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CONSEQUENCES OF RAPE: INJURIES, POSTTRAUMATIC STRESS, AND NEUROENDOCRINOLOGICAL CHANGES

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Consequences of Rape: Injuries, Posttraumatic Stress, and Neuroendocrinological Changes

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To all the women who participated in the studies in spite of the
traumatic experience they had just been exposed to

ABSTRACT

Each year, approximately 3-4% of the Swedish female population experiences a sexual assault. Only a small percentage of these women will report the assault to the police, and even fewer will seek medical help. This thesis is based on studies on women seeking medical help at the Emergency Clinic for Raped Women at Stockholm South General Hospital, in Stockholm, Sweden, after having been sexually assaulted. The aim of the thesis was to improve the knowledge about women seeking medical help after rape, explore risk factors for the development of PTSD, and explore the neuroendocrinological changes in PTSD patients.

Study I compared intimate partner assaults to assaults by other known assailants and to assaults by strangers in terms of the use of physical violence and risk of sustaining injuries. A retrospective review of patient files and forensic examinations from the acute visits of 690 consecutive women showed that women who were sexually assaulted by their intimate partners more frequently reported physical violence (OR 4.1) than women assaulted by strangers (OR = 2.0) and acquaintances (OR = 1.0). Extragenital injuries showed a trend towards being more frequently seen after intimate partner assaults as compared to the two other groups. Genital injury prevalence was not related to the victim-assailant relationship.

Study II aimed to explore the prevalence of PTSD six months after sexual assault and explore the potential risk factors for the development of PTSD. Two hundred and one women were assessed at baseline regarding mental health using self-rating questionnaires and followed up after six months with questionnaires, as well as a clinical interview for PTSD diagnosis. Thirty-nine percent of the women had developed PTSD at the six-month assessment, and 47% suffered from moderate or severe depression. The major risk factors for PTSD were having been assaulted by multiple assailants, suffering from acute stress disorder shortly after the assault, having been exposed to several acts during the assault, having been injured, having co-morbid depression, and having a history of two or more earlier traumas.

Study III was conducted in order to adjust the concentrations of various endogenous steroids in Study IV for possible diurnal variation. Blood samples were taken every 4th hour during a 24-hour period in 10 premenopausal women in the follicular phase of the menstrual cycle and assessed regarding their concentrations of allopregnanolone, cortisol, cortisone, 11-deoxycortisol, progesterone, 17OH-progesterone, pregnenolone, 17OH-pregnenolone, DHEA, androstenedione, testosterone, estrone, and estradiol. The results suggested that all steroids, apart from the estrogens, had a diurnal variation in the follicular phase. All steroids, apart from allopregnanolone, had a diurnal curve similar to that of cortisol (i.e., with a peak in the morning just after awakening and the lowest concentrations during the night). Allopregnanolone had a less steep curve, with high concentrations throughout the day and a peak around noon.

Study IV assessed whether concentrations of the same endogenous steroids measured in Study III in the immediate aftermath of rape could predict the development of PTSD and depression. The study design was the same as in Study II but with a blood sample added at the acute visit. Low concentrations of cortisol and the $\Delta 5$ steroids (pregnenolone, 17OH-pregnenolone, and DHEA) shortly after rape were associated with a history of earlier traumatization, and low allopregnanolone concentrations shortly after rape were associated with a psychiatric treatment history. However, there was no association between any of the steroids and pre-existing PTSD or the development of PTSD after six months. Results also suggested an association between menstrual cycle phase and the HPA axis.

Study V assessed the sensitivity of the GABA-A receptor in 10 drug naïve patients with PTSD as compared to 10 healthy controls measured with saccadic eye velocity (SEV) and subjective ratings of sedation. SEV was measured after injections of the positive GABA-A receptor modulator allopregnanolone, the GABA-A receptor agonist diazepam and the GABA-A receptor antagonist flumazenil, each on separate occasions, and during the follicular phase of the menstrual cycle. The results showed that the PTSD patients were less sensitive to GABA-A-receptor-active substances, probably due to an acquired chronic tolerance to these substances caused by chronic exposure of neuroactive steroids over a long period of time.

Conclusions: Sexual assaults by intimate partners are more violent and result in injuries just as often as assaults by strangers. However, physical injuries after sexual assaults are generally few and genital injuries minor. PTSD and depression, on the other hand, are common after sexual assaults, and an increased risk of developing PTSD is caused by a combination of victim vulnerability and the extent and nature of the current assault. Concentrations of endogenous steroids in the immediate aftermath of sexual assault (after having been adjusted for their diurnal variation) cannot predict the development of PTSD. However, low concentrations of several steroids are seen in previously traumatized women and in women with a psychiatric morbidity, two factors that have both been shown to increase the risk of developing PTSD. Finally, as a consequence of the reduced sensitivity of the GABA-A receptor in PTSD patients, the use of GABA-A-receptor-active compounds, such as sleeping pills, will be less useful for this group of patients.

LIST OF PUBLICATIONS

- I. Möller AS, Bäckström T, Söndergaard HP, Helström L. Patterns of injury and reported violence depending on relationship to assailant in female Swedish sexual assault victims.
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Manuscript
- IV. Tiihonen Möller A, Bäckström T, Söndergaard HP, Kushnir MM, Bergquist J, Helström L. Endogenous steroids in the immediate aftermath of rape as predictors for the development of PTSD and depression.
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- V. Tiihonen Möller A, Bäckström T, Nyberg S, Söndergaard HP, Helström L. Women with PTSD have changed sensitivity to GABA-A receptor active substances.
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LIST OF ABBREVIATIONS

PTSD	Posttraumatic Stress Disorder
ASD	Acute Stress Disorder
WHO	World Health Organization
IPV	Intimate Partner Violence
IPSV	Intimate Partner Sexual Violence
DSM	Diagnostic and Statistical Manual of Mental Disorders
SCID	Structured Clinical Interview according to DSM
SNS	Sympathetic Nervous System
CNS	Central Nervous System
HPA	Hypothalamus-Pituitary-Adrenal
CRH	Corticotropin-Releasing Hormone
ACTH	Adrenocorticotrophic Hormone
GABA	Gamma-Aminobutyric Acid
SEV	Saccadic Eye Velocity
VAS	Visual Analogue Scale
RIA	Radioimmunoassay
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
DHEA (S)	Dehydroepiandrosterone (Sulfate)
OR	Odds Ratio
CI	Confidence Interval
CBT	Cognitive Behavioral Therapy
EMDR	Eye Movement Desensitization and Reprocessing therapy

1 INTRODUCTION

In October 2005, all sexual assault victim care in Stockholm was centralized to the Emergency Clinic for Raped Women (AVK) at Stockholm South General Hospital. The clinic started taking care of almost all sexually assaulted women who sought help within one month of the assault and offered not only medical care and forensic examinations but also psychological help and support. The clinic garnered a large amount of attention in the media and soon became well-known to the population in Stockholm. Since then, the number of help-seeking women at the clinic has been quite stable, with about 600-700 acute visits each year. This makes the clinic the largest sexual assault center (SAC) in Europe and the possibility to perform research after sexual assaults is enormous.

Soon after its opening, Lotti Helström, senior consultant and head of AVK, initiated clinical research at the clinic. In 2007, we received our first ethical permit, and I started gathering data for a study that was originally planned as a project within my residence training to become a specialist in Obstetrics and Gynecology, but eventually, it became the first study in this thesis. We established contact with the Crisis and Trauma Center and psychiatrist Hans Peter Söndergaard. Söndergaard had broad experience from working with traumatized patients and performing research on posttraumatic stress. A project to assess mental health in our patients after rape was therefore initiated in 2008. In 2010, I registered for PhD studies and Lotti Helström became my main supervisor. Söndergaard's earlier research on patients with posttraumatic stress disorder had also suggested interesting alterations in stress steroids. Therefore, we initiated collaboration with Professor Torbjörn Bäckström at the Umeå Neurosteroid Research Center, Professor Jonas Bergquist at Uppsala University, and Mark Kushnir at the ARUP laboratory in Utah. We started taking blood samples from all women immediately after they presented at the clinic in order to see if concentrations of various stress steroids could predict the development of PTSD. Furthermore, the majority of Professor Bäckström's earlier research had been on GABA-A receptor function in various diseases. As altered receptor sensitivity had been seen in patients with anxiety and work-related stress, we began to question whether changes could also be seen in patients with PTSD after rape.

In sum, this thesis is a mixture of gynecology, forensic medicine, psychiatry, and endocrinology, with sexual assaults being the connecting factor.

2 BACKGROUND

2.1 SEXUAL ASSAULT

2.1.1 Definitions

In 2002, the World Health Organization (WHO) released the first *Report on violence and Health* [1]. In this report, violence was divided into three categories: self-inflicted, interpersonal, and collective. Sexual violence is a type of interpersonal violence and is defined as “any sexual act, attempts to obtain a sexual act, or acts to traffic for sexual purposes, directed against a person’s sexuality using coercion, harassment or advances made by any person regardless of their relationship to the victim, in any setting, including but not limited to home and work” [1,2]. This definition encompasses a broad spectrum of activities, ranging from violent forcible sex to sexual harassment.

Sexual violence includes rape, which has a more narrow definition. Rape is generally defined as physically forced or otherwise coerced penetration of the vulva or anus using the penis, other body parts, or an object. Attempts to do so are defined as “attempted rape”. The term “sexual assault” is often defined identical as rape.

According to the Swedish Penal Code, a rape or a sexual assault is defined as sexual intercourse or any kind of sexual act forced by violence, any sexual intercourse or sexual act with someone under the age of 15 years of age, and sexual intercourse or a sexual act with someone who is unable to consent [3].

For the purpose of this thesis, I used the definition of rape found in the Swedish Penal Code. I did not make any distinction between the terms “rape” and “sexual assault”, and both terms are used interchangeably.

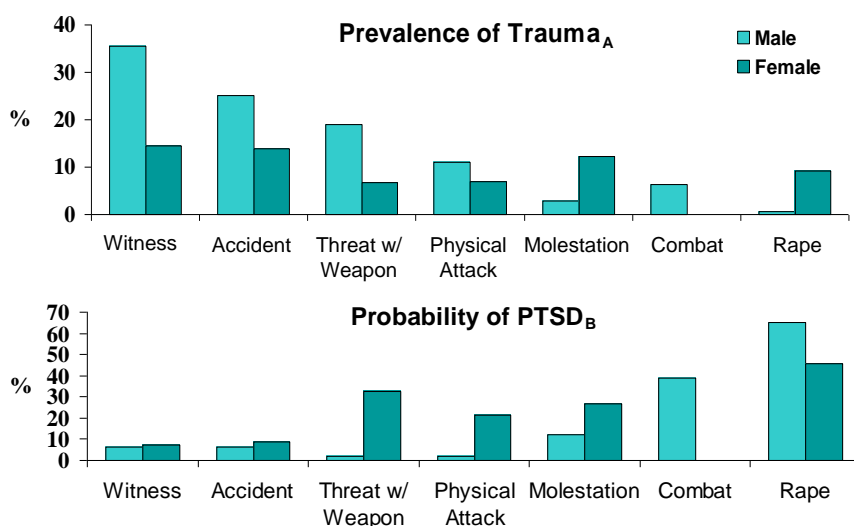
2.1.2 Prevalence

Sexual assaults are a serious public health problem all over the world. Comparing the prevalence between countries is problematic because of widespread underreporting, unclear definitions of sexual assaults in different laws, and varying survey methodologies. A recently published literature review reported that the worldwide prevalence of non-partner sexual violence after the age of 15 years was 7%, varying between 10-20% in sub-Saharan Africa, 7-10% in Europe, 5-13% in North America, and 3-6% in Asia [4]. However, the authors concluded that even though the results may reflect some true variations, differences could be caused by different levels of disclosure; the prevalence in some regions was based on very few observations, and several of the regions were affected by conflicts (making the execution of population-based surveys even harder). One large issue was the fact that the majority of the reviewed studies focused on intimate partner violence and that the questions about non-partner sexual violence were too broad or insufficient. It has been shown that majority of all sexual assaults occur within an intimate partner relationship. According to the WHO’s study of 10 middle-and low-income countries, 6-59% of the women reported ever having

experienced a sexual assault by an intimate partner, and 0.3-12% reported being assaulted by a non-partner [5]. The prevalence was higher in the poorest countries and in the rural areas as compared to the urban areas.

In the US, the National Intimate Partner and Sexual Violence Survey (NISVS) found that 18% of the women reported ever having experienced a sexual assault [6]. Furthermore, in the large National Co-morbidity Study, Kessler and colleagues [7] reported that the trauma experienced by the largest proportion of people was witnessing someone being badly injured or killed, both for men and women. However the risk of a women being raped was almost as high (Figure 1.A)

Figure 1. Prevalence of trauma and probability of PTSD



^A Kessler R et al. J Clin Psychiatry. 2000;61(Suppl 5):4-14.

^B Kessler R et al. Arch Gen Psychiatry. 1995;52:1048-1060.

In Sweden, the number of sexual assaults reported to the Swedish police has increased dramatically, more than tripling during the past two decades [8]. Recently, a population-based report from Sweden was published [9]. In this report, 10,000 women and 10,000 men between the age of 17 and 74 years were asked to complete a questionnaire regarding their experiences of sexual, physical and psychological violence during childhood, adolescence, and adulthood. According to this report, 20% of the women and 5% of the men reported ever having been sexually assaulted. During the year studied (spring 2011-spring 2012), 3.4% of the women and 0.9% of the men had experienced a sexual assault. Less than 10% of the women and 1% of the men had sought professional help from a counselor, psychotherapist, or doctor and only 5% of the women and 1% of the men reported ever having reported a sexual assault to the police. Furthermore, both women and men who had experienced a sexual assault before the age of 18 years had a higher prevalence of sexual assaults in adulthood as compared to those who had not experienced a sexual assault before the age of 18.

2.1.3 Victim-assailant relationship

In the majority of all sexual assaults, the assailant is known to the woman [2]. This is contrary to the myth that rapes occur in dark alleys and are perpetrated by assailants unknown to the women. Even though we have now reached the 21st century, myths about “a typical rape” remain [10]. Although there is no legal distinction between acquaintance and stranger rapes, there appear to be differences in the ways in which the cases are processed in court. If the victim and suspect knew each other, it is easier to believe that the sexual encounter was consensual. Research also shows that women who are sexually assaulted by a known assailant are less likely to report the assault because of their fear that the legal system will not believe them [11]. This is clearly problematic given that the vast majority of all sexual assault victims know their assailants as intimate partners and that the assaults occur in private settings [12]. The majority of studies comparing stranger assaults to known-assailant assaults have not discriminated between sexual assaults by intimate partners to other known-assailant assaults. This has often led to the misconception that all known-assailant assaults are less violent than stranger assaults. The majority of studies report that sexual assaults within a relationship most often co-occur with physical and psychological violence, thus suggesting the term “intimate partner violence” (IPV). Women who have been sexually assaulted by their partners often suffer from repetitive assaults, and physical violence is just as common as sexual assaults in these relationships [13,14]. One could therefore assume that the epidemiology of sexual assaults in intimate-partner relationships is uniquely different when compared to stranger assaults, as well as other known-assailant assaults.

2.1.4 Mental and physical health consequences

A growing number of studies have documented that sexual assaults in childhood, as well as in adulthood [9,15], are associated with a large array of both immediate and long-term consequences. The experience of a sexual assault correlates with several serious mental health problems, including anxiety disorders, depression, sleep disturbances, eating disorders, substance abuse, re-victimization, deliberate self-harm, and suicidal thoughts or attempts [16,17,18,19]. Although posttraumatic stress disorder (PTSD) is the most commonly researched trauma disorder (described in Section 2.2), major depression occurs at similar rates after trauma and frequently co-occurs with both PTSD and substance abuse [20,21,22].

Furthermore, sexual problems are commonly associated with a history of sexual assault [23]. Preliminary results from a study we conducted assessing sexual functioning after sexual assaults (not included in this thesis) were presented at the annual conference for the Nordic Association for Clinical Sexology, 2014, in Malmö, Sweden [24]. Using the Swedish version of the Female Sexual Function Index (FSFI) [25], we explored sexual function six months after sexual assaults. The FSFI has 19 questions regarding desire, arousal, lubrication, orgasm, satisfaction, and pain. For each question, we also added a question in which the subjects were asked to grade their function before the assault. Results suggested that 71% of the 79 completers at the six-month follow-up reported impaired sexual function as compared to before the assault. However, interestingly, we saw that 20% actually reported an

improvement, and 9% reported no difference. Impaired sexual functioning was associated with having a PTSD diagnosis, co-morbid depression, being un-employed, and having a psychiatric treatment history. The factor with the strongest association with improved sexual function was having a partner at the time of the assault.

Sexual assault is also associated with physical health problems. Apart from sustaining general body trauma and anogenital injuries (discussed in a separate section), sexually transmitted infections (for updated summary of studies, see [26]), unwanted pregnancy [27], and preterm birth [28] have been reported. Furthermore, sexual assaults, just like IPV, have negative long-term impacts on women's physical health. Various kinds of chronic pain (e.g., headache and musculoskeletal pain) are common in women with a history of sexual assault. Studies have also reported an association with chronic pelvic pain and pelvic floor dysfunction [29,30,31]. In a large Nordic cross-sectional study of women visiting gynecology clinics in Norway, Denmark, Finland, Iceland, and Sweden, the life-time prevalence of sexual abuse was 19-37% [32]. The authors concluded that sexual and physical abuse was associated with gynecological problems but that very few of the victims were identified by their gynecologists. As a consequence of this, women with a history of sexual assault often had increased healthcare consumption. Finally, associations with a number of adverse conditions involving the cardiovascular, gastrointestinal, endocrine and immune systems have been found [31]. These associations have not been fully explained, but one hypothesis is that stress-related endocrine and immune reactions serve as a pathway between assaults and cardiovascular disease.

It is beyond the scope of this thesis to review all outcomes associated with sexual assaults. Instead, I have focused on injuries and the development of PTSD after rape.

2.1.5 Injuries

Of all rapes reported to the Swedish police departments during 1995 and 2005, 60% of the cases remained unsolved, and only 12% led to prosecution [8]. The presence of anogenital injuries has been shown to be a major contributing factor in the various decision-making points from a criminal justice perspective [33]. Even though a recent study from Norway found that the documentation of injuries was not associated with charge filing [34], several studies have reported that conviction rates are higher when there is evidence of genital injuries [35,36,37]. The doctor is often asked to make a statement as to whether the intercourse was consensual or non-consensual, thereby providing support for the common misconception, both among the general public and among legal experts, that sexual assault is invariably associated with physical injuries. Studies show that consensual as well as non-consensual intercourse can lead to genital injuries [38]. For example, one study [39] showed that 30% of women had genital injuries after consensual intercourse, while 32% of women showed signs of genital injuries after non-consensual intercourse. However, in a recently published Danish case-control study [40], the results suggested that the patterns of injury differed between the consensual and non-consensual group. Even though the overall

frequency of at least one lesion was similar between the groups, victims of non-consensual intercourse more often had multiple, larger, and more complex lesions.

Studies examining genital and non-genital injuries in female rape victims have provided deviating results. The prevalence of genital injury ranges from 6% [41] to 87% [42], which may reflect the different methods of detection being used or differences in patient populations, injury definition, and the experience of the examiner. Three techniques, or combinations of these three techniques, are being used in forensic examination: visual inspection, staining techniques, and colposcopy. The colposcopic technique with photographic capture has become a standard for evidence collection in sexual assault forensic examination. However, it is not routinely performed in all sexual assault centers [43]. Examiners using colposcopy have found an anogenital injury prevalence as high as 64% - 87% [42,44,45]. However, the majority of published studies show a lower injury prevalence that more frequently ranges between 20- 40%, that injuries are small, and most often located in the posterior forchette of the vaginal opening [46,47,48]. Non-genital injuries have been found to be almost twice as common as genital injuries after sexual assaults and are most often seen as bruises on arms and legs. [46,47]. Furthermore, non-genital injury prevalence has been found to be higher when there are reports of alcohol intake prior to the assault, when the assault occurs outdoor, and when the victim is older [48].

The timeframe is crucial because genital injuries tend to disappear quickly. Maguire and colleagues [48] found that women examined within 72 hours of rape had significantly more injuries than those examined after 72 hours (40% vs. 7%, OR 3.7, 95% CI [1.05-13.09], $p < 0.05$). After consensual intercourse, Astrup and colleagues [49] found that the median survival time for lesions was 24 hours using the naked eye, 40 hours using a colposcope, and 80 hours using toluidine blue dye.

As described earlier, studies comparing assault characteristics between various assailant groups tend to compare stranger assaults to known-assailant assaults. As we know that rapes committed within a relationship represent a special and uniquely different kind of assault, they should be separated from the rest of known-assailant assaults. After having done so, studies have indicated that intimate-partner assaults involve more violence and result in injuries more often than stranger assaults [50,51].

2.2 POSTTRAUMATIC STRESS

2.2.1 Definitions

2.2.1.1 Definition of PTSD

Posttraumatic stress disorder (PTSD) is a disabling psychiatric condition that can develop in an individual who has experienced an extremely stressful or traumatic life event, such as a sexual assault. A person with PTSD suffers from constant symptoms of the trauma. Persistent memories of the trauma can be re-lived over and over again in the form of flashbacks and/or nightmares. The individual tries to avoid circumstances that remind him or her of the trauma, such as certain places, activities, or people, sometimes leading to isolation. A person with PTSD also has symptoms of increased arousal that often present as sleeping disturbances, concentration problems, and being hyper-vigilant. Furthermore, emotional numbness can be a major manifestation in PTSD, causing problems experiencing and expressing loving feelings for someone new or someone they had previously been close to. As a consequence of all these symptoms, a person with PTSD may become even further isolated, lose interest in daily activities, and lose the capacity to work or study. Finally, a person with PTSD often feels that he or she has been changed by the traumatic experience.

According to the 4th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM- IV-TR) [52], PTSD is classified as an anxiety disorder and is characterized by symptoms that are divided into three clusters. The disorder follows experiencing, witnessing, or being confronted with events involving actual or threatened death, physical injury, or other threats to the physical integrity of the self or others (criterion A₁). The person's response to the event also has to involve intense fear, helplessness, or horror (criterion A₂). For a diagnosis of PTSD, the B-cluster should involve at least one symptom of persistent re-experiencing of the traumatic event, the C-cluster should involve a minimum of three avoidance symptoms, and the D-cluster should involve two or more symptoms of increased arousal. The duration of the symptoms has to be over 1 month (criterion E). These symptoms sometimes lead to severe personality changes and effect important areas of functioning (criterion F). For a diagnosis of PTSD in the DSM IV, all six criteria have to be fulfilled (see Table 1).

Symptoms can occur at any age and generally present within 3 month of the trauma, but they may occur years later. When the disease onset occurs at least six months after the traumatic event, this is called "late or delayed onset of PTSD"[53].

Symptoms' durations vary widely, with over 50% resolving within 3 months, but many victims have persistent symptoms for years. Symptom duration of less than 3 months is often referred to as "acute PTSD". Symptoms persisting beyond 3 to 6 months have high probability of becoming chronic [54]. Symptoms are often intermittent, and relapse can occur.

Table 1. DSM-IV-TR criteria for posttraumatic stress disorder (PTSD)

A The person has been exposed to a traumatic event in which both of the following were present:

- (1) The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.
- (2) The person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior.

B The traumatic event is persistently reexperienced in one (or more) of the following ways:

- (1) Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
- (2) Recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.
- (3) Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience; illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). Note: In young children, trauma-specific reenactment may occur.
- (4) Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
- (5) Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

C Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

- (1) Efforts to avoid thoughts, feelings, or conversations associated with the trauma
- (2) Efforts to avoid activities, places, or people that arouse recollections of the trauma
- (3) Inability to recall an important aspect of the trauma
- (4) Markedly diminished interest or participation in significant activities
- (5) Feeling of detachment or estrangement from others
- (6) Restricted range of affect (e.g., unable to have loving feelings)
- (7) Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal lifespan)

D Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

- (1) Difficulty falling or staying asleep
- (2) Irritability or outbursts of anger
- (3) Difficulty concentrating
- (4) Hypervigilance
- (5) Exaggerated startle response

E Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.

F The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

2.2.1.2 *Definition of ASD*

The use of a diagnosis of acute stress disorder (ASD) has two purposes: to recognize posttraumatic stress within the first month after the trauma and to identify those victims most at risk of developing PTSD [55]. ASD, just like PTSD, is defined in the DSM-IV as a disorder that follows a trauma. Whereas PTSD reflects a disturbance that has lasted for more than 1 month, acute stress disorder must last for a minimum of 2 days and can only be diagnosed up to 1 month after the traumatic event. Acute stress disorder also differs from PTSD in being formulated as a dissociative response to trauma. Thus, a diagnosis of acute stress disorder requires at least three dissociative symptoms (criterion B) but only one symptom from each of the reexperiencing (criterion C), avoidance (criterion D), and arousal (criterion E) categories. As in PTSD, impairment (criterion F) is also necessary in an ASD diagnosis.

2.2.1.3 *DSM-V*

In May 2013, the American Psychiatric Association revised the PTSD and ASD diagnostic criteria in the 5th Edition of its Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [56]. PTSD and ASD were moved from the class of anxiety disorders into a new class of "trauma and stressor-related disorders."

Overall, the symptoms of PTSD are mostly the same in the DSM-V as in the DSM-IV, apart from some key changes. Criterion A2 (fear, helplessness, or horror just after the trauma) has been removed in the DSM-V because research suggested that Criterion A2 did not improve diagnostic accuracy [57]. Furthermore, DSM-IV Criterion C, avoidance and numbing, has been separated into two criteria: Criteria C (avoidance) and Criteria D (negative alterations in cognition and mood). By doing this, at least one avoidance symptom is required for diagnosis. Finally, a clinical subtype "with dissociative symptoms" was added. The dissociative subtype can be applied to individuals who meet the criteria for PTSD and experience additional depersonalization and derealization symptoms [58].

The changes in the classification of ASD in the DSM-V as compared to the DSM-IV are concordant with changes in PTSD diagnosis [59]. For a comparison, see Table 2.

Table 2. A comparison between DSM-IV and DSM-V diagnostic criteria for acute stress disorder

• DSM-IV	• DSM-V
• A1 Experiencing or witnessing actual or threatened death, serious injury, or threat to physical integrity	• A1 Experiencing or witnessing actual or threatened death, serious injury, or sexual violation, or learning that the event occurred to a friend or close relative
• A2 Response involves intense fear, helplessness, or horror	• Nine or more out of the following:
• ≥ 3 Dissociative symptoms (numbing, derealization, depersonalization, being dazed, amnesia)	- 2 Dissociative symptoms (numbing, depersonalization, amnesia)
	- 4 Intrusion symptoms (including flashbacks)
• ≥ 1 Intrusion symptom	- 1 Negative mood symptoms
• ≥ 1 Avoidance symptom	- 2 Avoidance symptoms
• ≥ 1 Arousal symptom	- 5 Arousal symptoms
• Clinical distress or impairment	• Clinical distress or impairment
• Symptoms last between two days and four weeks after trauma	• Symptoms last three days to one month after the event
• Symptoms not due to physiological events, general medical condition, etc.	• Symptoms not due to physiological events, general medical condition, etc.

As the enrollment of all patients in this thesis was done before the year 2013, I have consistently referred to the DSM-IV definition of full PTSD and ASD in this thesis.

2.2.2 Epidemiological aspects

In the national co-morbidity study [60], Kessler reported the life-time prevalence of PTSD being 10% for women and half, 5%, for men. It is not clear whether this discrepancy is caused by women being more vulnerable or the fact that women and men experience similar events differently. Women are more likely than men to be molested and to subsequently develop PTSD after having been molested. However, women are also more prone to develop PTSD after a physical assault, such as mugging, despite the fact that these events are far more common in men. In contrast, the prevalence of PTSD after rape is actually higher in men (65% vs. 46%), although women are more than 10 times more likely than men to be raped; see Figure 1. In summary, these statistics argue against women having an increased vulnerability to the disorder and instead point towards the fact that certain experiences may involve different degrees of actual threat and physical injury and therefore result in different risks of developing PTSD.

Further, Kessler reported that rape victims were at the highest risk of developing PTSD [60] compared to victims of other trauma types (Figure 1.B). This finding was replicated in 2005 in a reproduction of the large co-morbidity study [61].

Later studies have reported that about one-third to one-half of victims will develop PTSD after rape [62,63,64]. Rape appears to be more likely than other traumatic events to result in PTSD at least in part because of specific traumatic characteristics (e.g., perceived life threat) that are more common in rape than in other traumatic events. However, even after adjusting for the traumatic circumstances around the assault, rape is still one of the traumas most associated with PTSD. This implies that it is something about the assault itself, in form of its enormously personally intrusive nature and post-assault responses that leads to the increased risk [65,66].

2.2.2.1 Risk factors for PTSD after sexual assaults

Studies exploring risk factors for the development of PTSD after rape tend to divide the risk factors into three groups: pre-assault factors, assault-related factors, and post-assault factors. Pre-assault factors, such as prior victimization [18,67,68], have been found to be a major risk factor. Child sexual abuse is a risk factor for adult sexual and physical victimization and greater current PTSD symptoms [18,69]. Apart from its link to adult victimization, child sexual abuse alone is not a significant independent predictor of current post-rape PTSD symptomatology, but it is linked indirectly to PTSD through its relationship with adult sexual and physical victimization [18]. The researchers suggested a cumulative effect of child sexual abuse and prior adult victimization. Further, younger age [68], less education [62,65], and psychiatric co-morbidity [70] may be related to more severe PTSD symptoms.

Among the assault-related factors, perceived life threat has been found to be an especially predictive factor for PTSD [62,68,71]. The degree of violence used during the assault has been found to be predictive of PTSD in some studies [62,70,72,73] but not in others [68]. Contradictory findings have also been reported regarding whether a completed rape, as well as having been exposed to several rape types during the assault, influences PTSD development [71] or not [68,73]. Further, the importance of the victim-assailant relationship has been debated. Bownes and colleagues [73] and Ullman and colleagues [74] found that victims of stranger assaults were more prone to develop PTSD, whereas Temple and colleagues [75] documented that sexual assault committed by a partner can be as traumatizing to a victim, if not more so, than sexual assault committed by a non-partner.

Finally, several post-assault variables have been described as important in recovery after a sexual assault. Self-blame, loss of control, late disclosure, and avoidance coping, as well as unsupportive reactions and interpersonal friction with others following an assault, have all predicted worse PTSD symptoms at follow-up [65,68]. A large meta-analysis found that social support appeared to be the most important factor off all in protecting against the development of PTSD [76]. The prediction of PTSD through the presence of acute stress disorder (ASD) shortly after a traumatic event has mainly been used after non-interpersonal traumas [55,77,78]. After these traumas (mainly motor vehicle accidents), the positive predictive power of ASD was fairly high (i.e., many trauma victims who suffered from ASD went on to develop PTSD), but the sensitivity was only low to moderate (i.e., most of those who developed PTSD did not meet the initial criteria for an ASD diagnosis). This may have

been caused by the fact that many of those who developed PTSD had not met the initial dissociation criterion. Studies of ASD as a predictor of PTSD after interpersonal violence show a different picture. To my knowledge, only three studies have been published assessing ASD after interpersonal traumas [63,79,80], of which only one exclusively assessed female rape victims [63]. The results suggested that even though the sensitivity of ASD is higher after interpersonal trauma, especially after rape, the specificity of ASD is only low to moderate (i.e., the majority of those who did not develop PTSD had an ASD diagnosis), and therefore, the ASD diagnosis is of limited use.

The majority of all studies examining risk factors for the development of PTSD after rape are of cross-sectional designs. These studies are often from large national probability samples or a group of college students. This causes some limitations, and it can be more difficult to identify any causal relationship between certain variables and the development of PTSD. Furthermore, a cross-sectional design relies on the woman's ability to recall violent experiences and circumstances around the event and may cause recall bias. Thus, additional longitudinal studies of rape victims are important.

2.2.3 Biological aspects

2.2.3.1 Allostatic load

Effectively coping with a stressful situation requires a fast response and its quick termination afterward [81] and the process underlying the reaction to stress is called "allostasis" [82]. The stress response corresponds to the severity of the stressor. Reactions to chronic or cumulative stressors, however, can be more pronounced or may have residual effects. The stress response may be insufficient, excessive, or inadequate, and the effort to recapture homeostasis may fail, leading to a condition called "allostatic load" [81,82].

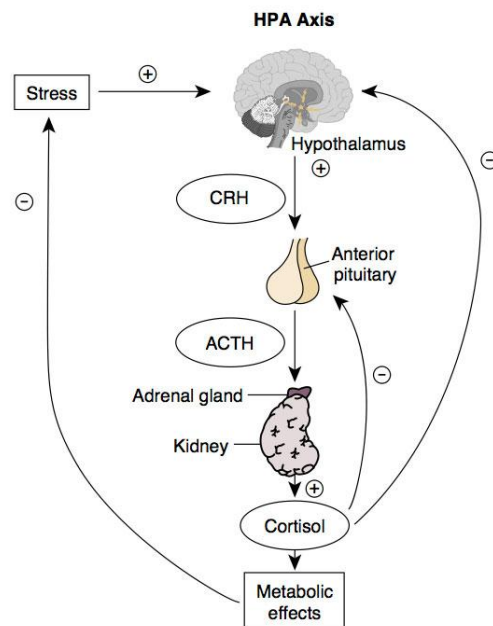
The sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis are the major systems when the body responds to physical and emotional threat and stress. The SNS response is normally brief, mobilizing the acute fight-or-flight response via the release of norepinephrine and adrenaline. The immediate response by the SNS is followed by an HPA axis response that reinstates homeostasis. When this fails, it can lead to long-lasting adaptive changes and may be one of the biological explanations for the development of several diseases, such as PTSD [83].

2.2.3.2 HPA-axis

The majority of research on neuroendocrinological changes in PTSD has focused on examining the role of the HPA axis. In response to stress, corticotrophin-releasing hormone (CRH) is released from the hypothalamus [84], and through the hypothalamic portal vessels, it reaches the anterior pituitary, which subsequently releases adrenocorticotrophic hormone (ACTH) [85], resulting in the release of the glucocorticoid cortisol from the adrenal cortex into the blood stream (Figure 2). The stress response is kept in check by a negative feedback

loop, with cortisol present in the blood stream acting on brain areas to shut down the release of CRH [86].

Figure 2. The hypothalamus-pituitary-adrenal (HPA) axis



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https://embryology.med.unsw.edu.au/embryology/index.php/File:HPA_axis.jpg#filelinks

It has been hypothesized that during the acute stress response after trauma, the HPA axis is initially hyperactive but that repetitive trauma and the constant retraumatization occurring in PTSD development cause alterations in the HPA axis, leading to reduced cortisol levels. This is a well-known phenomenon for the hypothalamic-pituitary-gonadal (HPG) axis; long-acting GnRH agonists are used to down-regulate the production of gonadotrophins and gonadal hormones. A possible explanation for the alterations in the HPA axis during chronic stress is the down-regulation of the CRH receptors in the pituitary. Elevated concentrations of CRH have been found in cerebrospinal fluid in patients with PTSD [87]. It has been assumed that the repeated exposure to stress-associated stimuli and subsequent cortisol release eventually leads to an up-regulation of glucocorticoid receptors, which in turn causes lower cortisol levels but at the same time a decrease in the degree of negative feedback inhibition on the hypothalamus and anterior pituitary, leading to increased CRH levels [81]. Although most research has found no differences in plasma cortisol concentrations between chronic PTSD patients and controls, some have shown other results. For example, 24-hour urinary cortisol levels were found to be lower than normal in Holocaust survivors with PTSD, even when a considerable amount of time had passed since the trauma [88]. However, a large meta-analysis [89] found that after reviewing a large number of studies, lower cortisol concentrations in PTSD patients were found only under certain conditions. Lower concentrations of cortisol in PTSD were especially common when plasma or serum was used

for analysis, when the patients were women, and when PTSD after physical and sexual abuse was assessed. The same researchers therefore suggested that the deviating results were due to the different methodologies used. However, another meta-analysis concluded that studies using a low-dose of the synthetic glucocorticoid dexamethasone all pointed towards PTSD patients having increased feedback inhibition, leading to reduced cortisol concentrations [90]. The PTSD patients' cortisol signaling capacities seem to be elevated so that lower levels of cortisol suppress the HPA axis. Cortisol has a huge range of effects in the body, including controlling metabolism, affecting insulin sensitivity, affecting the immune system, and even controlling blood flow [91].

One hypothesis regarding the development of PTSD is that the biologic stress response after trauma fails, resulting in a cascade of alterations. An inadequate stress response, without an increase of cortisol concentration, will consequently lead to a failure in the inhibition of the SNS, leading to increased norepinephrine concentrations after a trauma. This, in turn, may affect the consolidation of the memory of the incident. The memory of the event will not only be strongly encoded but fragmentary. The memory will also be associated with strong, subjective feelings of distress. Memory consolidation during an extreme stress response will lead to an increased risk of having intrusive recollections of the event and symptoms of hyperarousal. Prospective studies have suggested that low cortisol concentrations immediately following a trauma are related to a higher risk of developing PTSD [92,93,94] and that lower concentrations are seen in victims of prior trauma [95]. Only a few studies have been conducted on sexual assault survivors [96,97]. Resnick and colleagues found that female sexual assault survivors with prior assault histories had lower cortisol concentrations in the acute aftermath of the incident and were more likely to develop PTSD than women without similar histories. These results have recently been reproduced [97].

Studies have shown that patients with depression also have elevated CRH levels in the cerebrospinal fluid, but unlike patients with PTSD, they have higher than normal plasma cortisol concentrations, suggesting a hyperactivity of the HPA axis. Furthermore, studies show an insufficient suppression of corticotrophin and cortisol following a low-dose dexamethasone test [98,99]. This has been especially common in patients with melancholic depression without co-morbid PTSD.

2.2.3.3 *Endocannabinoid system*

Recently, there has been research suggesting that especially in the case of psychological stressors, the endocannabinoid system plays a crucial role in HPA axis regulation [100]. The endocannabinoid system is a neuroactive lipid signaling system that functions as a gate for synaptic transmitter release. It has been suggested that it is involved in the fast and the delayed stress systems via e.g., the disinhibition of the prefrontal output neurons that regulate HPA axis activity, as well as gamma-aminobutyric acid (GABA) release in the hippocampus [101]. Subsequently, it seems to not only be involved in the control of acute stress but also to influence chronic stress reactions via neuroplastic changes, as in the case of PTSD [102].

2.2.3.4 *Neuroanatomical changes*

Recent neuroanatomical studies have identified alterations in two major brain structures, the amygdala and the hippocampus, in patients with PTSD. Positron-emission tomography (PET) and functional magnetic resonance imaging (MRI) have shown that the reactivity of the amygdala and frontal brain areas to trauma-related stimuli is increased and that the reactivity of the hippocampus, anterior cingulate, and orbitofrontal areas is decreased [103]. These areas of the brain are involved in fear responses. The amygdala is involved in recognizing stressors and sending out signals to the hypothalamus. The hippocampus plays an important role in the consolidation of short-term memory into long-term memory, as well as the termination of the stress response. Differences in hippocampal function suggest a neuroanatomical cause for the intrusive recollections and other cognitive problems that characterize PTSD [104]. Hippocampal volume has been found to be decreased in patients with PTSD, and even though the majority of studies have claimed that this is a result of stress, some others have claimed that it may be a pre-existing risk factor [103].

2.2.4 Treatment

Early intervention after a sexual assault is often indicated because of distress, although randomized controlled studies indicate that psychological debriefing in groups, rather than individualized approaches, may harm rather than benefit victims [105]. Instead, the key elements are psycho-education (including written information), a space to ventilate and feel safe, the reduction of shame and guilt, stabilization, and the consideration of coping mechanisms, sexual matters, social support, and legal support. Support in a safe environment can often be provided by a sexual assault center, victim support and rape crisis services, and general practitioners, as well as families, friends, and partners. Early interventions may also prevent the development of PTSD [106,107].

Once PTSD has developed, effective psychotherapies are available. Several PTSD treatment guidelines recommend trauma-focused cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing therapy (EMDR) as first-choice treatments [108,109]. CBT and EMDR are both referred to as “exposure-based” therapies, which confront patients with their traumatic memories. There are different CBT techniques, but prolonged exposure therapy is the one that has proven to be most effective. Other CBT techniques include cognitive processing therapy and acceptance and commitment therapy. Studies have shown that the effects of prolonged exposure and EMDR are comparable but that EMDR may be easier for some patients because it involves a faster processing of traumatic memories and no homework is needed [110]. Over the years, several different techniques have been described as useful in treating PTSD symptoms (e.g., biofeedback, lifespan integration, emotional freedom technique (EFT), yoga, and mindfulness). However, none have proven to be more effective than prolonged exposure or EMDR.

The overall efficacy of medical treatment for PTSD is not superior to CBT or EMDR, and it often results in side effects. However, sometimes, medical treatment is the only option (i.e.,

when no psychotherapy clinic is available in the area), and sometimes, it has to be added to an existing psychotherapy [111]. Medical treatment can be especially needed when the patient has a co-morbid disorder, such as depression or an anxiety disorder. Most studies involve antidepressants: selective reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and other serotonergic agents (trazodone and nefazodone). Antiadrenergic drugs tested for specific problems, such as nightmares, include the alpha-1 receptor (prazosin), the alpha-2 receptor agonists (clonidine and guanfacine), and the beta receptor antagonist (propranolol) for excessive arousal. Evidence supports the use of SSRIs and SNRIs as first-line drugs for PTSD. Recent results for prazosin and mirtazapine are also promising. MAOIs and TCAs are moderately effective, but they both have potentially severe side effects [53].

The use of benzodiazepines in treating anxiety and insomnia in PTSD patients has been debated. Benzodiazepines have not been proven to be effective in treating PTSD symptoms [112] and are therefore not recommended [113]. Furthermore, because of reports of several side effects (i.e., withdrawal symptoms, interaction with alcohol, and an increased risk of substance abuse), as well as benzodiazepines' lack of effect in this patient group, they have also been proposed as contraindicated [114]. The actual reason for these drugs' effects is still unknown. The presence of extreme stress and inability to sleep after a traumatic event sometimes warrants treatment. The use of non-benzodiazepine sedative-hypnotics is thus recommended for only a short period, and traditional benzodiazepines should be used with caution. In an animal study in which intravenous injections of alprazolam were given in the immediate aftermath of stress exposure, the researchers found that this caused alterations in the HPA axis response, which consequently led to increased stress responses after additional trauma [115].

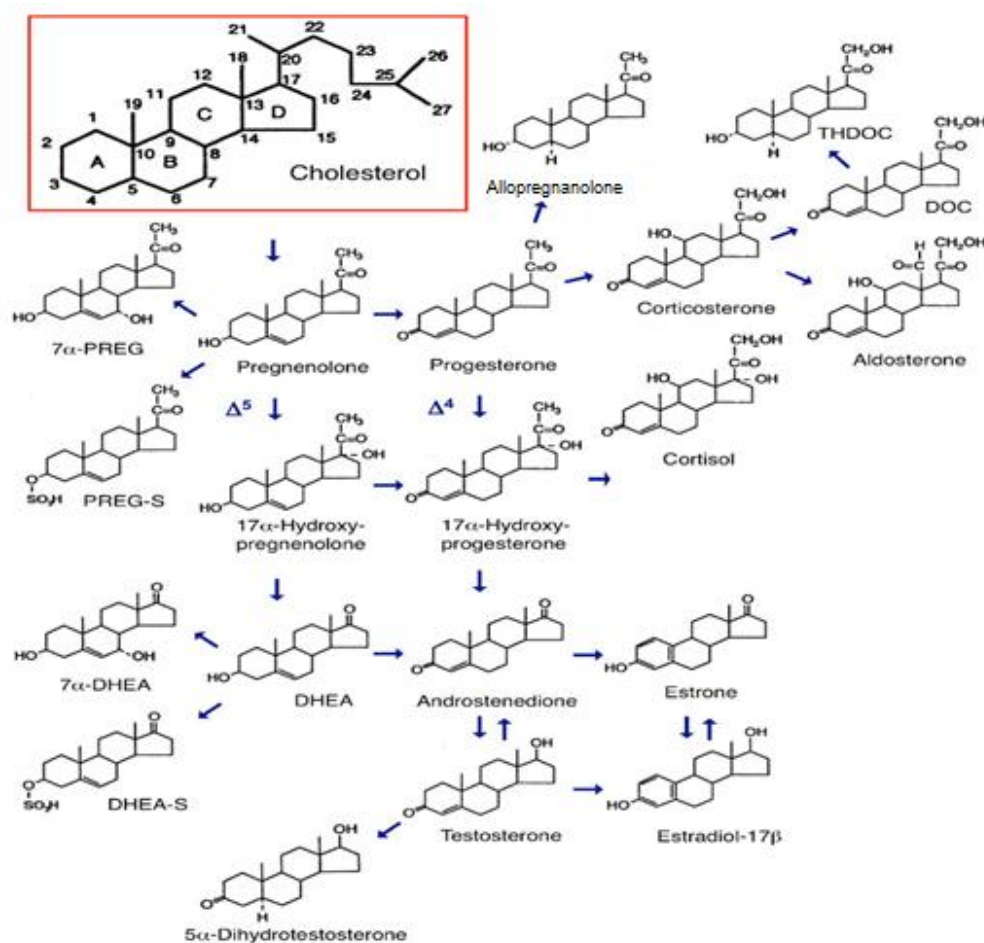
2.3 STEROID HORMONES

As it has been suggested that low cortisol concentrations in the acute aftermath of rape are associated with the development of PTSD it would be interesting to also assess other endogenous steroids and neuroactive steroids. To further understand these responses and their effects on PTSD development, a study using validated techniques measuring serum concentrations of several classes of steroids in the aftermath of rape would be interesting. When conducting such a study, blood samples would have to be taken at the acute visit after the sexual assault, no matter what time of the day it is. The diurnal variation of cortisol and cortisone is well-described [116]. However, even though other steroids further up the biosynthesis pathway would probably have a similar variation, this is not clearly described in the literature. Allopregnanolone has been shown not to have a diurnal variation in the luteal phase of the menstrual cycle [117]. However, it is still possible that there is a variation in the follicular phase.

2.3.1 Steroid synthesis

To better understand the pathophysiological changes in PTSD, one has to know about the steroid biosynthesis pathways. The major pathways are shown in Figure 3. All steroids are derived from cholesterol. The core of all steroids is 17 carbon atoms bound together to form 4 rings. Cholesterol is the precursor of the 5 major classes of steroid hormones: glucocorticoids, mineralocorticoids, progestins, estrogens, and androgens. The first step is the conversion of cholesterol to pregnenolone, which is catalysed by the P-450 enzyme, which is under pituitary hormone control (ACTH or LH, depending on the tissue). From pregnenolone, steroid biosynthesis proceeds either through the so-called "delta-5" pathway (17 α -hydroxypregnenolone, dehydroepiandrosterone (DHEA), testosterone) or through the "delta-4" pathway (progesterone onwards). Progesterone is the starting point for mineralocorticoid synthesis (corticosterone, aldosterone), whereas glucocorticoids (cortisol, cortisone) are derived from its metabolite, 17 α -hydroxyprogesterone. Estrogens are formed from androgens (androstenedione and/or testosterone). Most reactions are irreversible (single arrow). Reversible reactions (double arrows) depend on cofactor availability (e.g., the NADP/NADPH ratio) and steroid concentrations.

Figure 3. Major pathways of steroid biosynthesis



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2.3.2 Neuroactive steroids

Even though cortisol is the most studied steroid hormone in patients with PTSD (see Section 2.2.3.2), alterations in the concentrations of other steroids along the biosynthesis pathways have been suggested.

Apart from in the adrenals and gonads, steroid synthesis and/or metabolism exist in the CNS as well, for instance, in the glial cells. These steroids are called neurosteroids or neuroactive steroids, and they are either produced within the brain or pass through the blood-brain barrier from the periphery. They have an effect on both the peripheral and central nervous systems. Unlike ordinary steroids, which bind to receptors within the nucleus, neurosteroids have effects on neurotransmitter receptors on the cell surface. Instead of calling them neurotransmitters, they could be called neuromodulators. The major groups of neuroactive steroids are metabolites of progesterone, deoxycorticosterone, testosterone, and some other androgens, notably dehydroxyepiandrosterone (DHEA) and especially its sulfate (DHEAS). These compounds show increased concentrations both in the blood and in the brain following stress, and they have also been associated with sedative, anti-depressive, anxiolytic, and antiepileptic effects [119]. Because several of the stress steroids are potent endogenous positive GABA-A receptor-modulating steroids (e.g., allopregnanolone and 3 α -hydroxy-alpha-cortisol), they constitute a feedback loop to the CRH-ACTH production and down-regulation of the cortisol production.

Dehydroepiandrosterone (DHEA) is mainly secreted by the adrenal cortex after ACTH stimulation. DHEA has anti-stress effects, blocking the effects of glucocorticoids on peripheral tissues and the hippocampus, and decreases anxiety [120]. Studies of DHEA and DHEAS in patients with stress-related psychiatric disorders are contradictory. In one study on sexual abuse victims with PTSD, both DHEA and DHEAS were found to be increased [121], while another study only found DHEAS to be increased and that DHEA did not differ between patients and controls [122]. Another heavily traumatized group studied is apathetic refugee children [123]. Here, the results suggested a negative association between concentrations of cortisol and cortisone and a positive association with pregnenolone, 17OH-pregnenolone, and DHEA with the severity of the symptoms. However, in another study of sexual assault victims [124] and of war veterans with PTSD [125], DHEA concentrations have been found to be reduced.

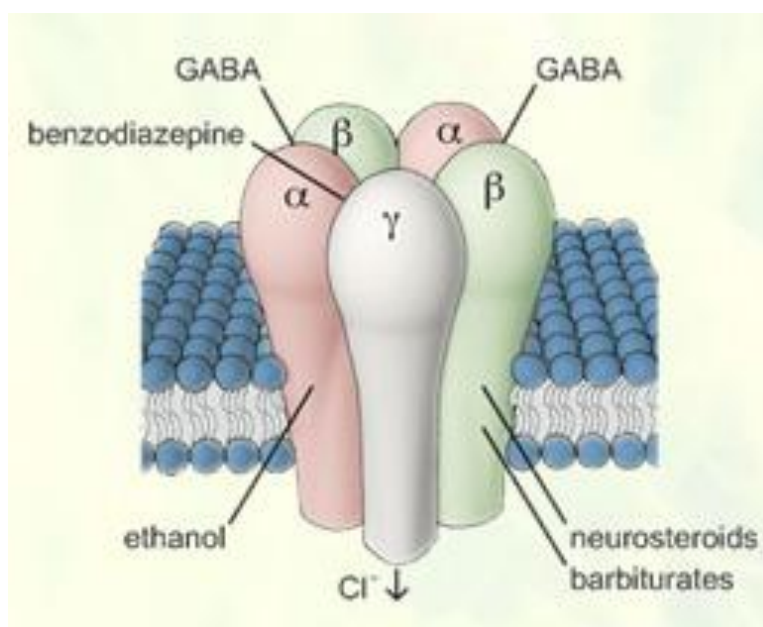
Studies of DHEA in depression have been equally contradictory, but the majority of studies have shown elevated levels [126,127] and decreased concentrations during remission of the disease [128]. However, so far, no definite conclusion can be drawn regarding the impact of DHEA/DHEAS levels as a biomarker for depression.

Also, alterations in the neuroactive steroid allopregnanolone have been suggested in PTSD patients. Allopregnanolone is a stress-related steroid that has anesthetic and anxiolytic effects, and it has been found to be decreased in the cerebrospinal fluid and serum in both patients with PTSD and depression [129,130].

2.4 GABA-A RECEPTOR

The mechanism for the majority of the effects of the neuroactive steroids is through their effect on receptor-mediated binding to ligand-gated ion channels. The GABA-A receptor is the most important inhibitory receptor in the nervous system. The activation of the GABA-A receptor complex results in the opening of its central chloride channel, leading to the repolarization of the plasma membrane and the inhibition of further neuronal firing [131]. Activation by a positive modulator therefore causes sedation, amnesia, and ataxia, while activation with an inverse agonist or antagonist causes arousal, restlessness, insomnia, and exaggerated reactivity (Sigel and Steinmann 2012). Because the latter symptoms are all described in PTSD patients, it would be of interest to investigate the GABA-A receptor function in PTSD patients.

Figure 4. GABA-A receptor



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The receptor is a pentameric transmembrane receptor that consists of five subunits (($\alpha 1$)₂, ($\beta 2$)₂, and ($\gamma 2$)) arranged around a central pore (see Figure 4.). There are at least 19 subunit compositions described in the mammalian brain. The different subunit isoforms of the receptor determine the receptor's agonist affinity, chance of opening, conductance, and other properties. The various subunits of the GABA-A receptor also have different sensitivities to different drugs and endogenous GABA-A receptor-modulating steroids.

The benzodiazepine binding site is situated between the α - and γ -subunits, and the presence of a γ -subunit is required for action by benzodiazepines. While the majority of GABA-A receptors (those containing a γ -subunit combined with an $\alpha 1$ -, $\alpha 2$ -, $\alpha 3$ -, or $\alpha 5$ -subunit) are benzodiazepine-sensitive, there exists a minority of GABA-A receptors (containing the δ -

subunit mainly combined with the $\alpha 4$ - or $\alpha 6$ -subunit) that are insensitive to classical benzodiazepines, but instead are hyper-sensitive to other classes of GABAergic drugs, such as neurosteroids and ethanol [132]. Alterations in the benzodiazepine receptor in PTSD patients have been suggested, and Bremner and colleagues [133] found fewer benzodiazepine receptors and/or a reduced affinity for receptor binding in the medial prefrontal cortex in patients with PTSD as compared to controls. The authors therefore suggested that alterations in the GABA-A (benzodiazepine) receptor in this area could be one of the explanations for the symptoms of PTSD. DHEAS and, to some extent, DHEA have been found to have a non-competitive antagonistic effect on the GABA-A receptor, causing a blockage, and to some extent, reduced benzodiazepine binding [134]. Whether this is one of the explanations for the reduced effect of benzodiazepines in patients with PTSD has also been discussed.

The GABA-A receptor subtype $\alpha 4$, β , δ is hypersensitive to the positive GABA-A receptor-modulating steroid allopregnanolone, while it is subsequently insensitive to benzodiazepine. Flumazenil, on the other hand, is known to change its action from being a benzodiazepine antagonist or inert compound to being an agonist with a benzodiazepine-like effect on its own in GABA-A receptor subtype $\alpha 4$, β , δ . Therefore, the three drugs allopregnanolone, diazepam, and flumazenil are suitable for use in challenge tests to bring to light whether there are changes in GABA-A receptor sensitivity and relate the effect of compounds to possible changes in GABA-A receptor subtypes in a disorder.

In a previous study of female patients with burn-out syndrome, the authors saw an increased sensitivity to allopregnanolone and a changed action of flumazenil suggesting an up regulation of GABA-A receptor subtype $\alpha 4$, β , δ , [135] in this group of patients. In another study, providing increasing doses of intravenous diazepam to patients with a panic disorder [136], results suggested subsensitivity of the GABA-benzodiazepine receptor complex in this patient group. In both mentioned studies, saccadic eye velocity (SEV) was used as an outcome measure. This technique is a validated and objective way of estimating sensitivity to GABA-A receptor drugs in the neural circuits controlling the saccade, and it has been used by Bäckström and colleagues in several studies [137,138,139,140]. To our knowledge, the SEV technique has not before been used before in investigating the GABA-A receptor complex in patients with PTSD.

3 AIMS OF THE THESIS

The overall aims of this thesis were to improve the knowledge about women seeking medical help after rape, explore risk factors for the development of PTSD after rape, and explore neuroendocrinological changes in patients with PTSD.

Specific aims were as follows:

- | | |
|------------------|--|
| Study I | To address differences in intimate-partner assaults compared to other known-assailant assaults and to sexual assaults by strangers. |
| Study II | To explore the prevalence of PTSD six months after sexual assault.

To explore whether it is possible to identify those women at the highest risk of developing PTSD after a sexual assault. |
| Study III | To explore whether endogenous steroids have a diurnal variation in the follicular phase of the menstrual cycle. |
| Study IV | To explore whether the concentrations of endogenous steroids in the immediate aftermath of rape can predict the development of PTSD and depression. |
| Study V | To explore possible differences in the GABA-A receptor sensitivity in patients with PTSD compared to healthy non-traumatized controls. |

4 METHODS

4.1 SETTING

All studies were conducted on female patients and controls, and all patients were recruited from the Emergency Clinic for Raped Women at Stockholm South General Hospital (Södersjukhuset), Stockholm, Sweden. The Emergency Clinic for Raped Women opened in October 2005 within the Obstetrics and Gynecology Department and about 600-700 women are seen every year. Women who have been referred from other healthcare clinics, emergency departments, and the police, as well as those presenting themselves, are met at the clinic. All sexual assault victim care in Stockholm is centralised to the Emergency Clinic for Raped Women, and the clinic is open 24 hours a day. The victims are offered medical and forensic examination within one month after the sexual assault. About 65% of the women have reported their assault to law enforcement. However, this is not mandatory for care.

4.2 STUDY DESIGNS

Different designs and methods have been used, depending on the purpose of the study. An overview of designs and participants is presented in Table 3.

Table 3. Overview of study designs

Study	Design	Inclusion criteria	No. of studied participants
I	Retrospective observational study	Consecutive patients from the Emergency Clinic for Raped Women.	503
II	Prospective longitudinal study	Patients seeking help at the Emergency Clinic for Raped Women, > 18 years old, literate in Swedish	201
III	Observational study	Healthy, non-traumatized, drug-naïve women, 18-40 years old	10
IV	Prospective longitudinal study	Same as Study II	108
V	Explorative study	Patients: Drug-naïve women, 18-40 years old, with PTSD 6 months after sexual assault. Controls: Drug-naïve, non-traumatized women, 18-40 years old, without PTSD.	12 patients 16 controls

Study I was a retrospective study of patient files and forensic examinations from consecutive patients seeking acute medical help after sexual assault during a period of 13 months between 2007 and 2008. Victim-assailant relationships were assessed regarding their association with injuries and reported violence.

Study II was a prospective, longitudinal follow-up study exploring whether certain variables measured at the acute visit and at the two-week follow-up could predict the development of PTSD at the six-month assessment. Women were asked for consent at the two-week follow-up. The study started in February 2009 and was completed in June 2012. Participants were asked to fill out a number of self-rating questionnaires at the two-week and six-month follow ups, as well as to participate in a clinical interview at six months for the diagnosis of PTSD.

Study III was an explorative observational study regarding the diurnal variation of a battery of endogenous steroids in the follicular phase of the menstrual cycle. This study was conducted so that blood samples taken at various hours of the day in Study IV could be adjusted for their possible diurnal variations. Blood samples were drawn every 4th hour over 24 hours.

Study IV was a part of Study II and was started in April 2010 and completed in June 2012. The study had the same design as Study II, but with a blood sample added at the acute visit. When the women were asked for written consent at the two-week follow-up, blood samples from consenting women were stored. Blood samples were destroyed if the women did not consent. If the women came back for the six-month assessment, the blood sample from the acute visit was analyzed regarding steroid concentrations and assessed to determine whether they could predict the development of PTSD or depression at six months.

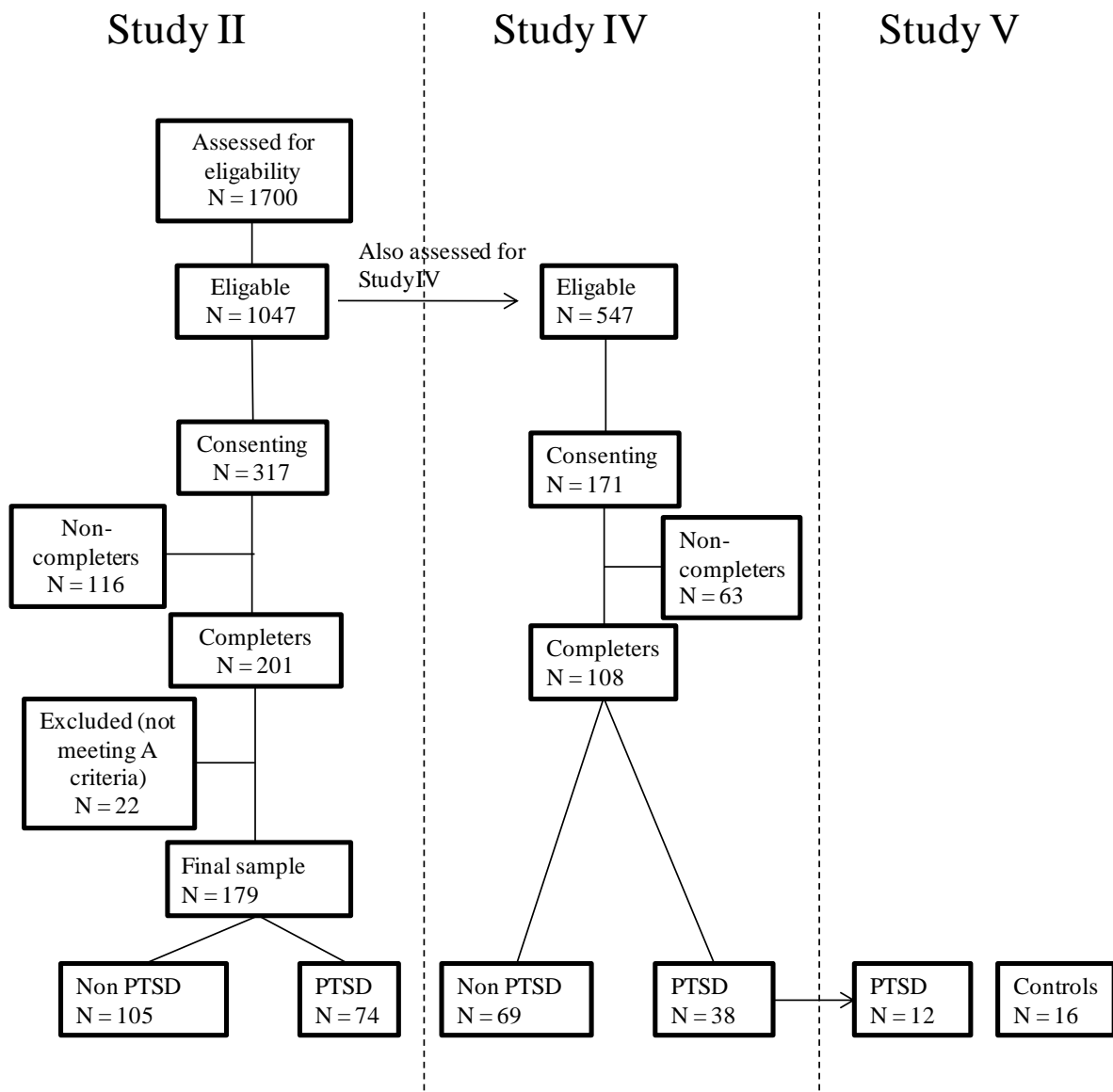
Study V was an explorative study of patients diagnosed with PTSD at the six-month assessment in Study IV. The PTSD patients were compared with non-traumatized controls without PTSD regarding the sensitivity of the GABA-A receptor. Challenges with diazepam, flumazenil, and allopregnanolone were performed on three separate occasions, and the effects were measured in saccadic eye velocity (SEV) and subjective ratings of sedation (VAS). The study was started in April 2012 and was completed in March 2013.

4.3 PARTICIPANTS

In **Study I**, 690 women sought help at the clinic during the study period. After excluding those cases with too much incomplete information in the data files ($n = 21$), those in which the relationship to the assailant was not documented ($n = 3$), and those who were incorrectly registered as emergency visits, we obtained 655 included patients. Of these 655 cases, 17% ($n = 114$) were defined as single-stranger assaults, 43% ($n = 287$) as acquaintance assaults, and 16% ($n = 102$) as intimate partner assaults. This resulted in a final sample size of 503 patients. The mean age among the women was 25 years (range 11-95), and 25% were under the age of 18 at the time of the sexual assault.

A flow diagram of participants in **Studies II, IV, and V** is shown in Figure 5. Because the blood sampling started approximately one year after the start of Study II, the number of participants included in Study IV was lower. Thus, all patients in Study IV were also included in Study II. The inclusion criteria for both Study II and IV were being over the age of 18 years old and literate in Swedish. Women were excluded if they were believed to be unable to provide informed consent (e.g., mental retardation or severe mental illness).

Figure 5. Flow diagram of study population in Studies II, IV, and V



Participants in **Study III** were all non-traumatized controls who were recruited through advertisement. The inclusion criteria were being between 18 and 40 years old, not taking any hormonal contraceptives or daily medication, and being physically and mentally healthy. All blood sampling had to be performed in the follicular phase of the menstrual cycle.

Patients included in **Study V** were recruited from the six-month assessment in Study IV and were all diagnosed with PTSD according to the SCID interview. A total of 12 patients with PTSD were recruited, of which 10 were planned for each of the three challenges. Patients

were compared to 16 controls, of which 10 were planned for each challenge. The inclusion criteria for both patients and controls consisted of being 18-40 years old, having fairly regular menstruations, not taking any hormonal contraceptives, and being drug-naïve regarding antidepressants, anxiolytics, and sedatives. Furthermore, all participants were excluded if they had a history of psychosis, major or bipolar depression, alcohol or substance abuse, neurological disease, endocrine disease or polycystic ovarian syndrome (PCOS) or if they were pregnant or planning on becoming pregnant within three months after the last challenge. At the time of the challenge, participants had to be in the follicular phase of the menstrual cycle and not have consumed any alcohol in the past 72 hours.

4.4 MEASURES AND DATA COLLECTION

An overview of the measures used in each study is presented in Table 4.

Table 4. Overview of measures

Study	Measures
Study I	Self-reports Forensic examinations
Study II	BDI, SASRQ, PDS at two weeks follow-up SCID-I, BDI, SASRQ at six months follow-up
Study III	SCID-I, BDI, SASRQ
Study IV	Same as Study II + Blood sample from acute visit
Study V	SEV, VAS, SCID-I, BDI, ASI, PSS, STAI, SADS

4.4.1 Victim and assault characteristics

In **Studies I, II, and IV**, all data on assault and victim characteristics were collected from the clinics' structured data files and findings from the forensic examination at the acute visit. Data on victim and assault characteristics were therefore based on the woman's self-report, while data on injuries were based on the physician's findings.

The victim-assailant relationships were defined as *intimate partner* (husband/cohabiter, partner, ex-partner), *family member* (other than intimate partner), *acquaintance* (an assailant known by the woman but not as an intimate partner or family member), *stranger* (single assailant not known by the woman), *group* (more than one assailant,) or *uncertain* (the victim had amnesia and could not recall).

The different types of assaults were defined as *vaginal, oral, or anal* penetration (with penis, hand, or foreign object) or a *combination* of the three. Alternatively, an assault was defined as *other* when no penetration was involved but other kinds of touching or kissing had occurred (involving the genitals or body parts).

Violence was defined as *hitting, kicking, holding, attempts of strangulation, or by other means*. In Study I, if two or more types of violence were used, the violence was defined as *multiple violence*. In Studies II and IV, the violence was defined according to the NorVald Abuse Questionnaire [141] as *none, mild* (hitting, smacking your face, holding you firmly), *moderate* (hitting with fist(s) or hard object, kicking, pushing violently), or *severe* (threat to life, strangulation, showing weapon or knife).

Genital and non-genital injuries were defined according to a modified version of the TEARS system [45] when Tears (breaks in tissue including fissures, cracks, cuts, and lacerations), Ecchymoses (skin or mucous membrane discolorations, known as bruising), Abrasions (skin excoriations), Redness (erythemous skin), Swelling (oedematous tissues) or Several of these (more than one of the mentioned injuries) were observed, and the occurrence of each was coded as yes/no.

Further, information on influence of alcohol during the assault was solely based on the woman's own report and was not quantified in most of the cases. In Study I, a prior assault history was based on the women's answer to the question "Have you ever before been sexually assaulted?" In Studies II and IV, prior sexual assault history was established through the Posttraumatic Stress Diagnostic Scale (defined below). Finally, the time lapse between the sexual assault and the acute visit was defined as within 72 hours (< 72hrs) or later than 72 hours (> 72hrs).

4.4.2 Psychometrics

The PTSD Module of the Structured Clinical Interview for DSM-IV (SCID-I) was used in **Studies II-V** to establish current PTSD status. In Studies II and IV, the interview was used at the six-month assessment. In Study III, the interview was used to establish the absence of PTSD in the non-traumatized controls, and in Study V, to establish full PTSD in the included patients and the absence of PTSD in the controls. The SCID-I is a widely used structured clinical interview, and a diagnosis of full PTSD was made using the DSM IV-TR (i.e., when clusters A and F were fulfilled).

The Beck Depression Inventory (BDI) [142] was used both at the two-week and six-month follow-ups in **Studies II and IV**. It was also used in **Studies III and V** to exclude depression in both patients and controls. The inventory has 21 items measuring depressive mood and vegetative symptoms of depression. The cut-off points for the sum scores were 0-9 (no depression), 10-16 (mild depression), 17-29 (moderate depression), and scores ≥ 30 (severe depression).

The Posttraumatic Stress Diagnostic Scale (PDS) was used in **Studies II and IV** at the two-week follow-up to assess PTSD symptom scores (0-51), pre-existing PTSD, and lifetime

histories of traumatic events [143]. Pre-existing PTSD was diagnosed at baseline when the respondent in PDS part 1, reported having been exposed to or having witnessed a traumatic event that, according to PDS part 2, involved threat to life or physical integrity and, according to PDS part 3, reported having at least 1 re-experiencing symptom, more than 2 avoidance symptoms, and more than 1 arousal symptom, as well as having a symptom duration over 1 month and, that the symptoms according to PDS part 4 also caused impairment in the respondent's daily life in at least one area.

The Stanford Acute Stress Reaction Questionnaire (SASRQ) [144] was used in **Studies II and IV**, mainly for diagnosis of ASD at the two-week follow-up. The SASRQ is a 30-item self-report instrument with 3 additional questions relevant to the diagnosis of ASD, including a description of the event, how disturbing it was, and how many days the individual experienced the worst symptoms for. The instrument can be used as a Likert-type scale (0-5) or dichotomously (0-2: 0, 3-5: 1) to test for the presence of a symptom. The questionnaire was also used as a total score (adding all items) for measuring PTSD symptom severity at the two-week and six-month assessments in Studies II and IV and during inclusion in **Studies III and V**.

In **Study V**, the Anxiety Sensitivity Index (ASI), the Panic Symptom Scale (PSS), the State-Trait Anxiety Inventory (STAI), and the State Anxiety and Discomfort Scale (SADS) were used before the start of each challenge and at home 24 hours after each challenge. SADS ratings were also taken throughout the challenge at 5, 13, 18, 25, 30, 45, 60, 120, and 180 minutes.

The Anxiety Sensitivity Index (ASI) measures the fear of panic or anxiety [145]. The overall score ranges from 0-64, and a mean score of 19.1 has been reported for a normal population [146].

The Panic Symptom Scale (PSS) is a 19-item questionnaire regarding different symptoms of panic on a scale from 0 (not at all) to 4 (extreme) [147].

The State-Trait Anxiety Inventory (STAI) has a total score of 20 to 80 points. A total score below 40 indicates low anxiety, between 40 and 59 indicates moderate anxiety, and 60 or more indicates a severe state of anxiety [148].

The State Anxiety and Discomfort Scale (SADS) ranges from 0 (no discomfort) to 5 (worst imaginable discomfort) and measures changes in anxiety level when used repeatedly.

4.4.3 Steroid analysis

Allopregnanolone concentrations in **Studies III-V** were analyzed at the Umeå Neurosteroid Research Center (UNC) in Umeå, Sweden. For a more detailed description of the analyses, see [140]. Briefly, the samples (0.4 ml) were extracted with diethyl ether (Merck KGaA, Darmstadt, Germany). Allopregnanolone was separated from cross-reacting steroids with celite chromatography. Allopregnanolone was measured via Radioimmunoassay (RIA) using a polyclonal rabbit antiserum raised against 3 α -hydroxy-20-oxo-5 α -pregnan-11-yl-

carboxymethyl-ether coupled to bovine serum albumin, provided by RH Purdy (The Scripps Research Institute, La Jolla, CA, USA) [149].

In **Studies III** and **IV**, the LC-MS/MS technique was used for analyzing concentrations of the glucocorticoids (cortisol, cortisone, 11-deoxycortisol), androgens (androstenedione, testosterone, DHEA), pregnenes (pregnenolone, 17OH-pregnenolone), progestins (progesterone, 17OH-progesterone), and estrogens (estrone, estradiol). Analyses were performed at the ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, USA. For further details, see [123]. The progesterone concentrations were only used in order to identify those women being in the luteal phase of the menstrual cycle.

4.4.4 Saccadic Eye Velocity (SEV)

In order to address the research question in **Study V**, saccadic eye velocity (SEV) was used to assess the sensitivity of the GABA-A receptor in patients with PTSD as compared to healthy non-traumatized controls.

SEV was measured using a non-invasive videonystagmographic device (Ulmer VNG, Atos Medical AB®). The device has an open mask (Visio 50) for measuring rapid eye movements, with a camera that provides binocular analysis. The model allows unlimited calibration in horizontal movements and $+90 / -20^\circ$ vertically, and it has an accuracy of 0.1° . The camera sensor is mounted on a rigid helmet. Before the start of the study, the camera sensor was adjusted so that it was positioned several centimeters from the eyes, at the level of the tip of the nose, and pointed up towards the pupil in mid-position. The target was at a distance of 115 cm from the eye and consisted of a white light on a black background. Participants were instructed to watch the white light and try not to anticipate where the next target would be. Calibration was achieved by asking the participant to fixate on targets at 20° and 30° to the right and left, as well as above and below the center before each series of measurements. Recalibration minimized error due to head movements. After calibration, measurements were conducted using a target moving rapidly back and forth in the horizontal plane from the left of center to the right of center at a constant velocity. The subject was asked to move the eye to the new point and fixate on that. The speed of the eye movement in degrees/second was calculated by a computer. Saccades of 20° were used in this study. Eye position data were stored and displayed on the computer, and data from both eyes were combined. The peak velocity was calculated and displayed for each saccade.

SEV was measured before and after injections of three separate substances. The challenges with diazepam (a GABA-A receptor agonist), flumazenil (a benzodiazepine antagonist at the GABA-A receptor), and allopregnanolone (a positive GABA-A receptor modulator), were performed in the mentioned order, and all were performed at separate occasions usually with 1 month in between, but always at a minimum of 3 days in between. After the injection, SEV and sedation were measured after 5, 13, 18, 25, 30, 45, 60, 120, and 180 minutes.

4.4.5 Visual Analogue Scale (VAS)

The sensitivity of the GABA-A receptor in the PTSD patients compared to the controls in **Study V** was also measured by assessing the participants' subjective ratings of sedation

during the challenges. This was done by using a visual analogue scale (VAS) [150]. The scale measured from 0 to 10, where 0 represented the complete absence of sleepiness and 10 represented nearly falling asleep. The ratings were made at baseline, as well as at the same time points as the saccadic eye measurements.

4.5 METHODS OF ANALYSIS

An overview of statistical methods used in each study is shown in Table 5. In all studies, a statistical significance was considered when p-value was <0.05.

Table 5. Overview of methods of analysis

Study number		I	II	III	IV	V
Method	Pearson’s chi-square test	X	X		X	X
	Fisher’s exact test	X				
	Independent T-test		X			
	Logistic regression	X	X		X	
	Repeated measures ANOVA			X		X
	Mann-Whitney U test				X	X
	Bivariate correlations			X	X	
Package	SPSS 20.0	X	X			
	SPSS 22.0			X	X	X

In **Study I**, Pearson’s chi-square test or Fisher’s exact test were used to compare assault and victim characteristics between the three assailant groups. The three assailant groups were analyzed regarding their associations with the three main outcomes (multiple violence, extra-genital injuries, and genital injuries) using logistic regression. In a multivariable model, associations were adjusted for age, ethnicity, type of assault, influence of alcohol, and time lapse between assault and examination.

In **Study II**, differences between the PTSD group and the non-PTSD group were analyzed using Pearson’s chi-square test for categorical variables and independent t-test for continuous variables. A multivariable regression model was conducted to assess possible risk factors for the development of PTSD. First, the results from the psychometrics used at the two-week follow-up were examined for their association with the development of PTSD. Second, victim characteristics and, last of all, assault characteristics were examined for their association with the development of PTSD. Significant factors from each of the three models

were then simultaneously inserted into a final model predicting PTSD. In the final model pre-existing PTSD was also adjusted for.

In **Study III**, potential diurnal variations in the endogenous steroids were assessed by using repeated-measures ANOVA to establish possible within-subject variations, and the bivariate correlations between the steroids were analyzed using Spearman's correlation.

In **Study IV**, steroid concentrations were first adjusted for their diurnal variation, as established in Study III. This was done the following way: First, the mean and standard deviation of the steroids for each time interval were calculated in Study III. The concentrations of each steroid in the acute blood samples were then normalized according to their diurnal variations. This was done by calculating z-scores for each sample according to the mean and standard deviation for each steroid and time interval among the healthy controls in Study III ($z = (x - \mu) / \sigma$, where x = individual sample value, μ = the mean of the time interval in the controls, and σ = the standard deviation of the mean samples in that time interval). The z-scores were then used when exploring differences in the serum concentrations of the steroids between the patients who developed PTSD and the group that did not. Pearson's chi-square test for categorical variables and the Mann-Whitney U test for continuous variables were used when comparing the two groups. The relationships between the steroid concentrations, PTSD, and depression at both the two-week and the six-month follow-up, prior assault history, and psychiatric treatment history were also analyzed using bivariate correlations, as well as multivariable logistic regressions.

In **Study V**, differences in baseline demographic data, allopregnanolone concentrations, psychometrics, and sedation between patients and controls were calculated with the Mann-Whitney U test. SEV and self-rated sedation were calculated in terms of the difference from the baseline at each time point (i.e., delta degrees/s and delta sedations scores). The SEV parameters were analyzed after the three injections using analyses of variance (ANOVA) with repeated measures.

5 ETHICAL CONSIDERATIONS

Several ethical aspects were taken into account in the studies included in this thesis.

First, as all studies were conducted on humans, they were all conducted in accordance with the Helsinki declaration. This means, among other things, that the well-being of the individual was more important than all other aspects of the studies.

All five studies were approved by the Regional Ethics Committee at Karolinska Institutet, Stockholm, Sweden. Reference numbers: 2007/1265-31/5, 2008/759-31+ 2009/284-32/1 (supplement), 2011/851-31/3, and 2011/852-31/3 + 2012/492-32 (supplement).

Participants in Study I were not asked for consent, because this retrospective review of patient files and forensic examinations was considered part of the qualitative monitoring of the clinic. However, all data were anonymized, and all analyses were performed in anonymized datasets.

Participants in Studies II-V were all given written information about the study before they were asked for informed consent. They were informed about their participation being entirely voluntarily and that at any time and for any reason, they could leave the study without any consequences for their future care. They were also informed that all their personal information would be handled confidentially. To ensure the participants' anonymity, the baseline, as well as the follow-up questionnaires, interviews, data from challenges, and blood analyses, were coded with ID numbers and stored in a locked room. The key to the ID numbers was only available to the responsible study researchers. Because it could be ethically questionable to include patients in the emergency room directly after a sexual assault, all participants were informed and asked for consent at the follow-up appointment held after 10-14 days. Because Study IV, aimed to explore the concentrations of endogenous steroids in the immediate aftermath of rape, we obtained ethical approval to take blood samples at the acute visit, but the women were not asked for written consent until the next visit. If the women did not consent, their blood samples were destroyed.

Off course, it could be ethically questionable to perform studies on women who had recently experienced sexual assaults. The patients were in a vulnerable position, and many were affected by shock and anxiety. However, I believe that if everything possible is done to minimize the impact of the study on the patient's physical, mental, and social integrity and the patient is fully informed and given the reason for the study, it can be justified. I also believe that addressing one's feelings through answering a questionnaire or interview and the extra attention given to the participant within the study can actually be helpful.

6 RESULTS

This section is a summary of the results of the five studies in this thesis. For a complete presentation, all four studies are found at the end of the thesis.

6.1 STUDY I

6.1.1 Victim-assailant relationships in sexual assaults

As seen in Table 6, women who presented at the clinic after having been sexually assaulted by their intimate partners were older, were of Swedish ethnicity less often, were under the influence of alcohol at the time of the assault less often, had a history of prior assaults more often, and sought help later compared to women assaulted by a stranger or an acquaintance.

Table 6. Differences in victim characteristics between intimate partner, stranger, and acquaintance assaults

	Intimate partner	Stranger	Acquaintance	p^b	p^c	p^d
	n = 102 ^a	n=114 ^a	n = 287 ^a			
Mean age (SD)	32.9 ±12.7	24.2 ±12.0	23.8 ±10.3	< 0.001	< 0.001	NS
Victim's ethnicity (% Swedish)	54/102 (53%)	98/114 (86%)	234/287 (82%)	< 0.001	< 0.001	NS
Victim under influence of alcohol	27/94 (29%)	79/110 (72%)	204/280 (73%)	< 0.001	< 0.001	NS
Previous history of sexual assault	61/96 (64%)	34/102 (33%)	113/276 (41%)	< 0.001	< 0.001	NS
Time between assault and examination						
≤ 72hrs	66/102 (65%)	96/114 (84%)	223/287 (78%)	0.001	0.01	NS
≥ 72hrs	36/102 (35%)	18/114 (16%)	64/287 (22%)			

Pearson's Chi-square test or Fisher's exact test for categorical variables, ANOVA for continuous variables.

^a Variable analyses were based on differing denominators, as determined by missing data. ^b P-value intimate partner vs. stranger, ^c P-value intimate partner vs. acquaintance, ^d P-value stranger vs. acquaintance. NS = not statistically significant.

Further, the violence and sexual acts used in the intimate partner assaults were of a more severe kind, more frequently involving the use of multiple types of violence and multiple sexual acts (see Table 7).

Table 7. Differences in assault characteristics between intimate partner, stranger, and acquaintance assaults

	Intimate partner	Stranger	Acquaintance	p^b	p^c	p^d
	n = 102 ^a	n=114 ^a	n = 287 ^a			
Type of assault						
Vaginal	82/102 (80%)	61/114 (54%)	197/287 (69%)	< 0.001	0.03 ^c	0.03 ^c
Anal	26/102 (25%)	7/114 (6%)	41/287 (14%)	< 0.001	0.01	0.02
Oral	25/102 (25%)	14/114 (12%)	59/287 (21%)	0.02	NS	0.05 ^e
Vaginal + other	31/102 (30%)	15/114 (13%)	66/287 (23%)	< 0.001	NS	NS
Attempt	2/102 (2%)	22/114 (19%)	11/287 (4%)	< 0.001	NS	< 0.001
Others	6/102 (6%)	20/114 (18%)	28/287 (10%)	0.01	NS	0.03 ^e
Type of violence						
Any violence	91/101 (90%)	88/110 (80%)	159/287 (55%)	NS	< 0.001	< 0.001
Attempts of strangulation	21/102 (21%)	9/114 (8%)	2/287 (1%)	0.01	< 0.001	< 0.001
Kick	17/91 (19%)	3/88 (3%)	0/287 (0%)	0.001	(< 0.001)	(0.01)
Multiple violence	49/101 (49%)	32/110 (29%)	41/287 (14%)	0.004	< 0.001	0.001
Holding	28/102 (27%)	52/114 (46%)	101/287 (35%)	0.04 ^e	NS	0.04 ^e

Pearson's Chi-square test or Fisher's exact test for categorical variables. ^a Variable analyses were based on differing denominators, as determined by missing data. ^b P-value intimate partner vs. stranger, ^c P-value intimate partner vs. acquaintance, ^d P-value stranger vs. acquaintance. ^e Not statistically significant according to the Bonferroni correction. NS = not statistically significant.

6.1.2 Multiple violence

In the crude analysis, factors associated with an increased risk of being exposed to multiple violence were the assailant being either a stranger or an intimate partner and the victim being over 45 years old, not being of Swedish ethnicity, and not having been under the influence of alcohol during the assault. Furthermore, findings of extra-genital injuries and assaults consisting of multiple sexual acts were associated with an increased risk of being exposed to multiple violence. After adjusting for all factors in the multivariable model, only the assailant

being an intimate partner ($OR = 4.1$, 95% CI [1.9, 9.0], $p < 0.001$) and extra-genital injury ($OR = 5.0$, 95% CI [2.6, 9.5], $p < 0.001$) were associated with multiple violence.

6.1.3 Genital injuries

Genital injuries were only found in 20% of all women in this study. Genital injuries were most commonly located in the posterior fourchette (35%), in the vulva (13%), on the labia minora (12%) and in several locations (19%). The injuries were most often small lacerations. The genital injury prevalence was almost tripled in women examined within 72 hours compared with those examined after 72 hours (23.7% vs. 8.3%, $p < 0.001$). In logistic regression, the victim-assailant relationship was not associated with genital injury. The adjusted analysis showed that the only association between the risk of presenting at the clinic with genital injuries was with being examined within 72 hours after the assault ($OR = 6.4$, 95% CI [2.4, 17.4], $p < 0.001$).

6.1.4 Extra-genital injuries

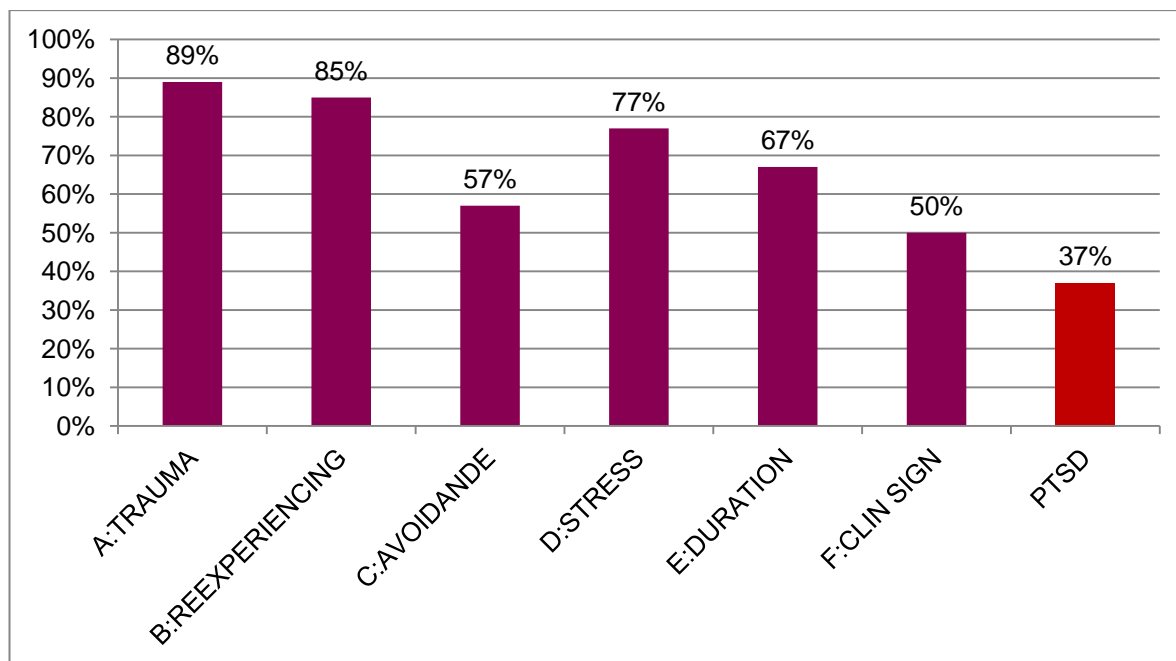
Extra-genital injuries were almost three times as common as genital injuries, 58% (263/465) compared with 20% (90/450). Injuries to the extremities were apparent in 52% (263/503) of the cases, to the head in 21% (107/503) of the cases, and to the trunk in 25% (115/462) of the cases. Injuries to the head were reported in 34% of the intimate partner assaults and in 29% of the stranger assaults, to be compared with 17% in the assaults committed by acquaintances ($p < 0.001$). In the crude analysis, extra-genital injuries were more often seen when the assailant was an intimate partner ($OR = 1.7$, 95% CI [1.1, 2.8], $p = 0.03$) compared to an acquaintance. In the adjusted analysis, the only factors that remained significantly associated with extra-genital injury were the examination being performed within 72 hours ($OR = 2.5$, 95% CI [1.4, 4.5], $p = 0.002$) and reports of physical violence ($OR = 5.5$, 95% CI [3.0, 10.4], $p < 0.001$).

6.2 STUDY II

6.2.1 PTSD and depression at six months

Of the 63% of victims who completed the six-month follow-up, 36.8% met all 6 criteria for PTSD according to the SCID-I interview. The results from the interviews are presented in Figure 6.

Figure 6. Results from the SCID interviews six months after sexual assaults (N = 201)



After having excluded those women who did not meet a Criterion A trauma ($n = 22$), the PTSD prevalence was 41.3% (74/179), and 54% had a high symptom load of B-, C-, and D-symptoms.

If one also excluded the 39 women who, according to the PDS questionnaire, already had pre-existing PTSD at the time of the assault, 38.6% (54/140) had developed PTSD at six months.

Regardless of PTSD status, 47.5% suffered from moderate or severe depression at six months according to the Beck Depression Inventory (BDI).

6.2.2 Predicting the development of PTSD in sexual assault victims

Three regression analyses were conducted separately. These analyzed psychometric variables, victim characteristics, and assault characteristics. The variables in these regressions were all found to be significant in crude analysis.

Of the psychometric variables entered (depression, dissociation, re-experience, avoidance, arousal, and ASD), severe depression ($OR = 2.75$, 95% CI [1.55, 4.52], $p = 0.002$) and ASD ($OR = 2.61$, 95% CI [1.14, 6.00], $p = 0.031$) at baseline were associated with the development of PTSD in the multivariable model.

Of the victim characteristics (lifetime depression, psychiatric treatment history, history of sexual assault in childhood, history of sexual assault in adulthood, history of ≥ 2 traumatic events, and employment status), a history of ≥ 2 traumatic events ($OR = 2.02$, 95% CI [1.10, 4.15], $p = 0.040$) and a psychiatric treatment history ($OR = 2.01$, 95% CI [1.05, 3.83], $p = 0.034$) were associated with the occurrence of PTSD.

Of the assault variables (physical injury, victim-offender relationship, perceived life threat, type of sexual assault, whether the victim had been under the influence of alcohol, and the severity of physical violence during the assault), perceived life threat ($OR = 2.15$, 95% CI [1.01, 3.76], $p = 0.044$), having been sexually assaulted by a group ($OR = 3.84$, 95% CI [1.16, 10.69], $p = 0.027$), having been subjected to several sexual acts ($OR = 2.71$, 95% CI [1.39, 4.29], $p = 0.004$), and having been injured ($OR = 2.07$, 95% CI [1.00, 4.54], $p = 0.050$) were found to be significant risk factors. Suffering from amnesia was found to be a protective factor for PTSD ($OR = 0.31$, 95% CI [0.07, 0.95], $p = 0.038$) in the crude analysis; however, not in the adjusted analysis. The significant predictors from these three initial regressions were then simultaneously entered into a final model predicting PTSD (Table 8).

Table 8. Factors associated with PTSD six months after sexual assault (final model, adjusted for initial PTSD status)

	<u>Univariable</u>		<u>Multivariable</u>
	% with PTSD	OR [95% CI]	AOR [95% CI]
Sexually assaulted by group	65.0	3.10** [1.29,8.03]	4.01* [1.18, 152]
ASD at baseline	43.2	3.92**[1.53, 10.06]	4.96* [1.30, 18.6]
Multiple acts during assault	48.2	2.32**[1.26, 4.29]	2.93** [1.49, 6.14]
Physical injury	40.4	3.11**[1.43, 7.24]	2.48* [1.22, 6.50]
Severe depression at baseline	57.1	3.36**[1.78, 6.32]	2.33* [1.03, 5.10]
History of ≥ 2 traumatic events	50.0	2.62**[1.41, 4.85]	1.91* [1.14, 3.72]
Psychiatric treatment history	59.6	2.45**[1.33, 4.50]	1.93 [1.00, 3.81]
Perceived life threat	53.8	2.30**[1.23, 4.32]	1.34 [0.60, 3.89]

Hosmer and Lemeshow Test: 0.86. OR = Odds Ratio, AOR = Adjusted Odds Ratio, CI = Confidence Interval, ASD = Acute Stress Disorder. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

6.2.3 ASD as a predictor of PTSD

Although ASD was found to be associated with the development of PTSD at six months in both the crude and adjusted analyses, the use of ASD as a predictor of PTSD had its limitations. Even though the majority of the women suffered from ASD at the two-week follow-up, only 43% of these women continued developing PTSD. Thus, ASD, as a predictor, had high sensitivity ($67 / [67+6] = 92\%$), but low specificity ($38 / [38+88] = 30\%$) and a low positive predictive value ($67 / [67+88] = 43\%$); see Figure 7.

Figure 7. ASD as a predictor of PTSD

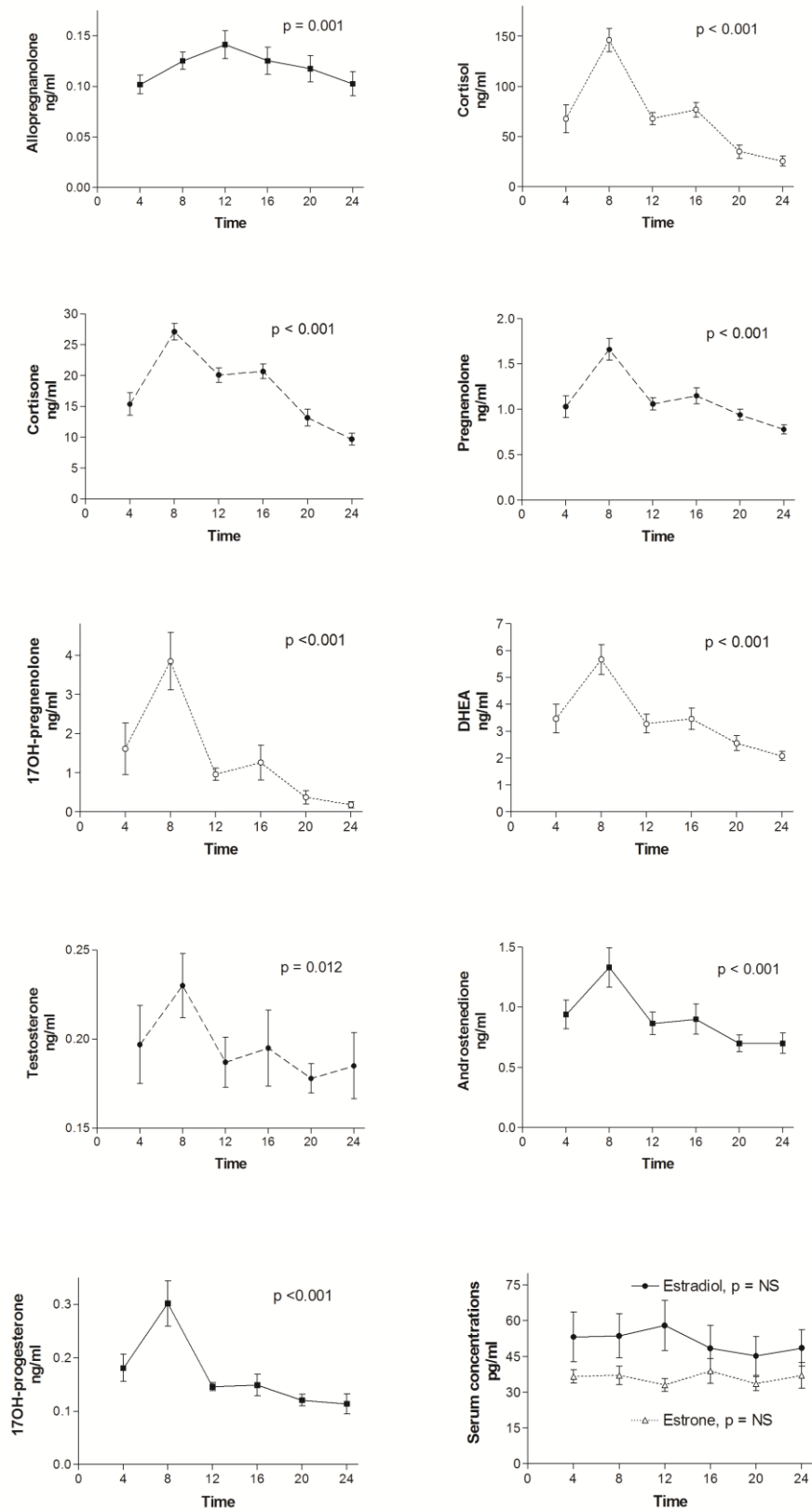
		PTSD	
		No	Yes
ASD	No	38	6
	Yes	88	67

6.3 STUDY III

6.3.1 Diurnal variations of stress hormones

Using repeated-measures ANOVA, we found that all steroids, apart from the estrogens, had a significant within-subject variation, indicating that a circadian rhythm existed during the follicular phase of the menstrual cycle (Figure 8). All steroids had their peak concentration around 08:00 (e.g., just after awakening), apart from allopregnanolone, that had a more flat curve with the highest concentrations throughout the day and peak concentrations around 12:00.

Figure 8. Serum concentrations of allopregnanolone, cortisol, cortisone, pregnenolone, 17OH-pregnenolone, DHEA, testosterone, androstenedione, 17OH-progesterone, estrone, and estradiol during 24 hours presented as mean \pm SEM.



6.4 STUDY IV

6.4.1 Steroid concentrations in predicting PTSD

In this cohort, 63% (108/171) completed the six-month follow-up, and of these, 36% had developed PTSD. The characteristics of the PTSD group and the non-PTSD group at six months are presented in Table 9.

Table 9. Demographic data, baseline characteristics in women with PTSD compared to those without PTSD at six months. Continuous data presented as median (range), and categorical data presented as percents

	PTSD N=38	Non-PTSD N=69	p-Value between groups
Age, years	26.4 (18-59)	26.6 (18-44)	NS
BMI	24.6 (19-28)	23.7 (19-29)	NS
Oral contraceptive use (%)	31.6	44.9	NS
Smoking	36.4	35.4	NS
Days between assault and acute visit	2.35 (0-16)	3.04 (0-24)	NS

BMI = Body Mass Index, NS = not statistically significant

Differences in steroid serum concentrations at the acute visit between women who developed PTSD and those who did not were analyzed using Mann-Whitney U test. As seen in Table 10, there were no differences in serum concentrations for any of the steroids between the two groups.

Table 10. Concentrations of steroids (ng/mL) in serum at the acute visit after sexual assault (T1) in women with PTSD compared to those without PTSD at six months (T3). Data presented as median (range).

	PTSD N=38	Non-PTSD N=69	p-value*
Allopregnanolone	0.11 (0.035-0.962)	0.12 (0.050-0.627)	NS
Cortisol	95.0 (29-292)	95.0 (34-329)	NS
Cortisone	21.00(11-31)	23.00 (4-36)	NS
11-DC	0.10 (0.99-1.40)	0.11 (0.00-1.43)	NS
Pregnenolone	1.40 (0.50-4.80)	1.50 (0.40-3.80)	NS
17OH-pregnenolone	1.29 (0.10-13.70)	1.35 (0.00-11.10)	NS
DHEA	4.60 (1.20-11.10)	5.00 (0.10-10.90)	NS
Total Δ 5 steroids	7.60 (2.50-29.60)	7.90 (1.90-25.80)	NS
17OH-progesterone	0.16 (0.00-2.00)	0.12 (0.00-1.06)	NS
Ratio Cortisol/17OH-progesterone	553.14 (17-6267)	833.33 (50-7700)	NS
Androstenedione	0.76 (0.15-1.94)	0.85 (0.25-2.50)	NS
Testosterone	0.24 (0.08-1.24)	0.24 (0.07-1.34)	NS

* P-value according to Mann-Whitney U test. Total Δ 5 steroids = Pregnenolone + 17OH-pregnenolone + DHEA.

The term “ Δ 5 steroids” was used for pregnenolone, 17OH-pregnenolone, and DHEA. These steroids all have a double bond between carbons 5 and 6 and are synthesized along the delta-5 pathway (see Section 2.3.1).

6.4.1.1 Bivariate correlations

As seen in Table 11, none of the steroids were correlated with PTSD symptoms at either the two-week or six-month follow-up. Low concentrations of all of the Δ 5 steroids were associated with greater depression symptoms at six months, and 17OH-pregnenolone was also associated with depression symptoms after two weeks.

Concentrations of cortisol and the Δ 5 steroids were negatively correlated with a prior assault history, and the concentrations of allopregnanolone and the Δ 5 steroids were negatively correlated with a psychiatric treatment history. PTSD and depression were positively correlated with each other at both time points; however, PTSD at two weeks was not correlated with PTSD at six months. None of the correlations or the absence of a correlation

changed when performing a subgroup analysis of patients who sought help within 24 or 72 hours.

Table 11. Correlations between serum steroid concentrations, oral contraceptives, smoking, PTSD, depression, prior trauma history, and psychiatric treatment history.

	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.
1. Allopregnanolone	-.25*	-.08	.05	.58**	.30**	.42**	.31**	.40**	-.50**	-.02	.12	.03	-.00	-.07	-.07	-.29**
2. Cortisol	1	.71***	0.55**	-.04	.58***	.39***	.45***	.30**	.13	-.01	-.15	-.01	-.03	.03	-.26*	-.16
3. Cortisone		1	0.60**	.17	.59***	.42***	.51***	.18	-.15	.06	.09	-.19	.08	.17	-.12	-.32**
4.11-DC			1	.44**	.35**	.53**	.44**	.59**	-.07	.15	-.15	.05	-.07	-.02	-.18	-.15
5.17OH-prog.				1	.33**	.54***	.25*	.35***	-.39**	.15	.01	.08	-.05	-.01	-.01	-.20*
6. 17OH-preg.					1	.76***	.87***	.69***	-.15	.08	.03	-.21*	-.02	-.22*	-.24*	-.29**
7. Pregnenolone						1	.71***	.73***	-.24*	.05	.05	-.21	-.11	-.25*	-.17*	-.27**
8. DHEA							1	.75***	-.12	.09	.11	-.19	.00	-.21*	-.21*	-.23*
9. Total Δ5 steroids								1	-.20*	.07	.06	-.21	-.06	-.25*	-.21*	-.29*
10. OC									1	.06	-.08	-.06	-.12	-.15	-.02	.07
11. Smoking										1	-.13	-.07	.01	-.06	.03	-.20*
12. PTSD T2											1	.19*	.11	.14	.31***	.20*
13. Depression T2												1	.27**	.57***	.34**	-.00
14. PTSD T3													1	.60***	.28**	.17*
15. Depression T3														1	.34***	.28**
16. PAH															1	.20*
17. PTH																1

OC = Oral Contraceptives, PAH = Prior Assault History, PTH = Psychiatric Treatment History. T1 = acute visit, T2 = 10-14 days follow-up visit, T3 = six-month visit. * P < .05, ** p < .01, *** p < .001.

6.4.1.2 Logistic regression

When using binary logistic regression none of the steroids were associated with the development of PTSD at six months. This result remained after adjusting for the number of days that had elapsed since the assault and the menstrual cycle phase. Low levels of the steroids in the Δ5 steroid group were associated with the development of depression at six months (OR = 3.9, 95% CI [1.08, 8.26], p = 0.035). However, this association did not remain after adjusting for trauma history, psychiatric treatment history, and menstrual cycle phase. Low concentrations of cortisol were associated with a history of earlier traumatization (OR = 2.5, 95% CI [1.01, 6.7], p = 0.048), an association that remained after adjusting for the number of days that had elapsed since the assault. The association between low levels of steroids in the Δ5 steroid group and earlier traumatization did not remain after adjusting for menstrual cycle phase. Low concentrations of allopregnanolone were associated with a psychiatric treatment history (OR = 6.0, 95% CI [1.7-21.8], p = 0.007), an association that remained after adjusting for earlier traumatization, oral contraceptives, and the number of days that had elapsed since the trauma.

6.5 STUDY V

In order to examine the sensitivity of the GABA-A receptor in patients with PTSD, a total of 12 patients and 16 controls completed a total of 57 challenges. Ten patients and 10 controls were meant to be included in each challenge. However, in the diazepam and flumazenil challenge 9 patients but 10 controls were included. In the allopregnanolone challenge, 10 participants were included in each group, but one control was excluded because of technical problems during the challenge.

Baseline characteristics between the PTSD patients and the non-traumatized controls without PTSD are presented in Table 12.

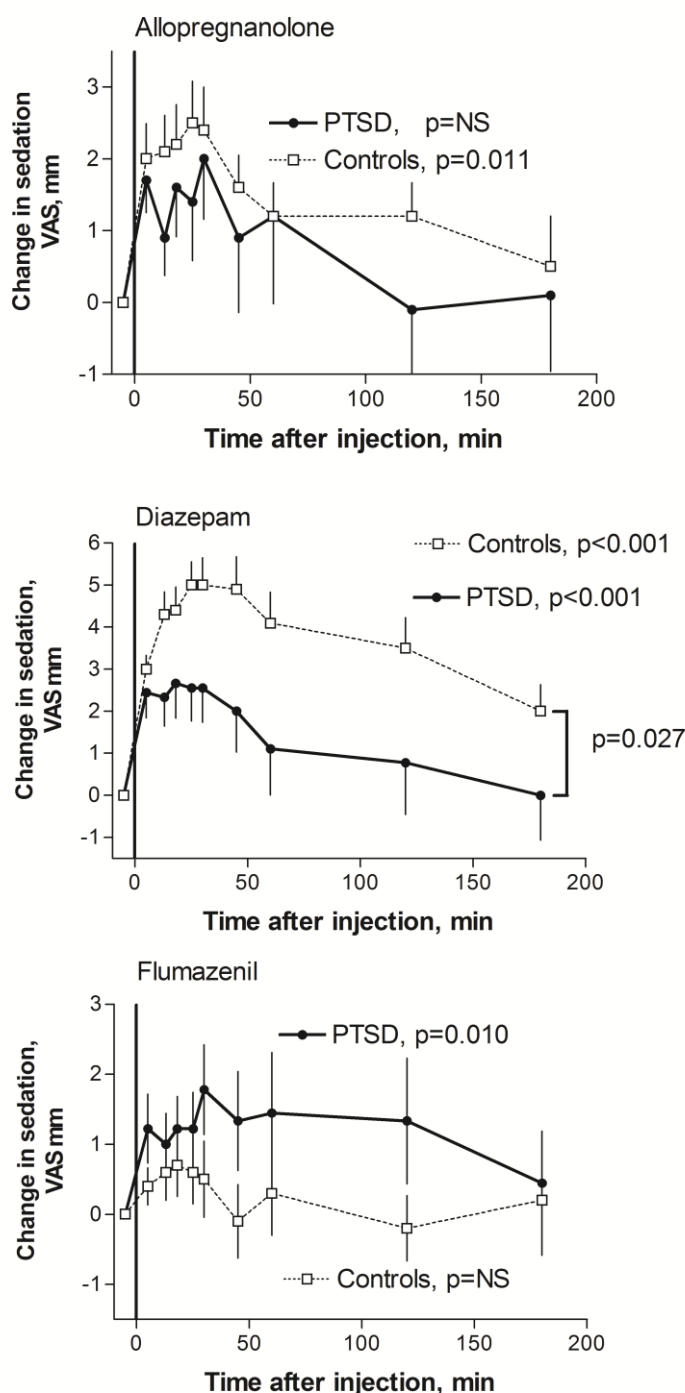
Table 12. Demographic data, baseline characteristics, and subjective scoring of anxiety in women with PTSD and controls. Data presented as median (range) and mean \pm SEM

	PTSD N=12	Controls N=16	p-Value between groups
Age, years	24.8 (18-37)	27.7 (20-39)	NS
BMI	24.6 (19-28)	22.6 (19-29)	NS
Cycle day	10.3 (6-12)	8.9 (5-12)	NS
S-allopregnanolone, nmol/L	0.51 \pm 0.06	0.54 \pm 0.42	NS
SEV, degrees/sec	490 \pm 13.4	490 \pm 12.8	NS
Sedation, VAS, mm	3.3 \pm 0.6	2.3 \pm 0.3	NS
SASRQ	108 (80-142)	2.7 (0-14)	< 0.001
BDI	25.9 (5-53)	1.0 (0-6)	< 0.001
STAI	49.0 (32-64)	26.8 (20-32)	< 0.001
PSS	15.0 (5-33)	1.1 (0-4)	< 0.001
SADS	1.8 (0-3)	0.1 (0-1)	< 0.001

BMI = Body Mass Index, SEV = Saccadic Eye Velocity, VAS = Visual Analog Scale 10 mm, SASRQ = Stanford Acute Stress Reaction Questionnaire, BDI = Beck Depression Inventory, STAI = State-Trait Anxiety Inventory, PSS = Panic Symptoms Scale, SADS = State Anxiety and Discomfort Scale.

6.5.1 Sedation

Figure 9. Subjective ratings of sedation (delta values from baseline) after injections of allopregnanolone, diazepam, and flumazenil in women with PTSD compared to healthy controls. The injections are indicated by the vertical lines. The bracket in the diazepam graph indicates the significance of the difference between patients and controls.



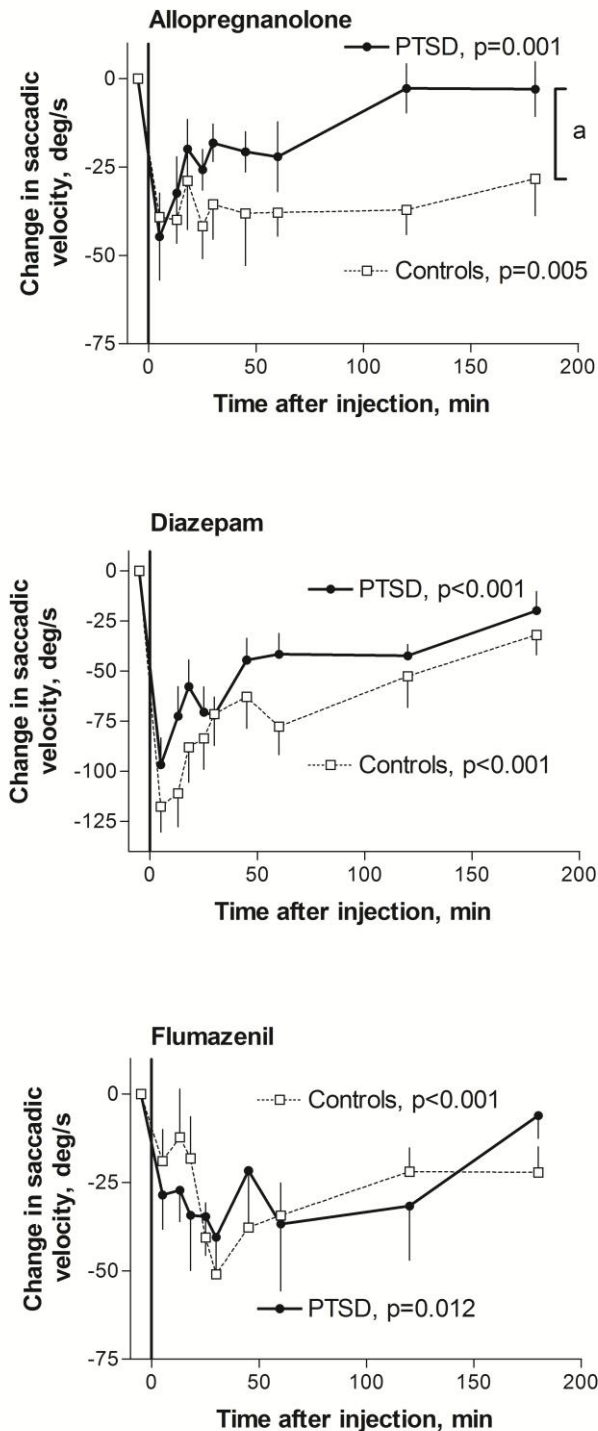
After an injection of allopregnanolone, controls showed an increase in sedation ($p = 0.011$). The PTSD patients showed a tendency towards increased sedation, though it was not significant. There was no significant difference between the groups (see Figure 9, Allopregnanolone).

After an injection of diazepam, both groups showed a significant increase in sedation. However, there was a difference between the groups in that the patients showed less of an effect compared to controls ($p = 0.027$) (see Figure 9, Diazepam).

After an injection of flumazenil, the patients showed an increase in sedation ($p = 0.010$), while the controls did not show any effect. However, there was no significant difference between the two groups regarding sedation (see Figure 9, Flumazenil).

6.5.2 Saccadic Eye Velocity (SEV)

Figure 10. Saccadic eye velocity (delta values from baseline) after injections of allopregnanolone, diazepam, and flumazenil in women with PTSD compared to healthy controls. The injections are indicated by vertical lines. Also, *a* indicates the significance of the difference between the two groups at different time points.



After an injection of allopregnanolone, both groups showed a decrease in SEV. Except for the first 5 minutes after injection, there was a difference between the two groups in terms of response (see a Figure 10, Allopregnanolone). Patients responded to a lesser degree than controls ($a = p = 0.047$). If one considers the response 18 minutes after the injection, the difference was even greater ($a = p = 0.038$).

After an injection of diazepam both patients and controls responded with a significant decrease in SEV (Figure 10, Diazepam). However, there was no significant difference in reaction between the two groups.

After an injection of flumazenil, there was a decrease in SEV in both groups (Figure 10, Flumazenil). This reaction was similar to what was seen after an injection of diazepam. There was no significant difference in the reactions between the two groups.

7 DISCUSSION

7.1 GENERAL DISCUSSION

7.1.1 Victim-assailant relationship in sexual assaults

The major findings of Study I confirmed the hypothesis that sexual assaults committed by an intimate partner differ from other victim-assailant assaults regarding the use of violence and coercion. Victims of intimate partners were exposed to more severe violence, including hits, kicks, and attempts of strangulation, while violence used in stranger and acquaintance assaults more often consisted of simply holding the victim down during the assault. Subsequently, women who were sexually assaulted by their intimate partners also showed a trend towards presenting with more extra-genital injuries. Genital injury prevalence, however, was not associated with the victim's relationship with the assailant.

These results are interesting because they differ somewhat from the majority of the international literature. Most of the earlier studies have reported stranger assaults as being more violent and more associated with injuries compared to assaults by a known assailant [48,151,152]. However, our results are in line with those studies that have separated intimate partner assaults from other known-assailant assaults [50,51,153]. When doing so, intimate partner assaults have been suggested to be more violent. There are, however, still some discrepancies between the studies. Murphy and colleagues [51], for example, found that genital injury prevalence was higher in intimate partner assaults but that extra-genital injuries were more common among stranger assaults. These discrepancies may be caused by the use of different methodologies but one could also speculate as to whether stranger assaults in Sweden are less violent compared to those in the US or whether Swedish women are more likely to report sexual violence than women from other western countries. The latter interpretation is at least partially supported by the fact that in crime statistics, a larger proportion of sexual assaults are reported in Sweden compared to in the US and the UK [12,154].

Despite the discrepancies described above, our study supports the knowledge that sexual assaults within a relationship most often co-occur with physical and psychological violence; these assaults are a form of intimate partner violence (IPV) that can be called intimate partner sexual violence (IPSV). A recently published review concluded that the average prevalence of IPSV within IPV survivors was about 36% [155]. Women who were sexually assaulted by their partners more often had a history of earlier assaults, suggesting repetitive assaults within the relationship. Also, women who were sexually assaulted by a partner had a high risk of being sexually assaulted in another relationship [156]. In our study, we found that women who were sexually assaulted by a partner presented at the clinic later than women who were assaulted by an acquaintances or a stranger. The reason for this is unknown, but it could be caused by increased self-blame, as well as lack of support in reporting and a desire to maintain a "whole" family. It is also well-known that along the same line as the results for late disclosure and presentation at the clinic, IPSV prevalence rates are underestimated

because women in relationships are hesitant to accept that the violence they have been exposed to is, in fact, a rape or a sexual assault.

Finally, women in intimate partner assaults were older, less often of Swedish origin, and less often under the influence of alcohol during the time of the assault compared to the other groups. This can be explained by the fact that in contrast to the two other assailant groups, in which an assault most often occurs during or after social interactions where alcohol is being served, intimate partner assaults occur within the home of the victim. It is also more common among older women to be in a steady relationship, and in a relationship, alcohol is not needed to attract or mislead the victim. The over-representation of women born outside Sweden in the group of women assaulted by their partners may be explained by socioeconomical and cultural factors, but it has to be backed up with further studies.

7.1.2 Predicting PTSD in sexual assault victims

After having excluded those women who had not met a criterion A trauma and those who were assessed as having pre-existing PTSD at the time of the assault, 39% of the women in Study II had developed PTSD six months after the sexual assault. Even though the percentage of women who dropped out between the two-week and six-month assessments was almost 37%, the PTSD prevalence was comparable to earlier longitudinal and larger cross-sectional studies. One can assume that the PTSD prevalence would have been even higher if less attrition had been seen (see Section 7.2.2.1 on selection bias).

The rationale for Study II was to see whether it was possible to identify those women who had the highest risk of developing PTSD within a group of acute-medical help-seeking women after rape. We therefore focused on risk factors for PTSD that could be identified at the acute visit and/or at a two-week follow-up visit. It has been suggested that post-assault psychosocial factors have more influence on the development of PTSD than pre-existing variables or the circumstances around the current assault [68]. However, the post-assault variables cannot as easily be identified at the acute visit and cannot be used as immediate predictors to identify those women at greatest risk. In the present study, the highest risk of developing PTSD was seen in women who had been sexually assaulted by multiple assailants, were suffering from ASD shortly after the assault, had been subjected to several acts during the assault, had been injured, had severe depression at the two-week follow-up, and had a history of ≥ 2 traumatic events.

The finding that women sexually assaulted by a group (i.e., more than one assailant) had the highest risk of developing PTSD probably indicates the extremely threatening nature of these assaults. In the same way, the association between having been exposed to several sexual acts during the assault and PTSD probably indicates more severe interpersonal violence. Surprisingly, single-stranger assaults were not associated with an increased risk of developing PTSD as compared to the other assailant groups in this cohort. This is contrary to two earlier studies in which the victims of strangers were found to have more PTSD symptoms than victims of intimate partners and acquaintances [73,74]. However, in reading these studies, it

is unclear whether they have discriminated between single- and multiple-stranger assaults. If this is not the case, the association between stranger assaults and PTSD may have become smaller. In the present study, even though the results are not significant, women assaulted by an intimate partner had the highest risk of developing PTSD as compared to the other single-assailant groups. This supports the finding from Study I that sexual assaults within relationships are the most violent.

Unlike study populations in large cross-sectional studies from national representative samples, the women in this study represented an already-heavily-traumatized group. The majority of the women had a history of earlier sexual assaults in both childhood and adulthood. We saw an almost linear effect between the number of traumatic experiences and the risk of developing PTSD. Because of the high degree of traumatization in this sample, a history of a single earlier trauma or sexual assault did not increase the risk of PTSD. However, a variable defined as having experienced two or more traumatic events (≥ 2 traumas) remained a significant risk factor in the final multivariable model. The findings regarding childhood sexual assault were in line with earlier studies; it was not found to be a significant predictor of PTSD on its own. However, the link between childhood sexual assault and PTSD seems to be mediated through the increased risk of being victimized in adulthood, which subsequently increases the risk of developing PTSD [18,69].

Consistent with the earlier literature [157], we found that women who had been depressed in the past and had severe depression in the immediate aftermath of the rape were at an increased risk of presenting with PTSD at the six-month assessment. Even though this finding could be partially due to the overlapping symptoms of these disorders (e.g., concentration and sleep disturbances), it is also very likely that the impact of the assault is intensified for previously depressed patients and that the trauma causes a new episode of depression.

Finally, the association between ASD and PTSD is worth mentioning. ASD was associated with the development of PTSD in the final multivariable model. However, the ceiling effect limits ASD's ability to predict PTSD. That is, even though a vast majority of the women had ASD at the two-week assessment, far from all of them continued to develop PTSD.

7.1.3 Diurnal variations of endogenous steroids

In Study III six classes of steroids were measured and analyzed regarding possible diurnal variations: the anesthetic steroid allopregnanolone, glucocorticoids (cortisol, cortisone, 11-deoxycortisol), androgens (androstenedione, testosterone, DHEA), pregnenes (pregnenolone, 17OH-pregnenolone), progestins (progesterone, 17OH-progesterone), and estrogens (estrone, estradiol). We found that all the measured steroids, apart from the estrogens, had a significant diurnal variation in premenopausal women in the follicular phase of the menstrual cycle. This has partly been described in the literature; however, the finding of a diurnal variation in allopregnanolone was surprising as this has not been described before and no such variation had been seen in the luteal phase of the menstrual cycle [117]. Because allopregnanolone is synthesized from progesterone, allopregnanolone concentrations are

known to be high during the luteal phase of the menstrual cycle [158] and therefore may blunt the nocturnal rhythm in the adrenals. Further, we found that the androgens, the pregnenes, and the progestins all had similar diurnal variation curves as the glucocorticoids (i.e., with a peak in the morning just after awakening and the lowest concentrations during the night). Allopregnanolone had a somewhat similar curve; however, it was more flat with a peak concentration around 12.00. The reason for this delay and the different steepness of the curve may be caused by the longer biosynthesis pathway to allopregnanolone; however, this must be explored in further studies.

Thus, these results suggested that when analyzing the serum concentrations of the steroids in Study IV, we had to adjust for their diurnal variation.

7.1.4 Concentrations of endogenous steroids in predicting PTSD

The major findings of Study IV were that low concentrations of cortisol and all of the $\Delta 5$ steroids (pregnenolone, 17OH-pregnenolone, and DHEA) shortly after rape were associated with a history of earlier traumatization and that low allopregnanolone concentrations shortly after rape were associated with a psychiatric treatment history. However, there was no association between any of the steroids and pre-existing PTSD or the development of PTSD at six months. The $\Delta 5$ steroids were negatively correlated with depression at six months; however, not in the adjusted analysis.

The finding that cortisol concentration measured in the aftermath of rape was not associated with the development of PTSD is contrary to what has been found in patients after motor vehicle accidents [92,93,94,95], where low cortisol concentrations were found to be associated with the development of PTSD. The results are, however, concordant with earlier studies of sexually assaulted women, in which low cortisol concentrations on their own were not associated with the development of PTSD [96,97]. Instead, lower concentrations of cortisol were seen in women with a prior trauma history, who subsequently had an increased risk of developing PTSD. Similarly, we found that allopregnanolone concentrations were negatively correlated with a psychiatric treatment history (i.e., women who reported a history of psychiatric illness presented with reduced allopregnanolone concentrations in the aftermath of rape). A psychiatric treatment history and a prior trauma history were found to be risk factors for the development of PTSD after rape in Study II, and this association was also seen in this study.

Another interesting observation in this study was the possible interaction between allopregnanolone and cortisol and perhaps the subsequent interaction between the menstrual cycle and the HPA axis. We saw a small but significant negative correlation between allopregnanolone and cortisol ($r = -.25, p < .01$) (i.e., cortisol concentrations were lower when allopregnanolone concentrations were high). This finding is in line with findings in rodents, where low allopregnanolone concentrations were found to potentiate cortisol responses and *vice versa* [159]. In a study of patients with premenstrual dysphoric disorder (PMDD) [117], the patients and the healthy controls had comparable concentrations of cortisol. However,

patients with higher concentrations of allopregnanolone displayed blunted nocturnal cortisol levels. The researchers therefore suggested that the diurnal secretion of cortisol in the luteal phase could be influenced by allopregnanolone concentration. Further, they suggested that the timing of the blood sampling, as well as individual levels of allopregnanolone, could explain the discrepancies in studies examining the HPA axis in PMDD patients. We therefore assume that when interpreting the HPA axis in PTSD patients, allopregnanolone concentrations must be taken into account. Not making adjustments for female patients being in the luteal phase of the menstrual cycle (i.e., when allopregnanolone concentrations are known to be high) [158,160] could potentially blunt the results. Also, in a recent study, Inslicht and colleagues [161] discussed the difficulties involved in interpreting neurosteroid responses in premenopausal women, suggesting that the reproductive hormones may be involved in the modulation of the HPA axis. In the present study, we also saw a highly positive correlation between allopregnanolone and the $\Delta 5$ steroids (pregnenolone, 17OH-pregnenolone, DHEA). The $\Delta 5$ steroids are mainly synthesized in the adrenal cortex but to some extent, also in the ovary [162]. Because the correlations were based on z-scores (i.e., after each sample had been adjusted for the diurnal variation), the correlations cannot solely be caused by similar diurnal variations. Instead, we assumed that this correlation was associated with the phases of the menstrual cycle. Higher concentrations of at least pregnenolone and 17OH-progesterone in the luteal phase compared to the follicular phase have been shown before [158]. When we, in the present study performed subgroup analyses excluding those patients who, according to their progesterone levels, were in the luteal phase, the negative association between the $\Delta 5$ steroids and the development of depression was erased. The association between low levels of $\Delta 5$ steroids and depression was also erased after adjusting for earlier trauma and a psychiatric treatment history.

The present study is unique because it is the first study to explore the relationship between the concentrations of steroids, intermediates and final products in the steroid biosynthesis pathway in the immediate aftermath of a trauma and the development of PTSD and depression. In this study samples were analyzed mainly using high-specificity validated LC-MS/MS methods, technique considered to be the “gold standard” for the analysis of endogenous steroids [163]. However, it is possible that the use of other techniques to measure the HPA axis would have provided more information. As a single blood or urine sample only provides a small “snapshot”, 24-hour sampling or low-dose dexamethasone tests might have given a more complete picture of the HPA axis function. Still, our interpretation of these results is that even though steroid concentrations in the aftermath of rape could not predict the development of PTSD in this study, the low steroid concentrations in women with earlier trauma and a psychiatric treatment history represent an increased vulnerability in the victim and probably an impairment of the HPA axis due to repetitive stress.

7.1.5 GABA-A receptor function in PTSD

The major findings in Study V were that the PTSD patients were less sensitive to allopregnanolone compared with healthy controls. This was seen in the form of a difference in SEV between the groups after injection. The PTSD patients were also less sensitive to diazepam compared to the controls, with a significantly lower increase in sedation. Further, the PTSD patients responded with an increase in sedation after injections of flumazenil, while this was not seen in the controls.

Our hypothesis that PTSD patients would have an increased sensitivity to allopregnanolone in the same way as burn-out patients [135] was not confirmed. Hence, an up-regulation of the $\alpha 4$, β , δ subunit, as had been suggested, is unlikely. Instead, our results indicating decreased sensitivity in the receptor is more in line with the findings for patients with panic disorder [136] and PMDD [160]. In these studies, the decreased sensitivity was explained by an acquired tolerance, probably due to a down-regulation of the GABA-A receptor. As allopregnanolone concentrations are known to be high during stress [164], the trauma and constant re-experiencing seen in PTSD patients (probably leading to repetitive periods with high allopregnanolone concentrations) could theoretically have caused an acquired chronic allopregnanolone tolerance [165].

The reduced sensitivity to diazepam in patients with PTSD was not confirmed via differences in SEV between the groups but through differences in sedation. The regulation of sedation has been suggested to be dependent on the $\alpha 1$, γ subunit [166], leading us to assume that PTSD patients also have tolerance in this system. Such tolerance could, of course, also have been caused by the patient having repeated alcohol or benzodiazepine intake; however, all forms of substance abuse were part of the study's exclusion criteria.

Finally, we found that in line with our hypothesis, the PTSD patients experienced an agonistic effect when given flumazenil. The patients reacted with increased sedation, while this was not seen in the controls. However, we made the surprising discovery that the controls also experienced an agonistic effect when given flumazenil regarding SEV. Both patients and controls reacted with a decrease in SEV after flumazenil injection. To our knowledge, this has not been described earlier, and in the study of burn-out patients [135], this effect was not seen in the controls.

To our knowledge, this is the first time that the GABA-A receptor has been examined in PTSD patients using an objective and reliable measure such as SEV. Even though subjective ratings of sedation are not as objective as SEV, the results in sum suggest that PTSD patients have an altered sensitivity to GABA-A-receptor-active substances. Subsequently, benzodiazepines and other GABA-A-receptor-active substances will be less effective in patients with PTSD. We know that benzodiazepines are still being widely used in patients with PTSD [114] and that some even claim that the use of benzodiazepines can increase PTSD prevalence after trauma [167]. The results from the present study therefore provide further proof of the impropriety of the use of benzodiazepines in this group of patients.

7.2 METHODOLOGICAL CONSIDERATIONS

7.2.1 Random errors

Research errors can be classified as random or systematic [168]. Random error stands for variability in the data that we cannot explain and that affects the precision of the estimates presented by the width of the confidence interval. Variation may reflect hidden biases that may not have been measured and perhaps not even discovered. The confidence intervals indicate the amount of random error in the estimate, and the random error will decrease as the size of the study population increases.

Study I represents a fairly large sample of consecutive women seeking help at the Emergency Clinic for Raped Women. However, when we performed sub-group analyses of different perpetrator groups, the confidence intervals increased and the study would have benefited from a larger sample.

Studies II and IV represent a cohort of sexually assaulted women recruited at the two-week follow-up after sexual assault. Even though the confidence intervals indicate that a higher validity would have been established with a larger sample, the majority of errors (as in all cohorts) are probably mainly caused by systematic errors.

In **Study III**, only 10 women were examined regarding the diurnal variation of various endogenous steroids. However, the results were clear, and probably would not have been drastically affected by a larger sample.

In **Study V**, the use of 10 individuals in each group at each challenge was based on earlier studies in which similar sample sizes have been able to provide sufficient results [135,138,139]. However, as we saw that the results had a large amount of variability within the groups as well, a larger study population might have made results more clear, if not changed them.

7.2.2 Systematic errors

Systematic errors (or biases) distort the estimates in a given direction and are generally a greater threat than random errors in epidemiological studies. Unlike random errors they are not reduced by increasing sample size. The systematic errors can be caused by the way subjects have been selected (selection bias), the way the study variables are measured (information bias) and by confusion or mixing of effects (confounders) [168].

7.2.2.1 Selection bias

Study I included all consecutive patients who sought medical help during a 13-month period. In Stockholm, all emergency sexual assault victim care is centralized to the Emergency Clinic for Raped Women, and the center takes care of women from both urban and suburban areas. Women belong to a wide variety of ethnic and age groups, something that reduces selection bias. However, the results are, of course, still biased by not having any information about the women who did not seek any help, something that also caused selection bias in **Study II** and

IV. We know that the number of rapes reported to the police in the area are far greater than the number of women who seek medical help and that the number of rapes reported to the police probably is just a small portion of the actual number of women who were sexually assaulted during the same timeframe [8].

Selection bias in **Studies II** and **IV** was also caused by the low participation rates, 30% (317/1047) and 31% (171/547), respectively. This was not unexpected, because a prospective design involves approaching survivors in the acute aftermath of the assault; it is only natural that many will not be willing to share details about the experience. In a recent review of longitudinal studies on sexual assault survivors, participation rates were similar, ranging from 12% to 69% but mostly being less than 45% [169].

The high level of attrition between the acute visit and the six-month follow-up in **Studies II** and **IV**, could of course, also have caused selection bias. However, in these two studies, the proportion of completers by victim-assailant relationship was the same as in Study I, suggesting that the samples were at least representative of help-seeking women in the Stockholm area. However, in our attrition analysis we saw that non-completers more often had an alcohol abuse, were depressed, and had more avoidance symptoms at baseline than the completers. Both alcohol abuse and depression are known to have a high co-morbidity with PTSD [170,171,172] and if we are to draw any assumptions from this, it would be that PTSD prevalence could have been even higher at six months if attrition was lower.

7.2.2.2 *Information bias*

Information bias refers to the accuracy of the collected data, and it can also be described as the misclassification of discrete variables. If a variable is measured on a categorical scale, this misclassification leads to a person being placed in an incorrect category.

In **Studies I, II,** and **IV**, the majority of baseline data was based on self-reports documented in the clinics' structured data files. Data collection was therefore dependent on the woman's report, and it is not clear how reliable it is to collect data within the context of a forensic examination shortly after a sexual assault. The women may still have been influenced by alcohol, been extremely upset, or suffered from peritraumatic dissociation. Missing data in the patient files and protocols from the forensic examinations were coded as "no". Although no more than 17% of responses were missing for any one variable, it is possible that these missing data could have impacted the study findings.

The psychometric self-assessed questionnaires used at the two-week and six-month follow-ups in **Studies II** and **IV** and during inclusion in **Studies III** and **V** may also have caused information bias. A self-assessed questionnaire can be incomplete, false, or exaggerated. If no more than 15% of the answers in an individual's questionnaire were missing, we imputed a number that was the mean of all the answers in the rest of the questionnaire. If more than 15% of the answers were missing in a questionnaire, these answers were kept as missing values. The diagnosis of pre-existing PTSD at baseline was based on the answers to the PDS questionnaire; a questionnaire not looked upon as the gold standard when assessing PTSD

diagnosis. Even though the questionnaire has been used with sexual assault victims in earlier studies and the women had the chance to ask about the interpretation of the questions during the session, the diagnosis of pre-existing PTSD may have to be treated with caution.

The occurrence or absence of PTSD at six months in **Studies II** and **IV** and during inclusion in **Studies III** and **V** was established using a structured clinical interview (SCID-I). Even though the use of interviews has been proven to be more accurate in assessing a psychiatric disease, it can still be biased by both the interviewer's own interpretation of the answers and the victim's ability to answer correctly. A patient may exaggerate her symptoms in order to get secondary disease gain and a healthy control may be willing to marginalize a symptom in order to fulfill inclusion criteria. The use of parallel psychometrics (i.e., both self-rating questionnaires and clinical interview) to assess PTSD symptoms, however, strengthens the studies.

One of the most common information biases is *recall bias*. This occurs in studies in which subjects are being interviewed to obtain exposure information and identify risk factors after the disease (or traumatic experience) has happened. Unlike many of the large cross-sectional studies performed in order to identify the occurrence of PTSD and risk factors for PTSD, a prospective design, as in **Studies II** and **IV**, allows data collection shortly after the event, thus reducing the risk of recall bias.

7.2.2.3 *Confounding and intermediary factors*

The purpose of the multivariable models used in **Studies I, II, and IV** was to better understand the variables associated with the presence of injuries, reports of violence, and the development of PTSD and depression. As the majority of the information was taken from the clinic's patient files, the number of variables was limited. For example, apart from information on current employment status and marital status, there was limited information on socio-economic status among the women. It is possible that more information on educational level and income would have affected the results. Variables can be confounders and/or intermediary variables in the causal link between a variable and a disease [173]. For instance, having been on sick leave for more than three months was associated with both alcohol abuse and PTSD. Occupational status would be a confounder if a woman who had PTSD used alcohol because she was unemployed. Conversely, occupational status would be an intermediary factor if a woman on sick leave used alcohol as a result of PTSD. Because it is commonly accepted that low socioeconomic status increases the risk of both alcohol abuse and PTSD, it can be considered as a confounder. On the other hand, PTSD has also been shown to negatively affect one's ability to sustain employment. Accordingly, socioeconomic status could also be an intermediary variable. The correction of intermediary factors in multivariable analyses can result in over-adjustment. Furthermore, including more independent variables would increase the risk of raising the number of women who would be excluded from the analysis due to missing data.

In **Study III**, confounding factors were prevented by restricting the study population, and in **Study V**, this was done by matching patients with controls.

7.2.2.4 External validity

Study I is based on women in all age groups (range 11 to 95) from both urban and suburban areas. However, the results may not be valid for women in more rural settings. The descriptive design also limits the chance to draw conclusions and identify causal relationships.

In **Studies II** and **IV**, the inclusion criteria were being over the age of 18. Therefore, causal relationship between variables and PTSD cannot be drawn for younger age groups. Further, women were excluded if they were not literate in Swedish, thus excluding many help-seeking immigrants, making generalizations to other nationalities and minority groups difficult.

In **Study V**, the sensitivity of the GABA-A receptor was explored in premenopausal women with PTSD during the follicular phase of the menstrual cycle. It is uncertain whether these results can be reproduced in the luteal phase of the menstrual cycle, in older age groups, and in male subjects with PTSD.

8 CONCLUSIONS AND CLINICAL IMPLICATIONS

- Sexual assaults committed by intimate partners involve more physical violence and result in injuries just as often as assaults committed by strangers. Thus, intimate partner assaults should be taken just as seriously as those committed by strangers and improved victim services and prevention strategies should be built on this knowledge.
- Development of PTSD is common in the aftermath of sexual assaults and in this cohort almost 40% had developed PTSD at the six-month follow-up. This finding supports the importance of sexual assault centers not only providing medical help and forensic examinations, but also psychological help and follow-up.
- An increased risk of developing PTSD is caused by a combination of victim vulnerability (prior trauma history and co-morbid depression) and the extent of the dramatic nature of the current assault (group assault, multiple acts during the assault, and having been injured). Because of the high ceiling effect, ASD on its own was found being a poor predictor of PTSD development. With this knowledge women at greatest risk of developing PTSD can be identified and therapeutic resources can be directed.
- All the endogenous steroids we measured, apart from the estrogens, had a significant diurnal variation in the follicular phase of the menstrual cycle. The pregnenes, progestins, and androgens had a similar diurnal variation curve as cortisol (with peak concentrations just after awakening), apart from allopregnanolone, which had a less steep curve and high concentrations throughout the day. These results suggest that when interpreting concentrations of these steroids their diurnal variation have to be adjusted for.
- None of the steroids were associated with the development of PTSD. However, low concentrations of cortisol, pregnenolone, 17OH-pregnenolone, and DHEA were found in patients with a prior trauma history, and low concentrations of allopregnanolone were seen in patients with a psychiatric treatment history. As both prior trauma history and psychiatric treatment history have been found to be risk factors for PTSD, our findings suggest an increased vulnerability in these patients and probably an impairment of the HPA axis due to repetitive stress.
- Patients with PTSD have a reduced sensitivity to GABA-A-receptor-active substances. As a consequence of this, benzodiazepines and other GABA-A-receptor-active compounds, such as sleeping pills, will be less useful for this patient group.

9 IMPLICATIONS FOR FUTURE RESEARCH

During the work on this thesis, some ideas for future research emerged.

Since we found an over-representation of immigrant women in the group of women who were sexually assaulted by their intimate partners, further research on sexual assaults in intimate partner relationships within minority groups is needed. More information about the prevalence of these assaults, as well as the circumstances surrounding and attitudes regarding disclosure, would be helpful for staff working in immigrant-dense areas, both in healthcare and social services.

As we found the prevalence of genital injuries to be fairly low, meanwhile injuries are still being given much attention in court, a study on injuries after consensual, compared to non-consensual, intercourse would be interesting. Results from a recently published Danish study [40] examining 39 cases and 98 controls suggested that differences between consensual and non-consensual intercourse could be identified. However, this must be backed up with larger studies. Preferably, this could be done in a large Nordic multi-center study.

As Study II suggests that it is possible to identify those women at a high risk of developing PTSD, even in this sample of heavily traumatized women, a study of early interventions focusing on those women is warranted. As follow-up of this patient group often suffers from high drop-out rates, interventions should be easily accessible. Suggestions for early interventions could include mindfulness or emotional freedom technique (EFT). These are both techniques that can be performed at home and can be aided via the Internet.

Another early intervention would be a form of “vaccination” against PTSD. Promising results regarding the prevention of PTSD have been shown in studies when subjects have been given high doses of cortisol immediately after a trauma. In a recently published Cochrane review [174] based on four RCTs [175,176,177,178], the authors concluded that there is moderate-quality evidence for the efficacy of hydrocortisone in preventing the onset of PTSD and that between 7 and 13 patients would need to be treated in order to prevent the onset of PTSD in one patient. These studies, however, were few, small, and had multiple limitations. Further, none of the studies were performed on sexual assault victims, a group of patients known to be at the highest risk of developing PTSD.

Finally, it would be interesting to explore associations between menstrual cycle phase at the time of the assault, the HPA axis response, and the development of PTSD. Studies have shown that women exposed to traumatic experiences during the luteal phase of the menstrual cycle develop more traumatic memories [179] and that women who watched emotional films during the luteal phase had more spontaneous intrusive recollections [180]. This was suggested to be caused by the higher levels of progesterone and glucocorticoids during the luteal phase, causing increased memory consolidation. This is, at least in part, contrary to the theory previously described, stating that low cortisol concentrations cause an increased risk of developing PTSD. However, none of the studies examining the role of menstrual cycle phase

explored the development of PTSD. The interaction between menstrual cycle phase and the HPA axis is still not fully understood [181] and must be further explored. Study IV suggests that cortisol concentrations are lower when allopregnanolone (as well as progesterone) concentrations are high, which would be a logical way to describe an eventually increased risk of PTSD development after having been traumatized in the luteal phase. This is also in accordance with findings in rodents during pregnancy (another condition when allopregnanolone levels are known to be high), when the HPA axis response to stress was suppressed [182].

10 POPULÄRVETENSKAPLIG SAMMANFATTNING

Varje år utsätts 3-4% av den kvinnliga svenska befolkningen för ett sexuellt övergrepp. Bara några få procent av dessa kvinnor polisanmäler händelsen och ännu färre söker medicinsk hjälp. I Stockholm är den akuta medicinska vården och omhändertagandet efter våldtäkt centraliserad till Akutmottagningen för våldtagna kvinnor (AVK) på Södersjukhuset. Mottagningen öppnade 2005 och tar varje år emot mellan 600-700 kvinnor som söker akut hjälp efter våldtäkt. Kvinnorna är välkomna inom en månad efter övergreppet och erbjuds medicinsk hjälp, rättsmedicinsk undersökning och uppföljande krisstöd. Den här avhandlingen är baserad på studier på just dessa kvinnor. Syftet med avhandlingen var att öka kunskapen om kvinnor som söker hjälp efter våldtäkt samt de psykologiska konsekvenserna av våldtäkt och påverkan på hjärnan.

I det första delarbetet undersökte vi hur kvinnans relation till förövaren påverkar förekomsten av fysiskt våld och uppkomst av skador i samband med en våldtäkt. Detta gjordes genom att granska journaler och rättsmedicinska undersökningar från 690 kvinnor som sökt hjälp under en 13-månadersperiod. Vi fann att de kvinnor som blivit våldtagna av en intim partner hade utsatts för grövre fysiskt våld och hade fysiska skador minst lika ofta som de kvinnor som blivit våldtagna av en annan för dem bekant förövare eller av en obekant (s.k. överfallsvåldtäkt).

Efter ett allvarligt trauma, i detta fall våldtäkt, finns det en stor risk att de symtom som ofta ingår i en akut stressreaktion kvarstår längre än en månad och då övergår i ett sjukdomstillstånd som heter posttraumatiskt stressyndrom (PTSD). En person som utvecklar PTSD lider av att ständigt återuppleva traumat i form av flashbacks eller mardrömmar, undviker saker och situationer som påminner om traumat samt har ett ständigt ökat stresspåslag. Dessa symtom påverkar individen så pass kraftigt att de har en handikappande effekt och många gånger påverkas individens arbetsförmåga samt förmåga till socialt umgänge. Tidigare internationella studier har visat att våldtäkt är ett av de trauman som innebär högst risk att insjukna i PTSD och att ungefär 30-40 % av våldtagna kvinnor utvecklar PTSD efter händelsen. För att kunna förebygga insjuknande är det viktigt att kunna identifiera de kvinnor som lider störst risk att utveckla PTSD. I avhandlingens andra delarbete fann vi att 39 % av kvinnorna som sökt på AVK hade utvecklat PTSD efter 6 månader och att de som hade störst risk att utveckla PTSD var de som utsatts för en gruppvåldtäkt, liksom de som hade en kraftig akut stress reaktion efter övergreppet, de som utsatts för multipla sexuella handlingar under övergreppet samt ådragit sig skador. Vidare såg vi att de som hade en historia av tidigare traumatiska händelser och någon form av tidigare psykiatrisk sjuklighet (oftast depression) hade en ökat risk att utveckla PTSD.

Ett trauma som våldtäkt är en enorm stressituation för kroppen. Vid akut stress vet vi att kroppen utsöndrar ett flertal stressteroider från binjurebarken, t.ex. den välkända steroiden kortisol. Dessa steroider hjälper till att hantera stressen i kroppen och ser till att stressreaktionen stängs av efter att hotet är borta. Vid upprepat eller kroniskt trauma finns

dock teorier att kroppens förmåga att utsöndra t.ex. kortisol sänks. Om man inte får detta kortisolpåslag har tidigare studier pekat på att risken att utveckla PTSD ökar. Vi ville ta reda på om nivån av en viss steroid kan förutse utvecklandet av PTSD efter våldtäkt. Eftersom kvinnor söker akut efter våldtäkt under dygnets alla timmar behövde vi också veta om nivåerna av steroider varierar under dygnet för att kunna justera för en eventuell dygnsvariation av steroiden. Kortisol har en känd dygnsvariation med högst nivåer på morgonen strax efter uppvaknandet, dock är det inte helt klart beskrivet i litteraturen hur det är för andra steroider t.ex. den stressrelaterade och mycket potenta steroiden allopregnanolon. I det tredje delarbetet undersökte vi just detta och fann att de flesta stressrelaterade steroiderna har en dygnsvariation liknande kortisol som därför behöver justeras för. I fjärde delarbetet fann vi ingen skillnad i koncentrationen av stressrelaterade steroider direkt efter våldtäkten mellan de som senare utvecklade PTSD eller inte. Däremot såg vi att de som hade upplevt flera tidigare trauman hade sänkta kortisolnivåer direkt efter våldtäkten och att de som hade en tidigare psykiatrisk sjuklighet hade lägre allopregnanolonnivåer. Riktigt hur vi ska tolka detta vet vi inte men det verkar ändå som om de med tidigare trauman och sjuklighet har en ökad känslighet och en påverkad stressrespons.

Då patienter med PTSD ofta har kraftiga sömnbesvär och ångestsymtom är det viktigt att kunna hjälpa och behandla på bästa sätt. Hos andra patientgrupper brukar dessa symtom ofta behandlas med s.k. benzodiazepiner, dvs. klassiska sömn- och ångestlindrande tabletter. Då det finns beskrivet att dessa läkemedel inte fungerar tillfredställande på patienter med PTSD ville vi undersöka detta. Gemensamt för alla benzodiazepiner är att de har sin verkan genom att binda till en receptor i hjärnan som heter GABA-A receptorn. Detta är samma receptor som t.ex. alkohol binder till och som vi vet leder intag av alkohol i tillräcklig mängd till ökad trötthet. Även allopregnanolon, som utsöndras vid stress binder till denna receptor. Ett sätt att mäta påverkan på GABA-A receptorn hos en patientgrupp är att mäta ögonrörelsehastigheten efter att man gett ett ämne som binder till receptorn. I femte och sista delarbetet fann vi att patienter med PTSD var mindre känsliga för benzodiazepiner och allopregnanolon jämfört med friska kontroller. PTSD patienterna blev mindre trötta och fick mindre påverkan på ögonrörelsehastigheten. Vi har tolkat att detta beror på en toleransutveckling i receptorn pga. att PTSD patienter går med ett ständigt stresspåslag och höga nivåer av stressteroider.

Min konklusion från denna avhandling är att de flesta våldtäkter inte leder till fysiska skador men däremot psykiska. Vi såg att intimpartnerövåldtäkter innehåller mer våld och resulterar i skador minst lika ofta som efter överfallsvåldtäkter. Dock är skadorna oftast i form av blåmärken på armar och ben och inte skador i underlivet. PTSD efter våldtäkt är vanligt och risken att insjukna ökar genom en kombination av kvinnans sårbarhet och våldtäktens allvarlighetsgrad. Vidare kunde vi i vår studie utifrån nivåer på olika stressrelaterade steroider inte förutse vilka som skulle utveckla PTSD men däremot såg vi lägre nivåer hos de med tidigare trauma och tidigare psykiatrisk sjuklighet. Slutligen, som en konsekvens av GABA-A receptorns minskade känslighet hos PTSD patienter så har GABA-A receptor aktiva ämnen såsom sömntabletter mindre effekt på denna patientgrupp.

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