General Introduction
Most adolescents do not give their sense of being male or female much thought; their fundamental sense of belonging to one gender, named gender identity, is congruent with their gender role, natal sex and sexual body characteristics. For some youth, however, gender identity is something of great and pervasive concern. They suffer from gender dysphoria, the distress resulting from an incongruence between assigned and experienced gender. Gender is the wide set of characteristics distinguishing male from female. In ordinary speech, it is used interchangeably with sex to denote the condition of being male or female. In this thesis, sex refers to biological maleness or femaleness, gender is used in all other instances.

According to the Diagnostic and Statistical Manual of Mental Disorders, someone suffers from a gender identity disorder (GID) when the following two criteria are met: (1) a strong and persistent cross gender identification and (2) persistent discomfort with one’s biological sex or gender role behavior associated with one’s sex. The disturbance should not be concurrent with a disorder of sex development (congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical) and should cause distress or impairment. In the ICD-10, the term transsexualism is used for adults and adolescents. A strong desire for hormonal treatment and gender reassignment surgery is part of the diagnostic ICD-10 criteria. In this thesis, the term male-to-female transsexuals (MtFs) refers to natal males who identify as members of the female gender; the term female-to-male transsexuals (FtMs) refers to natal females who identify as members of the male gender.

Gender reassignment, the treatment procedure for those who want to adapt their bodies to the desired gender, consists of cross-sex hormones and gender reassignment surgery. It is an accepted effective treatment in most Western countries for adults with GID, although the need for such an invasive medical and surgical treatment may still be hard to imagine for non-gender dysphoric individuals. For many people, it is complicated to understand that adolescents too can seriously experience and express these feelings and desire gender reassignment at a young age. Therefore, decisions on medical interventions for minors are considered even more difficult than for adult transsexuals.

This thesis focuses on gender dysphoria in adolescents, specifically on their mental health and clinical management. Compared to knowledge on GID in children and adults, knowledge in teenage youth is lagging behind. There are only a limited number of studies on psychological functioning of gender dysphoric adolescents and there is a woeful absence of research supporting the ideas about management of GID in young people.

**Typical gender identity development**

“Is it a boy or a girl?” is one of the obvious questions when a baby is born. Although babies are unaware of their gender or sex, there are gender differences in behavior
very early in life. For example, in one day old infants, boys show a greater interest in a physical-mechanical mobile while girls show a stronger interest in social objects (faces). Six-month old boys have greater difficulty than girls in maintaining affective regulation (they are, for example, more likely than girls to fuss, to gesture to be picked up, and to try to escape or get away by turning and twisting). Although mothers use different parenting strategies, these differences are insufficient to account for the gender differences in infants’ behavior.

Before any cognitive or social development have occurred, it are biological factors that influence these behavioral gender differences. Many experimental studies in nonhuman mammals show that prenatal hormones are responsible for gender differentiation of the brain and behavior. In studies on the role of prenatal testosterone in people, individuals with disorders of sex development (DSD) were often focus of attention, as they provide ‘an experiment of nature’ with atypical hormone exposure. In humans, there is now increasing evidence for the masculinizing effects of prenatal androgens for gender-typed interests, spatial ability and aspects of personality (for a review, see Cohen-Bendahan et al.). The size of testosterone-related influences however, varies from one gender-typed behavior to another. For example, the influence of prenatal testosterone on core gender-identity and sexual orientation seems not so substantial (for a review, see Hines).

Behavioral differences between boys and girls become more evident when children grow up. There is now ample evidence that cognitive psychological factors play an important role in further gender identity development. Cognitive psychologist Kohlberg proposed that children develop a sense of permanence of gender, gender constancy (I am a girl and will always be a girl). Gender constancy develops in three stages. These three stages are gender labeling, the realization that one is a boy or a girl, gender stability, the recognition that gender does not change over time, and gender consistency, the recognition that gender does not change, if someone’s appearance or activities change (for a review, see Ruble & Martin). Along with reaching the stage of gender constancy, most children develop a core sense of self as male or female, a gender identity congruent with their natal sex.

Studies suggest that most children develop the ability to label gender groups and to use gender labels in their speech between 18 and 24 months. Developing this ability has consequences: knowing basic gender information is related to increased play with the two most strongly stereotyped toys (trucks and dolls) (e.g. Zosuls et al.). Social cognitive psychology emphasizes the role of environment in gender development: modeling is one of the most pervasive means of transmitting values, attitudes and patterns of thought and behavior, and children tend to choose, attend to and associate with same-gender models. As gender stereotyped activities and interests are observed
before children reach complete gender constancy, it is argued that modeling influences are important even in children's early gender development. 

In the years between preschool and puberty, children consistently report spending more time with same-sex peers and siblings. Although many gender differences are quite small, gender accounts for a very large proportion of the variance in children's play partners. Children thus spend a major part of their time in all-male or all-female groups and grow up in different subcultures. Consequently, gender segregation influences children's social development and friendships. 

In their thinking about sex-typed traits and behavior, young children are fairly rigid; only after age 7 do they become more flexible. However, the gendered context of one's family may influence gender attitudes. Although most youth declines in gender traditionality, firstborn boys with brothers and traditional parents become more traditional across middle childhood and adolescence. Children growing up in less traditional families, on the contrary, show more nontraditional gender role attitudes. For example, children growing up in Dutch lesbian families showed less traditional gender stereotypical thinking compared to children in heterosexual families. Cultural differences play a role as well. Italian children, for example, were more likely to favor stereotypical toys and activities than were Dutch children.

Gender identity includes more than the ability to identify one's gender, which is now also acknowledged by cognitive developmental psychologists. It also encompasses affective components and it is emotionally valued. Feeling gender typical and feeling content with one's gender have generally positive influences on children's well-being, whereas feeling pressure to conform to gender stereotypes is generally a negative influence. Developmentally, older children seem to feel more gender typical compared to younger children, while at the same time they experience less pressure to conform to gender stereotypes.

**Gender variant development**

At the same time as gender typical behavior emerges, in early toddlerhood, some children will show what is also called gender atypical or gender variant development. These preschool children are boys displaying female interests and behavior and girls who strongly prefer male toys and playmates. They may even express an explicit desire to be the other gender as soon as they can talk.

Studies with the Child Behavior Checklist (CBCL), a parent-report behavioral problem questionnaire, show that cross-gender behavior in children is more common than the stated wish to be of the other gender. For example, in a large Dutch twin study, 3.4% of the 7 year old boys and 5.2% of the 7 year old girls were reported to behave like the
opposite gender while only 1.0% and 1.7% respectively had stated the wish to be of the opposite gender. At age 10, these percentages had decreased, although less so for the stated wish. This shows that cross-gender behavior diminishes when children reach their teenage years.

Presumably, only a small part of these children with gender variant behavior fulfill the criteria for a GID diagnosis. Although prevalence rates of GID in childhood are lacking, based on prevalence estimates in adults (MtFs 1:10.000, FtMs 1:30.000) these will probably be low. How extreme gender variant behavior should be to qualify for a psychiatric disorder and how much distress should be involved is a matter of serious debate, especially reconsidering the GID criteria for the upcoming DSM-5.

Prospective studies of boys and girls with GID show that at follow-up the proportion of participants with a homosexual or bisexual sexual orientation is substantially higher than the base rates in the general population. In one unique longitudinal general population study of 879 Dutch boys and girls, gender variant behavior was measured during childhood by the CBCL, while sexual orientation was assessed 24 years later, when participants were 27-36 years of age. The prevalence rates of homosexuality were, depending on the sexual orientation domain, 8.4 to 15.8 times higher in the childhood gender variant subgroup, as compared to the childhood non-gender variant subgroup. None of the gender variant subgroup in the general population was transsexual in adulthood, indicating that gender variant behavior in childhood is indeed more predictive of homosexual orientation in adulthood than later GID.

In gender variant development, psychosocial factors were traditionally considered etiologically important, but recent findings suggesting that brain anatomy is different in individuals with GID compared to non-GID individuals have led to a search for underlying genetic and/or hormonal, brain-specific mechanisms in gender variant development.

**Gender identity disorder in adolescence versus childhood and adulthood**

In the DSM-IV-TR, the GID diagnosis applies to the complete lifespan, although with distinct criteria sets for children versus adolescents and adults. GID in adolescence presents with some distinguishable characteristics compared with younger (<12 years) and older (>18 years) referrals in some clinically relevant ways: age of onset, sex ratio, and persistence of GID.

First, with regard to age of onset, in adults, both an early and a late-onset type of gender identity disorder seems to exist. Especially some MtFs have no apparent cross-gender behavior in childhood (e.g. for a review, see Lawrence). However, most typically, adolescents show some or all features of GID from a very young age on, during the toddler and preschool years. They may have expressed a desire to be of the other gender,
have preferred opposite-gender objects, activities, and peers, have shown cross-gender behaviors, or have been unhappy about their own biological sex.

Second, the sex ratio of male versus female referrals in adolescents is close to 1:1 whereas in both pre-pubertal children and adults there are more males than females seen at gender identity clinics. For example, the sex ratio of pre-pubertal boys to girls was 5.75:1 and 2.93:1 in a comparative study of two gender identity clinics in Canada and the Netherlands, respectively. This preponderance of males may be partly explained by the lower social acceptance of cross-gender behavior of boys compared with girls; as a result, the threshold for (parents of) girls to seek help may be higher compared to boys. In adults, a sex ratio of 3:1 MtFs versus FtMs is often reported, although the numbers vary widely across studies (for a review, see Zucker). The sex ratios of adult gender reassignment candidates may be explained by the ‘late-onset’ type of GID. These are men who never were GID boys who usually do not apply for treatment before adulthood.

Finally, prospective studies of developmental trajectories of children with GID show that gender dysphoria will diminish in most children. According to two recent studies persistence into late adolescence occurred in only 12% or 27%. Follow-up studies of gender identity clinic referred adolescents, however, suggest a much higher persistence rate (43%–66%) into young adulthood, although desistance seemed to occur mainly in youth with subthreshold GID. In that respect, the clinical picture is comparable to adults with GID, most of whom come with a strong desire for gender reassignment that will not abate. It is possible that either gender identity is malleable at a younger age but becomes more fixed with development or that the current child DSM-IV criteria for GID are too broad and capture too many gender variant children that are not truly gender dysphoric.

Some of these characteristics of GID in adolescence have treatment implications. As extreme gender dysphoria in adolescents is likely to persist and psychological interventions are not particularly successful in solving the gender dysphoria, gender reassignment might be considered the treatment of choice for very gender-dysphoric adolescents.

**Clinical management of adolescents with GID**

Since the mid-1990s, medical interventions have become available for gender dysphoric adolescents. Because the VUmc gender identity clinic in the Netherlands took a leading role in developing this model of care, it is often called the “Dutch” protocol. Various clinics around the world have adopted it. According to this protocol, after careful psychological evaluation, suppression of puberty by means of gonadotropin-releasing hormone analogs (GnRHa) may start in 12–16 year olds and cross-sex hormone treatment...
may be prescribed between the ages of 16 and 18 years. Arguments favoring this protocol are that by relieving the immediate stress accompanying puberty development in a direction gender dysphoric adolescents abhor, further psychological stress may be avoided and age appropriate social and intellectual development enabled. As in most adolescents gender dysphoria will not remit, the arrest of further growth of secondary sex characteristics has lifelong advantages for their physical appearance. For example, MtFs will not develop a low voice or facial hair growth and in FtMs breast growth continues, leading to a physical appearance in the desired gender and making surgical breast removal resulting in visible scars redundant. Finally, by relieving the preoccupation with biological puberty, adolescents may explore their desire for gender reassignment in a more reflective and less pressured manner. In the case the adolescent does not want further gender reassignment, GnRHa treatment can be discontinued and puberty of the natal sex restarts.

There is also criticism of offering puberty suppression. Some state that no medical intervention should be provided for minors with GID, as young adolescents with GID may desist from their wish for gender reassignment during psychotherapy. Others require adolescents to experience puberty at least to Tanner stage 4 or 5 (which is the end stage of puberty). They postulate that puberty is a necessary identity-creating experience. Other potential risks of blocking pubertal development relate to the development of bone mass and growth, both typical events of hormonal puberty, and to brain development.

The recommended procedure according to the Standards of Care of the World Professional Association of Transgender Health is to come to the decision regarding gender reassignment stepwise. Although most cross-gendered adolescents come to clinics with a straightforward wish for gender reassignment, some have more open questions regarding their identity. In every adolescent, the gender problem and potential underlying or related problems have to be examined comprehensively in the diagnostic phase. During the diagnostic phase, the clinician not only assesses whether the adolescent fulfills the criteria of GID, but also available social support and psychological resilience to handle the necessary life changes that accompany gender reassignment. The eligibility criteria for medical interventions in gender dysphoric adolescents are that gender dysphoria be present from early childhood on, that there is no psychiatric comorbidity interfering with the diagnostic work-up or treatment, and that the adolescent has adequate social support and demonstrates enough knowledge of the medical interventions to give informed consent. In addition, puberty should have reached at least Tanner stage 2, so that adolescents experience at least the beginning of their natal puberty.

According to the Royal College of Psychiatrist’s guidelines as well as the WPATH Standard of Care, no medical interventions are recommended for prepubertal children. For adolescents, a distinction is made between fully reversible, partly reversible and irreversible interventions. The fully reversible treatment with GnRHa will discontinue
progression of puberty by blocking the activity of the GnRH receptor at the pituitary (central nervous system) level, resulting in a decrease of gonadotropin release. This will, in turn, lead to prepubertal levels of sex hormones (estrogens in girls and androgens in boys). GnRHa treatment will lead to regression of the first stages of already developed sex characteristics and further development of secondary sex characteristics will be arrested.\textsuperscript{4,49}

The partly reversible treatment with cross-sex hormones induces secondary sex characteristics of the desired gender. Adolescents may be eligible for cross-sex hormones when they are 16 years of age or older. Age 16 was chosen because some cognitive and emotional maturation is desirable when starting partially irreversible interventions. In many countries 16-year olds are legal adults for medical decision making, and do not require parental consent.\textsuperscript{5} Cross-sex hormones in addition to GnRHa treatment induce an ‘other sex puberty’. Estrogens are prescribed to MtFs initiating breast development and female-appearing body shape. In FtMs, androgens are used in order to achieve virilization, including male body features, such as a low voice, facial and body hair and a more masculine shape.\textsuperscript{49}

The irreversible gender-reassignment surgery is only performed after the age of 18. In MtFs, female-looking external genitals are created by means of vaginaplasty, clitoroplasty and labiaplasty. When estrogen therapy has not led to enough breast tissue growth, breast enlargement may also be performed.\textsuperscript{22} Due to puberty suppression, MtFs may have such a small penis that there is not enough skin for a vaginaplasty. In that case, part of the colon is used to perform a colovaginaplasty. In FtMs, a mastectomy is often performed as the first surgery to successfully pass in the desired role.\textsuperscript{22} Due to puberty suppression, breasts are often fairly small, making a mastectomy not necessary at all or making removal possible resulting in scars only around the nipple. When breasts are larger, a “sous-mammaire” procedure is needed, resulting in visible scars on the chest. Removal of the uterus and ovaries is most often the next procedure for FtMs. Considering the still continuing improvements in the field of phalloplasty, some FtMs do not want to undergo genital surgery or choose to have a neoscrotum with testicular prosthesis with or without a metadoioplasty, which transforms the hypertrophic clitoris into a microphallus.\textsuperscript{22}

In the Netherlands, gender reassignment is covered by health insurance. However, in many countries individuals with GID have to pay for the hormones and expensive surgeries, making them inaccessible.

After gender reassignment surgery, the indication of sex at birth can be changed on the official birth certificate. First evaluations of this treatment policy, where cross-sex hormones were given between 16 and 18 years, showed no regret, great satisfaction with the disappearance of the gender dysphoric feelings, and normal psychological functioning.\textsuperscript{44,45} However, no evalutative studies of reasonable numbers of adolescents with GID receiving GnRH analogs have been published.
**Associated psychopathology / comorbidity in adolescents with GID**

Zucker, based on the few published studies, concluded that adolescents with GID appear to show about as many behavioral difficulties as other referred youth and more than nonreferred youth.\textsuperscript{46} He suggested that multiple factors likely contribute to their problems, including risk factors shared with sexual minority youth (gay and lesbian adolescents), who may be subject to stigmatization, rejection by the peer group and discrimination.\textsuperscript{56,57}

One recently emerging and challenging example of associated psychopathology, is the co-occurrence of autism spectrum disorders and GID reported by several gender identity clinics.\textsuperscript{58-60}

Clearly, comorbid psychopathology raises diagnostic and treatment dilemmas. Studies that examine the magnitude and type of associated mental health problems and their implications for clinical management are necessary.

**Aims of the thesis**

The overall aims of this thesis are to improve our understanding of psychological functioning in adolescents referred to a gender identity clinic, and to evaluate treatment starting with puberty suppression. Specifically, psychological (dys)functioning of adolescents with GID is compared with that of adults with GID. Furthermore, the prevalence of comorbid psychiatric diagnoses and the incidence of autism spectrum disorders in gender dysphoric adolescents are investigated. Finally, treatment with puberty suppression is evaluated twice. First, the short term effects are studied of puberty suppression only on psychological functioning and gender dysphoria. Second, the longer-term effects are assessed of complete gender reassignment treatment on quality of life, gender dysphoria, current social functioning and sexual behavior.

**Outline of the thesis**

Chapter 2 is a review study of individuals with various disorders of sexual development, a generic definition encompassing any problem noted at birth where the genitalia are incongruent in relation to the chromosomes or gonads. The conditions used to be referred to as intersex conditions.\textsuperscript{61} Individuals with disorders of sexual development have drawn the attention of those interested in gender identity development for quite some time. They may experience gender dysphoria, but it is unclear whether this is a result of their biological vulnerability (e.g. chromosomes, hormones), the environment or an interaction between these two.
In chapter 3 psychological functioning of adolescents with GID is compared with adults. In this study, age adapted versions of the same instrument, the Minnesota Multiphasic Personality Inventory (MMPI-2 or MMPI-A, respectively), were administered to measure psychological (dys)functioning. This study also took sex, age and sexual orientation into account, factors that may be associated with psychological functioning in adults with GID.

In chapter 4 the incidence of autism spectrum disorders is examined in children and adolescents referred to a gender identity clinic. Only case studies have been published on the co-occurrence of autism and GID, and no study has used a systematic approach. In this study, the Dutch version of the Diagnostic Interview for Social and Communication Disorders (10th rev., DISCO-10) was administered to ascertain ASD classifications.

In chapter 5 psychiatric comorbidity is investigated in gender dysphoric adolescents. To ascertain DSM-IV diagnoses, the Diagnostic Interview Schedule for Children (DISC) was administered to parents of gender dysphoric adolescents. We examined whether prevalence rates of comorbid disorders were different in adolescents with a complete GID diagnosis compared to subthreshold GID and whether there were differences in type of comorbidity between adolescents with GID considered immediately eligible compared to delayed eligible adolescents.

In chapter 6 a follow-up study is conducted on psychological functioning and gender dysphoria of adolescents with GID who have received GnRH analogs to delay puberty. Behavioral and emotional problems, depressive symptoms, anxiety and anger, general functioning, gender dysphoria and body satisfaction were assessed twice: at T0, when attending the gender identity clinic, before the start of puberty suppression; and at T1, shortly before the start of cross-sex hormone treatment.

In chapter 7 a follow-up study is performed after gender reassignment surgery on gender dysphoria, treatment satisfaction, current life situation and school or work career, sexual functioning and romantic relationships and quality of life of young adults who had been treated with puberty suppression during adolescence. Participation in romantic relationships during the teen years has been associated with several positive outcomes such as increased feelings of self-worth, competence, and enhanced social status. In gender dysphoric adolescents, understandably, sexuality is a delicate matter.

Finally, in chapter 8, the findings of the studies are summarized and discussed and implications for clinical practice and future studies are given.