska gravida kvinnor tillfrågades om att lämna salivprov för analys av salivkortisol på morgonen och kvällen i graviditetsvecka 25 och 36. I samband med den rutinmässiga blodprovstagningen i graviditetsvecka 25, då man regelmässigt tar blodprov på den gravida kvinnan för blodgruppsbestämning, togs extra blod för analys av stresshormonerna corticotrophin releasing hormon (CRH), adrenocorticotropin hormon (ACTH) och kortisol i serum.

I saliv återfinns den obundna och därmed den biologiskt aktiva formen av kortisol. På så sätt avspeglar salivkortisol bättre än serumkortisol aktiviteten i stresssystemet. Vid analys av materialet hade de gravida kvinnorna med blod- och injektionsfobi högre nivåer av kortisol i saliv jämfört med de friska gravida kvinnorna. Det fanns ingen skillnad i salivkortisolnivåerna mellan grupperna avseende ålder, hur många barn man fött eller tidpunkt på dygnet. Avseende

stresshormonerna i serum (CRH, ACTH och kortisol) kunde ingen skillnad mellan grupperna konstateras.

Från andra studier vet vi att det är ogynnsamt för den gravida kvinnan och barnet i magen att utsättas för höga kortisolnivåer då risken för bli för tidig födelse och tillväxthämning är större.

### *Konklusion*

Blod och injektionsfobi i en gravid population är ett vanligt fenomen med en förekomst på 7 %.

Kognitiv beteendeterapi i grupp för att behandla blod- och injektions fobi hos gravida kvinnor är en möjlig terapiform och ger ett bra behandlingsresultat med bestående effekt upp till 3 månader efter förlossningen.

Gravida kvinnor med blod- och injektionsfobi löper en större risk för ett sämre graviditets- och förlossningsutfall.

Gravida kvinnor med blod- och injektionsfobi har högre nivåer av salivkortisol jämfört med friska gravida kvinnor.



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## **Appendices**

Appendix 1. “Injection Phobia Scale -Anxiety” (IPSA)

Appendix 2. “Injection Phobia Scale -Avoidance” (IPSAV)

## Appendix 1

Läs igenom varje fråga och bedöm på en skala från 0 (ingen ångest)- 4 (max ångest) hur mycket ångest du skulle uppleva om du befann dig i situationen.

	Å n g e s t			
1. Lämna ett blodprov genom stick i fingret.....0	1	2	3	4
2. Få en spruta i överarmen..... 0	1	2	3	4
3. Se en bild på en spruta med nål.....0	1	2	3	4
4. Känna sjukhuslukt.....0	1	2	3	4
5. Få en bedövningsspruta hos tandläkaren..... 0	1	2	3	4
6. Lämna ett venprov (ta sänkan)..... 0	1	2	3	4
7. Se en annan person lämna venprov i verkligheten..... 0	1	2	3	4
8. Få en spruta i skinkan..... 0	1	2	3	4
9. Se en bild på en person som får en spruta.....0	1	2	3	4
10. Höra någon berätta om injektioner..... 0	1	2	3	4
11. Titta och ta på vener i armvecket..... 0	1	2	3	4
12. Se en film med en person som får en spruta..... 0	1	2	3	4
13. Se en annan person få en spruta i verkligheten..... 0	1	2	3	4
14. Se en person i sjuksköterskekläder.....0	1	2	3	4
15. Ta håll i öronen..... 0	1	2	3	4
16. Få en vaccination..... 0	1	2	3	4
17. Få en injektion i en blodåder..... 0	1	2	3	4
18. Se en annan person lämna blodprov i verkligheten..... 0	1	2	3	4

## Appendix 2

Läs igenom varje fråga och bedöm på en skala från 0-2 hur mycket du brukar undvika situationen.

	Undviker		
	aldrig	ibland	alltid
1. Lämna ett blodprov genom stick i fingret.....	0	1	2
2. Få en spruta i överarmen.....	0	1	2
3. Se en bild på en spruta med nål.....	0	1	2
4. Känna sjukhuslukt.....	0	1	2
5. Få en bedövningsspruta hos tandläkaren.....	0	1	2
6. Lämna ett venprov (ta sänkan).....	0	1	2
7. Se en annan person lämna venprov i verkligheten.....	0	1	2
8. Få en spruta i skinkan.....	0	1	2
9. Se en bild på en person som får en spruta.....	0	1	2
10. Höra någon berätta om injektioner.....	0	1	2
11. Titta och ta på vener i armvecket.....	0	1	2
12. Se en film med en person som får en spruta.....	0	1	2
13. Se en annan person få en spruta i verkligheten.....	0	1	2
14. Se en person i sjuksköterskekläder.....	0	1	2
15. Ta håll i öronen.....	0	1	2
16. Få en vaccination.....	0	1	2
17. Få en injektion i en blodåder.....	0	1	2
18. Se en annan person lämna blodprov i verkligheten.....	0	1	2