

THE PAST

THE PRESENT, THE FUTURE

GENITAL TREATMENT PRACTICES
IN DISORDERS OF SEX DEVELOPMENT

UNDER SCRUTINY

*“ The truth is rarely
pure and never simple ”*

Oscar Wilde

Promotor Prof. dr. Martine Cools
Vakgroep Pediatrie en Genetica

Copromotor Prof. dr. Piet Hoebeke
Vakgroep: Urogynaecologie

Overige leden promotiecommissie: dr. Griet De Cuypere
dr. Arianne Dessens

Decaan Prof. dr. Guy Vanderstraeten

Rector Prof. dr. Anne De Paepe

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NINA CALLENS

THE PAST, THE PRESENT, THE FUTURE:

GENITAL TREATMENT
PRACTICES IN DISORDERS OF
SEX DEVELOPMENT UNDER
SCRUTINY

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Thank you for reminding me that life needs to include love & play.

Nina Callens
Bruxelles, October 2013

List of Abbreviations

AIS:	androgen insensitivity syndrome
AMH:	anti-Müllerian hormone
CAIS:	complete androgen insensitivity syndrome
CAH:	congenital adrenal hyperplasia
DHT:	dihydrotestosterone
DSD:	disorders of sex development
GA:	gestational age
GD:	gonadal dysgenesis
LH:	luteneizing hormone
MIS:	Müllerian inhibiting substance
MRKH:	Mayer-Rokitansky-Küster- Hauser syndrome
PAIS:	partial androgen insensitivity syndrome
QOL:	quality of life
SPL:	stretched penile length

List of Definitions

17 β hydroxysteroid dehydrogenase deficiency (17 β HSD):

genetic disorder of steroid formation, caused by a deficiency of the testicular enzyme 17 β hydroxysteroid dehydrogenase that produces testosterone from androstenedione. Plasma testosterone and dihydrotestosterone (DHT) are decreased and androstenedione is increased. It is characterized in XY individuals by ambiguous or feminine-appearing external genitalia at birth, with masculinization at puberty.

5 α reductase deficiency (5 α RD):

genetic disorder of steroid formation, caused by a deficiency of the testicular enzyme 5 α reductase that produces dihydrotestosterone (DHT) from testosterone. Plasma DHT is decreased, testosterone is increased. It is characterized in XY individuals by ambiguous or feminine-appearing external genitalia at birth, with masculinization at puberty.

Androgen insensitivity syndrome (AIS):

X-linked genetic disorder that results in the inability of receptors to respond to androgens. The receptor deficiency can be partial (PAIS) or complete (CAIS). In XY individuals with CAIS, the external genitalia appear feminine at birth and at the time of puberty, breasts develop in response to estrogen produced from androgen, catalysed by aromatase. However, female internal genitalia are absent and menstruation does not occur. XY individuals with PAIS can be born with ambiguous genitalia.

Cloaca:

in mammalian embryology, the terminal end of the hindgut before division into rectum, bladder and genital primordium.

Cloacal exstrophy:

a developmental anomaly in which two segments of the bladder (hemibladders) are separated

by an area of intestine with a mucosal surface, which appears at birth as a large red tumor in the midline of the lower abdomen. It is more common in XY individuals, and they are typically born with a small or absent penis, which, like the bladder, can be bifid.

Congenital adrenal hyperplasia (CAH):

family of inherited (autosomal recessive) disorders caused by enzymatic defects in adrenal steroid biosynthesis. CAH results in hypersecretion of adrenocorticotropic hormone as well as excessive androgen production. In girls, it causes masculinization of the external genitalia (enlarged clitoris, fusion of labia, urogenital sinus).

Disorder of Sex Development (DSD):

a congenital condition in which development of chromosomal, gonadal or anatomical sex is atypical.

Epididymis:

the elongated cordlike structure along the posterior border of the testis. It provides for storage, movement and maturation of the spermatozoa and is continuous with the ductus deferens.

Gender identity:

the sense of oneself as male or female.

Gender role behavior (sex-typical behavior) :

behaviors that are culturally associated with gender or that show sex differences.

Gender dysphoria:

unhappiness with one's biological sex or its usual gender role, with the desire for the body and role of the other sex.

Genotype:

the entire genetic constitution of an individual.

Gonad:

gamete-producing gland; an ovary, testis or ovotestis (combined ovary and testis).

Gonadal dysgenesis:

incomplete or defective formation of the gonads, as a result of a disturbed process of migration of germ cells and/or their correct organization in the fetal gonadal ridge.

Gonadectomy:

surgical removal of one or both gonads (castration).

Gynecomastia:

excessive growth of the male mammary glands, in some cases including development to the stage at which milk is produced. Gynecomastia is usually associated with metabolic disturbances that lead to estrogen accumulation, testosterone deficiency and hyperprolactinemia.

Hermaphrodite:

an individual with both ovarian and testicular tissue.

Hypervirilization:

the presence of ambiguous or male external sexual characteristics in a 46, XX individual, exposed to androgens (endogenous, due to genetic defects in enzymes involved in adrenal steroid hormone production or of exogenous origin) during fetal life or thereafter.

Hypogonadism:

a condition resulting from abnormally decreased gonadal function, with retardation of growth, sexual development and secondary sex characteristics.

Hypospadias:

anomaly characterized by a defect on the ventral surface of the penis so that the urethral meatus (urethral opening) is more proximal than normal; may be associated with chordee.

Idiopathic hypogonadal hypogonadism:

a disorder involving reduced testicular production of androgens and other hormones caused by low levels of pituitary hormones and consequently reduced stimulation of the testes.

Intersex:

condition in which a person displays a mixture of both male and female physical forms of reproductive organs. Now called Disorder of Sex Development.

Libido: sexual desire, drive or interest.

Micropenis:

abnormally small penis (stretched penile length ≤ 2.5 cm at birth or ≤ 7 cm in Caucasian adults).

Müllerian ducts:

paired embryonic ducts adjoining the urogenital sinus that develop into the fallopian tubes and the uterus in the female and regress into a rudimentary structure in the male.

Perineal hypospadias:

hypospadias with anomalous development of the genitalia in which the rudimentary penis may be engulfed by an overlying bifid scrotum.

Perineum:

the pelvic floor and the associated structures occupying the pelvic outlet. Also the region between the thighs, bounded in the male by the scrotum and anus and in the female by the vulva and anus.

Phenotype:

the entire physical, biochemical and physiological makeup of an individual as determined both genetically and environmentally, as opposed to genotype.

Pseudohermaphroditism:

condition in which the external genitalia are at odds with the karyotype, gonadal morphology and internal genitalia.

Rough-and-tumble play:

a juvenile behavior characterized by overall body contact or playful aggression.

Scrotum:

the pouch that contains the testes in males.

Sexual dimorphism :

technically meaning 'two forms', mostly interchangeable with sex difference: any psychological or behavioral characteristic that differs on average for males and females of a given species.

Sexual orientation:

erotic attraction to and interest in sexual partners of the same versus the other sex.

Tomboy:

a girl who likes toys, clothes and activities associated with or usually preferred by boys and who likes to play with boys.

Transsexualism:

the most severe manifestation of gender identity disorder in adults. It is characterized by a prolonged, persistent desire to relinquish one's primary and secondary sex characteristics and acquire those of the other sex. It particularly describes those persons who go so far as to live as members of the other sex, and undergo hormonal treatment and surgical reassignment.

Undervirilization:

the presence of an ambiguous or female phenotype in a 46, XY individual with bilateral (intra-abdominal, inguinal or scrotal) well-differentiated testes, in whom testosterone production or action is inadequate.

Urethra:

the membrane canal conveying urine from the bladder to the exterior of the body.

Urogenital sinus:

anomaly in which the vagina and urethra open into a common channel, rather than separately. In a low confluence urogenital sinus anomaly, the common channel is short, the urethral opening is close to its normal location and the vagina is almost normal in length. In a high confluence urogenital sinus anomaly, the common channel is long, the urethral opening is internal and the vagina is quite short. This type is sometimes associated with an anus that is located too far forward.

Vanishing testes syndrome:

a disorder in males characterized by the absence of the testes and gonadal tissue at birth. When

it is bilateral, the individual will not undergo puberty or adolescent masculinization without testosterone supplements. The testes are thought to have been present in the embryo, but to have 'vanished' before completion of male sexual differentiation, also called embryonic testicular regression syndrome.

Vas deferens:

the excretory duct of the testis, which unites with the excretory duct of the seminal vesicle to form the ejaculatory duct.

Virilization:

masculinization

Wolffian ducts:

either of the pair of ducts that are present in the human embryo (alongside the pair of Müllerian ducts). They develop into the male internal reproductive tract if embryonic testes are present

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Foreplay

Sex is everywhere. Sex sells. Sex is a biological urge, a natural part of life, and the most fun you can have without laughing- though it's even better when you do [1]. For as many times as sex is painted as a natural enjoyable activity, it's also portrayed as problematic. For every stereotype of the undermotivated female, there is a supposedly sexually rampant male. For every prim and modest woman, there is someone whose sexuality is dark, threatening and dangerous. For every Eve, a Lilith [1]. Media coverage, as well as the commercial agenda of pharmaceutical companies only reinforce an oversimplification of human sexuality [2,3].

While sexual manuals like the Kama Sutra have existed for centuries, the systematic study of human sexuality really started in the late nineteenth century with Von Krafft-Ebings' 'Psychopathia Sexualis' and has only been a cohesive academic discipline since the mid-twentieth century [4]. Attitudes, tools of research and analysis have changed since. The focus on what is testable and verifiable has taken root in the study of sex and gender and there is less acceptance of personal opinion as the only source of evidence [1].

Although some are realizing the advantages of interdisciplinary study, with social science enriching the finds of quantitative methods and vice versa, the polarization of psychological research in sex differences and psychosexual development remains, however, enormous [5]. Researchers approach their work mainly from either a *social* (nurturist) perspective or *hormonal/genetic* perspective. Social factors do matter; parents, teachers and peers treat – intended or not- boys and girls differently. Society in general expects and encourages different behaviors from men and women (gender stereotypes). However, social learning research is limited mainly to the study of gendered social behavior, but these may not be connected to sexual activities or to gender identity [6]. Within a naturalistic sex research framework, sex is a biological fact, with only two mutually exclusive and oppositional sexual categories: male and female. The development of different facets of sexuality is assumed to be congruent with either male or female sex chromosomes, hormonal profile, brain, physique and reproductive capacity [6]. Within this framework, research is focused upon the correlational relationships between physiological variables and observable behavior. For instance, experiments are set up to identify 'masculine' and 'feminine' preferences and behaviors in boys and girls and to measure sex differences [7]. Studies have concentrated on the role of prenatal androgens in gender differentiation, while others have examined the activation potential of sex hormones, in casu testosterone, on sexual functioning (such as desire or partner orientation). To this

date, it remains unequivocal as to how closely adult human sexuality relates to the hormonal environment during fetal life. In animal research, the explanatory and predictive power of naturist hypotheses is great (for instance in relation to courtship and mating behavior), but the extent to which animal data can be extrapolated to humans remains a moot point [6]. Cultural determinants and socialization processes are probably competing influences next to 'pure' hormonal effects in human gendered development. Moreover and more importantly, the question remains how likely it is that the identification of hormones and culprit genes will remove blame from or accept people considered sexual anomalies in society.

Recent years have seen the surfacing of important clinical issues related to the proper guidance of children born with Disorders of Sex Development (DSD) in which atypical prenatal hormonal environments lead to atypical genitalia. Biological causes are crystal clear, but stigma remains [8]. Most psychological theories have failed to appreciate the force of the dominant culture and to question the (heterosexist) imperatives of sex. Our cultural ideology requires two oppositional sexual categories, their certification through acceptable frequency and duration of genital intercourse - consigning all other sexual activities to the secondary status of 'foreplay' - and the capacity for procreation [6]. In scrutinizing the sexuality of people with a non-normative physico-sexual development, we may have to pay more attention to the personal meanings of genital a-normality, the experience of living with genital ambiguity and how meanings and experiences are produced by dominant discourses of body and sex. We need to pay attention to the ways in which our own practice such as the treatment choices we offer, the language we use and our silence might lead to some of the negative effects we observe in patients with stigmatizing diagnoses [9-11].

By celebrating the complexity and power of human bodies and further unravelling entrenched gender stereotypes and myths, we should finally accept a greater truly natural variation and diversity of human sexuality [12,13]. We need to come out of our sexual closets and be able to talk about sex without shame and take pride in how we choose to enjoy our bodies and genitals [14]. Otherwise, the public discourse on sex, as well as the debate within the DSD community, will continue to focus on dysfunction and not *sucsex*.



CHAPTER 1

Genital (a)typia

The profound significance to parents of the sex of their newborn is without doubt. Two of the questions most usually asked immediately after the birth are 'Is it alright?' and 'Is it a girl or boy?' [11]. We assume that the answer to the latter will be easy. Penis and scrotum define a boy; clitoris and labia a girl [5]. However, parents and pediatricians sometimes find it difficult to answer this seemingly simple question. 'Disorders of Sex Development' (DSD) – formerly called 'intersex disorders' – refer to all congenital conditions in which there is a disagreement between a person's genetic (i.e. chromosomal) sex and the appearance of external and internal reproductive structures [15]. This chapter addresses sex differentiation as it occurs in DSD, as well as etiologies, physiological presentations, clinical management, and psychological outcomes.

Several sexes? Sexual determination and differentiation

Sex is not a simple matter. In fact, sex may be defined biologically in many ways [16]. The complete process of sex determination and differentiation involves a series of sequential events and is considered to occur within four stages [17].

1. Chromosomal sex

Genetic material including sex chromosomes is contributed from two parents. The female parent contributes the female sex chromosome, X, the male parent contributes either the female sex chromosome, X, or the male chromosome, Y, thus determining the genotypic sex of the fetus. The end result is an embryo who has a pair of sex chromosomes that are either XX (genetic female) or XY (genetic male). In a few instances, the chromosomal constitution, or karyotype, is more complex, such as in cases of mosaic individuals who carry a patchwork of cells with different chromosomal constitution, e.g. XX and XY or X and XY cells. In other situations, the karyotype appears to be normal, but the appearance of the individual is opposite the expectation. This disparity is caused by mutations in genes important for sex determination, thereby leading to XX males or XY females (see [16]).

2. Gonadal sex

A pair of primordial gonads, the genital ridges, appear in both genetic males and females during the fourth week of embryonic life. Two associated ducts develop, the Müllerian and Wolffian ducts, while presumptive external genitalia appear as folds of cloacal tissue [4,5]. The precursor organs for sexual development in the developing embryo are bipotential, meaning that they contain the intrinsic capability to evolve either along the male or female pathway [18]. The fate of these undifferentiated internal and external structures depends on the chromosomal sex of an embryo. The presence and expression of the testis-determining gene SRY, located on the distal part of the short arm of the Y chromosome (Yp) [19], determines the gonadal sex of an embryo by directing the development of the bipotential embryonic gonad into testes. Without the influence of the sex-determining gene, the development of the embryonic gonad will be driven along the female pathway [17] (*Figure 1*).

Genes involved in the organogenesis of the gonads are important for the development of the gonads in both sexes. They include SF1 (Steroidogenic Factor 1) and WT1 (Wilms Tumor 1) (for a full overview, see [16,20]). Both genes are transcription factors that, when mutated, are responsible for a severe defect of gonad formation. Mutations in these genes are also associated with other malformations, such as adrenal defects for SF1, and kidney disorders for WT1 [16]. Other genes are responsible for promoting male development, such as SOX9 (SRY related HMG-box, gene 9). Finally, some genes seem to antagonize male development, such

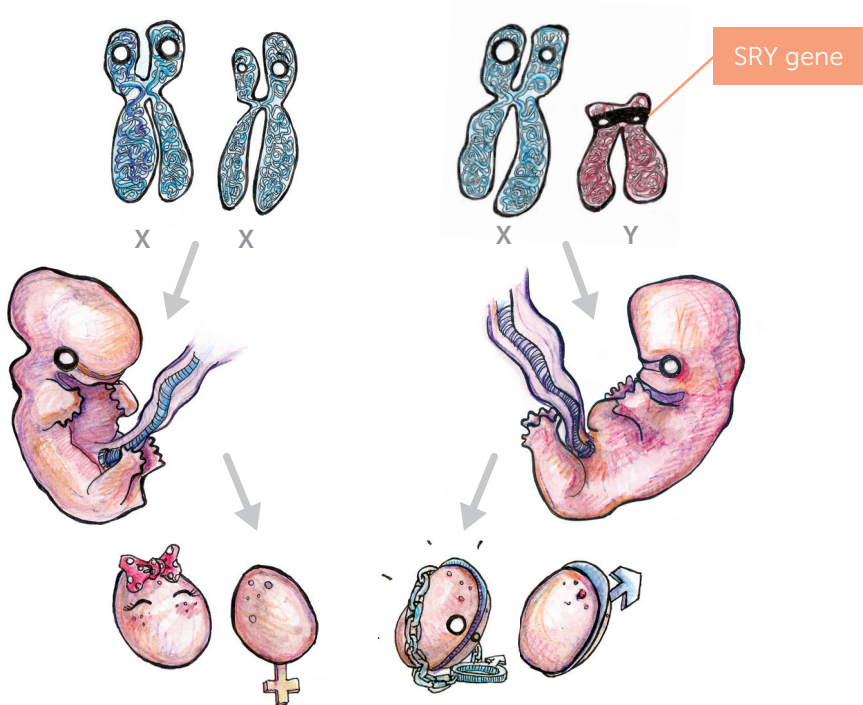
as DAX 1 (DSS-AHC critical region on the X chromosome protein 1) and WNT 4 (wingless-type MMTV integration site family, member 4), Both genes are expressed preferentially in female gonads, but there is no evidence, besides their "anti-testis" role, that they are actively involved in ovarian development [16].

Figure 1. Gonadal differentiation.

Before the fetus reaches the gestational age of 8 weeks, gonadal tissue has the potential to develop into either ovaries, or testes. The absence or presence of the SRY gene, usually located on the Y chromosome, determines whether this tissue will differentiate into ovaries (when SRY is absent) or testes (when

SRY is present). If the SRY gene is missing or does not work. Then the baby will not grow healthy testes despite having a male genetic sex (XY). Conversely, if a baby who is genetically female (XX) possesses the SRY gene on any chromosome, then testes will develop instead of ovaries (adapted from [21]).

Figure 1



3. Phenotypic sex: external and internal genitalia

The gonadal sex of a fetus directs the differentiation of external genitalia and internal reproductive structures (i.e., phenotypic sex) [18]. Genes involved in sexual differentiation are those that encode enzymes for testosterone biosynthesis, the androgen receptor (AR), and anti-Müllerian Hormone (AMH, also known as Müllerian inhibitory substance) and its receptor.

¹ SRY acts as a transcription factor, initiating the expression of a complex cascade of genes, controlling and fine-tuning testicular differentiation by activating and inhibiting mechanisms and gene-dosage effects [18,24]. Immediately after the expression of SRY, SOX9 is up-regulated in the male gonad, which is the main sex determining gene.

Sertoli cells of the fetal testes synthesize AMH which induces Müllerian duct regression during the 9th to 12th week of gestation, only between this narrow time interval [22]. Meanwhile, testosterone secretion from Leydig cells of the fetal testes induces Wolffian duct differentiation into vasa deferentia, epididymides and seminal vesicles [22,23]. The production of both testosterone and AMH is needed for a baby to develop male internal reproductive anatomy (Figure 2). In the absence of AMH, the Müllerian ducts are free to develop into the Fallopian tubes, cervix, uterus and upper portion of the vagina. In the absence of testosterone, the Wolffian ducts regress [22] (Figure 2).

Figure 2. Development of internal reproductive structures.

Fetal ovaries produce negligible amounts of testosterone and AMH, whereas testes produce significant amounts of both hormones. The presence or absence of these hormones influences the development of the internal sex ducts. Müllerian ducts are the forerunners of the uterus, cervix, fallopian tubes and upper portion of the vagina. They are found in both male and female fetuses but

typically disappear in male fetuses when the testes produce AMH. Wolffian ducts are the forerunners of vasa deferentia, epididymides, prostate gland and seminal vesicles. They are likewise found in all fetuses but typically disappear in female fetuses because there are no testes to produce testosterone (adapted from [21]).

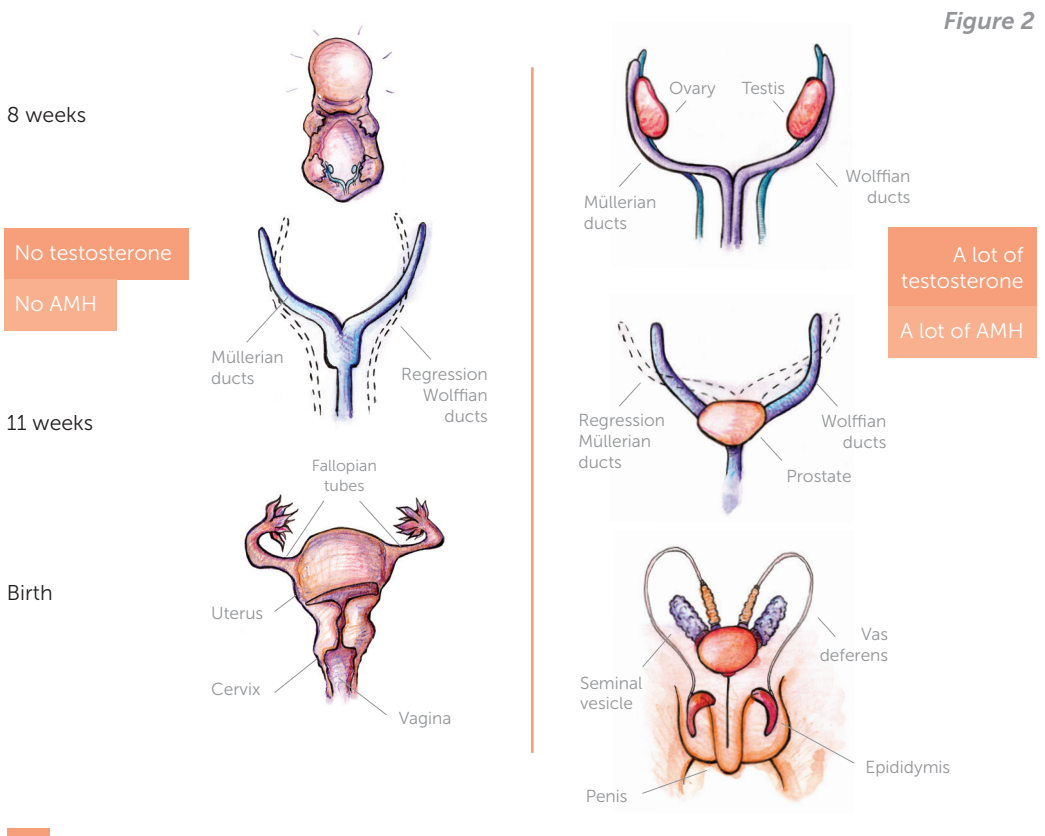


Figure 2

² The androgen receptor has a 10 fold greater affinity for DHT as compared to testosterone and its binding to DHT results in a more stable complex [22].

Virilization of the external sexual anatomy is established by conversion of testosterone by the enzyme 5 α reductase into dihydrotestosterone (DHT). Binding of DHT to the androgen receptors of the identical urogenital sinus in males and females leads in males to growth of the genital tubercle, which develops as a penis; fusion of the urethral folds to form the corpus spongiosum and penile urethra, fusion of the labioscrotal swellings to form the scrotum and ventral epidermal covering of the penis and differentiation of the prostate and bulbourethral glands [5,24] (Figure 3).

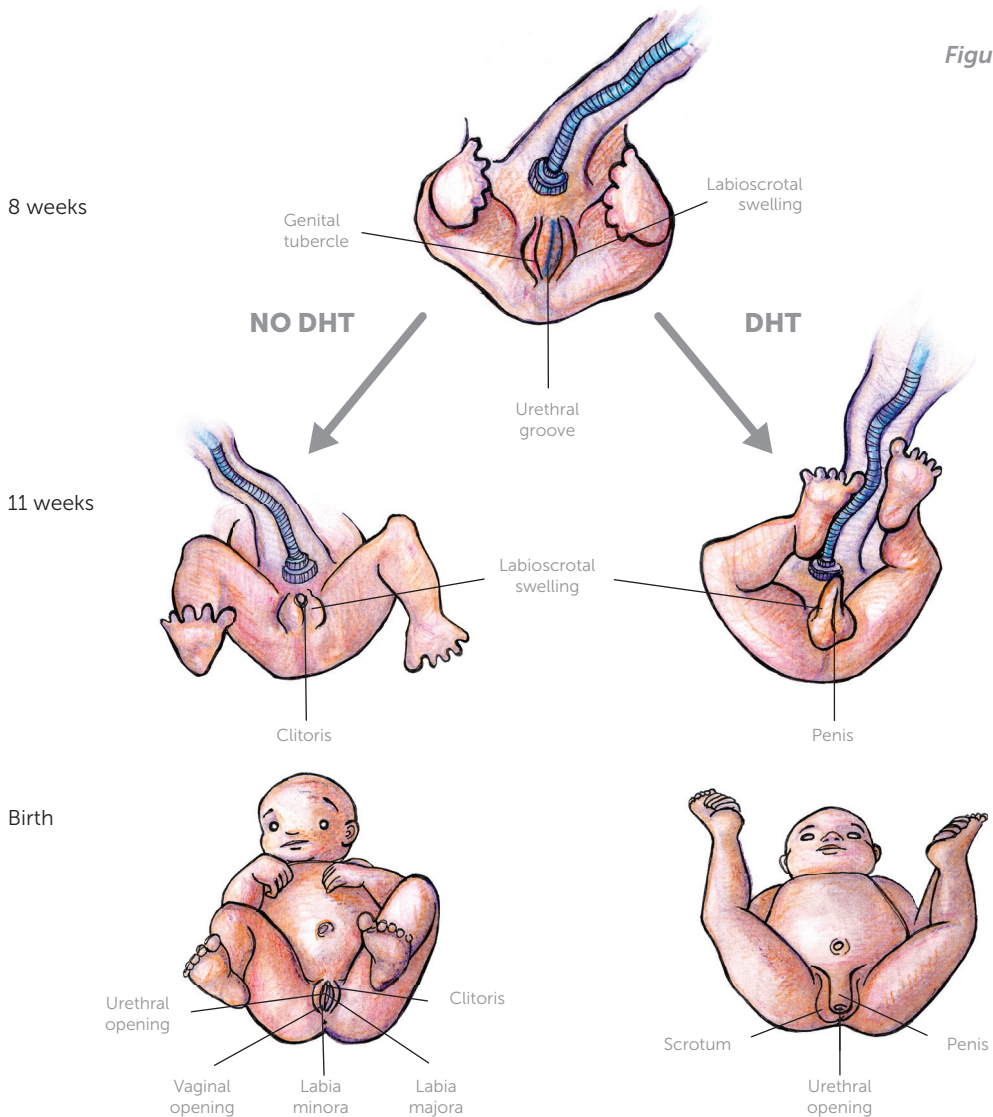
In the absence of androgens, the genital tubercle develops as a clitoris, the urethral folds form the labia minora and the labioscrotal swellings give rise to the labia majora. Proliferation of the vesicovaginal septum pushes the vagina posteriorly so that the urinary and vaginal opening become separated. Proper vagina formation additionally requires the contact and interaction of the urogenital sinus with the fused Müllerian structures [22].

The sensitivity of the urogenital sinus to DHT is limited to a critical time period between 8 and 12 weeks GA, because of a downregulation of the androgen receptors in the urethral folds and labioscrotal swellings. Complete masculinization of the external genitals is accomplished at 14 weeks of gestation, except for the genital tubercle; penile/clitoral growth continues after that period. Therefore, in females, exposure to androgens after 12 weeks GA can only result in clitoral hypertrophy and not fusion of labia minora and majora [22]. Since the genital tubercle consists of corpora cavernosa and glans tissue, the distinction between a penis and clitoris is primarily based on size and whether the urethral folds have fused to form the corpus spongiosum [22]. Around the seventh month of GA, the testes start to descend in the scrotum [25]. This process is considered to occur in two stages, comprising a transabdominal and transinguinal phase. The mechanisms controlling testicular descent are not fully understood. However, based on studies in mice and children with androgen insensitivity syndrome, it is currently believed that androgens are of importance in the transinguinal phase, whereas the transabdominal phase is relatively androgen independent and mainly controlled by the action of AMH and Insulin-like Factor 3 (INSL3), secreted by the Leydig cells [25,26].

Figure 3. Development of external genitals.

At 8 weeks of gestational age, the external genitals are bipotential, and can go on to form female-typical or male-typical structures depending on hormone exposure. The absence of DHT results in female external genitalia: the genital tubercle stays small and forms a clitoris, the urethral groove develops into a urinary opening that is located on the

perineum and the labioscrotal swellings form the labia (majora and minora). In the presence of DHT, male external genitalia develop: the genital tubercle grows into a penis, the urethral fold develops so that the urethral opening is at the tip of the penis and the labioscrotal swellings fuse to form a scrotum (adapted from [21]).



4. Secondary sexual differentiation

The final stage of sex differentiation occurs when hormones produced by the gonads further direct the development of the full complement of secondary sex characteristics at puberty. Such characteristics include breast growth and menarche in girls and increases in body hair and muscle mass as well as penile and testicular growth in boys. Sexual reproduction becomes possible at this stage [17].

In sum, the genetic sex (the presence or absence of the Y chromosome) determines the gonadal sex (the development of the bipotential gonad into a testis or an ovary) [18]. The production and

action of hormones by the functional gonads lead to a further differentiation in typical female or male anatomy [18]. At last, at puberty, the development of sex-specific secondary sexual characteristics confirms the established sex and reinforces the existing sexual dimorphism between individuals [22]. Errors occurring at any stage in this cascade may result in ambiguity of the external genitalia and/or incomplete or malformed internal reproductive structures [17]. From the sequence of these events, it becomes clear that the impact of sex chromosomes on differentiation is indirect. While genetic sex directs the development of the bipotential gonad, the male phenotype is strictly determined by gonadal hormones [17].³

1.2 Disorders of Sex Development

"One is not born a woman, one becomes one," said Simone de Beauvoir (1949) in *The Second Sex* [28]. From a biological standpoint, it seems that during all stages of fetal development, maleness is a permanent molecular fight [16]. The female phenotype is considered to be the "default" pathway in that the differentiation of female somatic sex structures is independent of gonadal hormones and can take place even in the absence of ovaries [22,23], making Eve, rather than Adam, the first or prototypical human being [5].

During the past decade, a number of genes responsible for the making of a male have been characterized. When mutated, these genes are responsible for "demasculinization" of fetuses carrying a male, XY, chromosomal constitution, resulting in individuals born "intersex" or females. The discovery of these sex-determining genes is the direct result of the study of patients with ambiguous genitalia, also known as "intersex"⁴ or "Disorders of Sex Development" (DSD). The umbrella term DSD was introduced in 2005 by the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) for describing those congenital disorders in which there is a mismatch between chromosomal, gonadal and anatomical sex [15].⁵ Revision of the nomenclature was necessitated, because terms such as "intersex" were controversial, perceived as potentially pejorative by patients, and confusing to practitioners and parents alike [15]. To some parents, "intersex" meant a third gender, something in between male and female, and was a label as off-putting and freakish as 'hermaphrodite'. Moreover, a modern lexicon was needed to integrate progress in molecular, genetic and

³ Genetics matter. The ability to distinguish the contributing role of genes versus gonads was markedly advanced by the development of the four core genotypes model of mice. These mice bear a Y chromosome from which the SRY gene has been deleted (denoted Y-) or carry SRY on an X chromosome or autosome, allowing the development of XX individuals with testes and XY individuals in which testes development has failed. Analysis of this model supports the view that sexual differentiation of reproductive endpoints is largely driven by the testicular hormone testosterone or estradiol synthesized in the developing nervous system from this testosterone. Conversely, many nonreproductive endpoints involve direct genetic contributions to variability between males and females [27].

⁴ Richard Goldschmidt was the first to coin the term 'intersex', after he had produced a sexual continuum of gypsy moths which were typically sexually dimorphic. Extending his theory to vertebrates, he proposed an intersexuality grounded in both genetic difference (labeled zygotic intersexuality) and hormonal action (labeled hormonal intersexuality). Intersexuality in invertebrates was grounded in genetic differences present in the zygote, whereas intersexuality in vertebrates included sexual differentiation later in life mediated by hormones and controlled by hormone-producing tissues [29]. Clinicians thereafter adopted this term intersex and began extending it to humans, because of the association of hermaphroditism with mythical creatures and perhaps even monsters. When the Intersex Society of North America (ISNA) was founded in 1993, 'Intersex' took on a political valence by consciously reclaiming the term 'hermaphrodite' (cfr Hermaphrodites with attitude), in an effort to call attention to the pathological associations with the congenital conditions that fall under that rubric and to erase stigmatization [8,30,31]

endocrine aspects of sex development. A descriptive terminology was agreed upon, reflecting genetic etiology when available, and accommodating the spectrum of phenotypical variation. The nomenclature and classification of DSD is shown in Table 1 (based on [15]).

TABLE 1

Nomenclature and current classification of disorders of sex development (based on [15,35])

SEX CHROMOSOME DSD	46, XY DSD	46, XX DSD
45,X (Turner syndrome and variants)	Disorders of gonadal (testicular) development	Disorders of gonadal (ovarian) development:
46, XXY (Klinefelter syndrome and variants)	<ol style="list-style-type: none"> complete /partial gonadal dysgenesis (e.g. SRY, SOX 9, SF1, WT1) testis regression ovotesticular DSD 	<ol style="list-style-type: none"> ovotesticular DSD testicular DSD (e.g. SRY⁺, duplicate SOX9) gonadal dysgenesis
45,X/46, XY (mixed gonadal dysgenesis, ovotesticular DSD)	Disorders in androgen synthesis or action:	Androgen excess:
46, XX/46, XY (chimeric, ovotesticular DSD)	<ol style="list-style-type: none"> androgen biosynthesis defect (e.g. 17β HSD, 5α RD) defect in androgen action (e.g. CAIS, PAIS) LH receptor defects (e.g. Leydig cell hypoplasia, aplasia); and disorders of AMH and AMH receptor (persistent Müllerian duct syndrome) 	<ol style="list-style-type: none"> fetal (e.g. 21-hydroxylase deficiency, 11-hydroxylase deficiency) fetoplacental (aromatase deficiency, oxidoreductase deficiency) maternal (maternal virilizing tumors e.g. luteomas), androgenic drugs)
	Other: e.g.	Other: e.g.
	<ol style="list-style-type: none"> Syndromic associations of male genital development (e.g. cloacal exstrophy) Vanishing testes syndrome Isolated hypospadias Congenital hypogonadotropic hypogonadism Cryptorchidism 	<ol style="list-style-type: none"> Syndromic associations (e.g. cloacal exstrophy) Mayer-Rokitansky-Küster-Häuser syndrome Vaginal atresia

Abbreviations: Complete androgen insensitivity syndrome (CAIS), Partial androgen insensitivity syndrome (PAIS), 17 β hydroxysteroid dehydrogenase deficiency (17 β HSD), 5 α reductase deficiency (5 α RD), Luteneizing hormone (LH), Anti-Müllerian Hormone (AMH), sex-determining region on Y (SRY), SRY-related HMG (High Mobility Group)- box, gene 9 (SOX9), Steroidogenic factor 1 (SF1), Wilms tumor 1 (WT1)

⁵ This nomenclature change has, however, not been universally embraced, because of the loaded word 'disorder', suggesting that atypicality is necessarily wrong and in need of repair. The term 'divergence or difference of sex development' has been proposed instead, underlying one of intersex activism's central tenets: unusual sex anatomy does not inevitably require surgical or hormonal correction (for a discussion, see [30]).

DSD is not rare. In its traditional definition (conditions where it is impossible to distinguish whether the individual is male or female), the incidence is estimated at 1 in 4,500 births [15]. If all minor variants of genital conformation are included in the definition of DSD, the incidence rises to close to 1%, due to the high frequency of hypospadias, an abnormal placement of the urethral opening (about 0.4%), and of cryptorchidism, undescended testes (around 1% at 3 months of age)[16]. These numbers show that, although not discussed as openly as other medical conditions, DSD is present at a high frequency throughout the world. Ethnic groups with high rates of consanguinity hailing from Southern Europe, North Africa and Asia are affected even more often [32]. Genetic diagnosis represents often an early stage in clinical management, but the tremendous heterogeneity associated with DSD conditions results in slow progress in the field [16]. More than a dozen medical diagnoses are associated with the same appearance of genitalia that taken alone gives the observer little or no clue to the underlying physiopathology [16]. A specific molecular diagnosis is identified in only approximately 20% of persons with DSD, and remains especially problematic in 46,XY gonadal dysgenesis and undervirilization syndromes [33,34].

Current classification

As sexual differentiation in humans is essentially determined by the presence or absence of male sex hormones, disorders of sexual differentiation can roughly be divided into 46, XX DSD and 46, XY DSD. 46, XX individuals with a DSD condition have an excess of male sex hormones (overvirilization) and 46, XY individuals with a DSD have a deficiency or resistance to male sex hormones (undervirilization). These can further be subdivided into defects of gonadal determination or subsequent differentiation, biosynthetic defects of male sex hormone synthesis/metabolism and sex hormone receptor defects [23]. In addition to 46, XX DSD and 46, XY DSD, other types of DSD exist, with an incomplete or defective formation of the gonads, due to structural or numerical sex chromosome anomalies.

1.2.1 46, XX DSD

The presence of ambiguous or male external sexual characteristics in developing 46, XX embryos results from exposure to androgens from several sources, during fetal life. These include exogenous androgens either ingested (progesterone, testosterone) or produced by the mother (ovarian and adrenal tumours, maternal congenital adrenal hyperplasia, virilizing luteoma of pregnancy) which cross the placenta. Approximately half of the 46, XX individuals with a DSD are due to virilizing neonatal Congenital Adrenal Hyperplasia (CAH)[36]. CAH comprises a group of autosomal recessive disorders with defects in the synthesis of steroid hormones in the adrenal cortex (*Figure 4*). More than 90% of the cases are caused by mutations in the CYP21 (21-hydroxylase) gene [37]. The incidence is approximately 1:140000 births and carrier status is found in about 1:80 individuals [38,39]. The enzyme deficiency results in impaired synthesis of cortisol and aldosterone. Reduced cortisol synthesis interrupts feedback inhibition of adrenocorticotrophic-hormone (ACTH) release from the pituitary, leading to continuous stimulation of the adrenals by ACTH and, consequently, adrenal hyperplasia [40] (*Figure 5*).

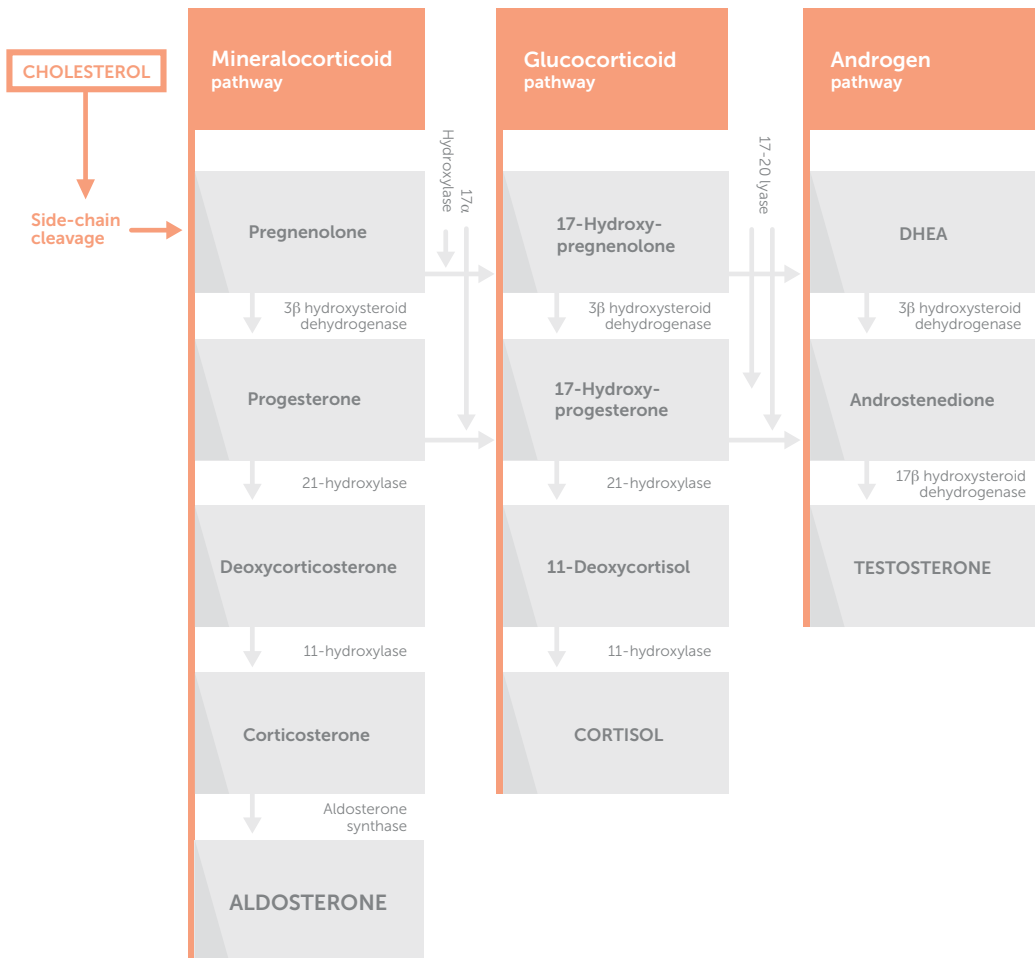


Figure 4. Genes associated with steroid biosynthesis in the adrenal cortex (adapted from [39]).

The three major types of adrenal steroid hormones, glucocorticoids, mineralocorticoids, and adrenal androgens, are each produced through a separate biosynthetic pathway. All three pathways, however, share common precursor molecules. If an enzymatic block occurs in any of the three biosynthetic pathways, precursor molecules are shunted into the remaining functional

pathway(s). Each step is catalyzed by a specific enzyme. Loss-of-function mutations in the gene *CYP21A2* account for about 90% of all cases of CAH. Other, rarer forms of CAH are due to loss-of-function mutations in the genes *CYP11B1*, *CYP17A1*, *HSD3B2*, or *StAR* (steroidogenic acute regulatory protein or lipoid CAH) [37].

Figure 5

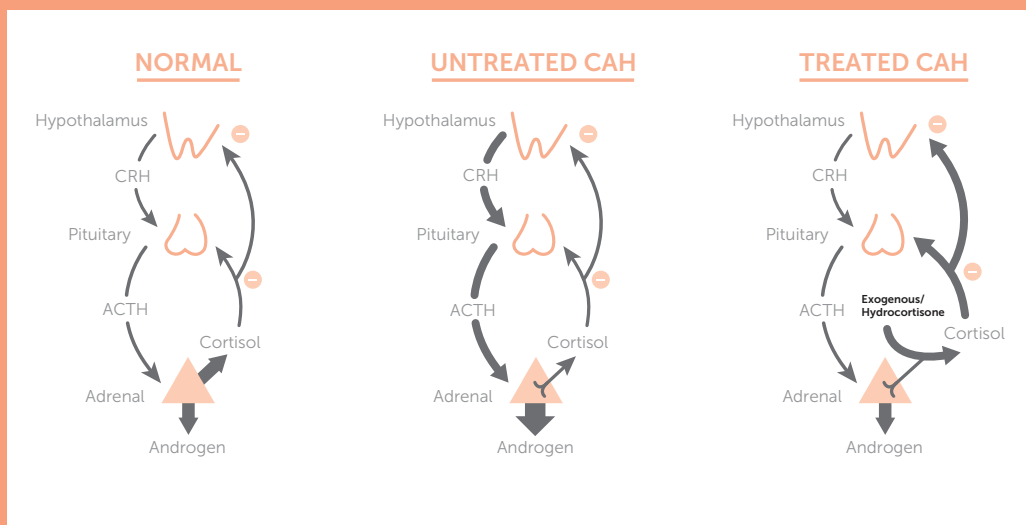


Figure 5. Hypothalamus-Pituitary-adrenal (HPA) axis.

The hypothalamic-pituitary-adrenal axis is controlled by negative feedback. In the untreated patient with CAH, a block in cortisol biosynthesis leads to a build-up of cortisol precursors and lack of negative feedback. Corticotropin is oversecreted, and adrenal hyperplasia occurs. The combination of accumulated cortisol precursors and increased ACTH results in massive androgen

production. In the treated patient with CAH, exogenous hydrocortisone replacement reduces androgen production and interrupts the vicious circle of corticotropin hypersecretion. However, supraphysiologic doses of hydrocortisone are often necessary to adequately suppress androgen production (CRH = corticotropin-releasing hormone) [40].

Increased androgen synthesis, before the 12th week of GA⁶, leads to a variable degree of virilization of the urogenital sinus (labioscrotal fusion, development of a penile urethra and clitoral enlargement), but ovarian development and differentiation of the Müllerian ducts occur normally. Prader developed a scoring system by which the degree of virilization can be quantified [41] (Figure 6). In severe cases the virilization can result in uncertain or wrong gender assignment at birth.

⁶ After week 12, androgen exposure causes isolated clitoromegaly [22].

⁷ Deletions or mutations that completely abolish the enzyme activity are referred to as null mutations. Patients who are homozygous for null mutations have the salt-wasting form of CYP21 deficiency. The I172N mutation causes the simple virilizing form. The V281L and P453S mutations cause the milder non-classical form [43].

There is a wide spectrum of severity of the disease with a good correlation between the CYP21 genotype (i.e. degree of enzyme deficiency) and clinical manifestations, with very few exceptions [42,43]7. Patients with the *classical salt-wasting* form of CAH typically develop electrolyte disturbances and adrenal crises at 2–3 weeks of age - characterized by life-threatening hyponatremia, dehydration, and shock - and girls with this form develop severe prenatal virilization of the external genitalia. Boys with this condition are more vulnerable to neonatal adrenal crises than girls, because, unlike girls, they are not diagnosed at birth because of genital ambiguity [43], making neonatal screening of utmost importance [44]. In patients with the *classical simple virilizing form*, there is no or little risk of developing salt loss, and there are varying degrees of virilization of the genitalia in girls [43]. In the milder *non-classical form*, there is no virilization of external genitalia at birth and no risk of developing electrolyte disturbances. Untreated, these patients develop symptoms of androgen excess later in life, such as growth acceleration, pseudoprecocious puberty, or hirsutism. Some patients with non-classical 21-hydroxylase deficiency are diagnosed as adults, when they seek help for infertility [45].

Figure 6. Prader's classification of genital ambiguity at birth.

Grade 1 represents external genitalia of female appearance, with an enlarged clitoris. Grade 2 represents a further enlargement of the clitoris, associated with a posterior fusion of the labioscrotal folds, but without a urogenital sinus. Grade 3 represents a significant increase in clitoral size, associated with almost complete fusion of the labioscrotal folds and the presence of a urogenital sinus with perineal opening. Grade 4 represents a clitoris

with penile appearance, associated with complete fusion of the labioscrotal folds, and a urogenital sinus with perineal opening at the base or ventral opening of the clitoris. Grade 5 represents a clitoris with the appearance of a well-developed penis, associated with complete fusion of the labioscrotal folds, and a urogenital sinus and opening in the body of the clitoris/phallus [41].

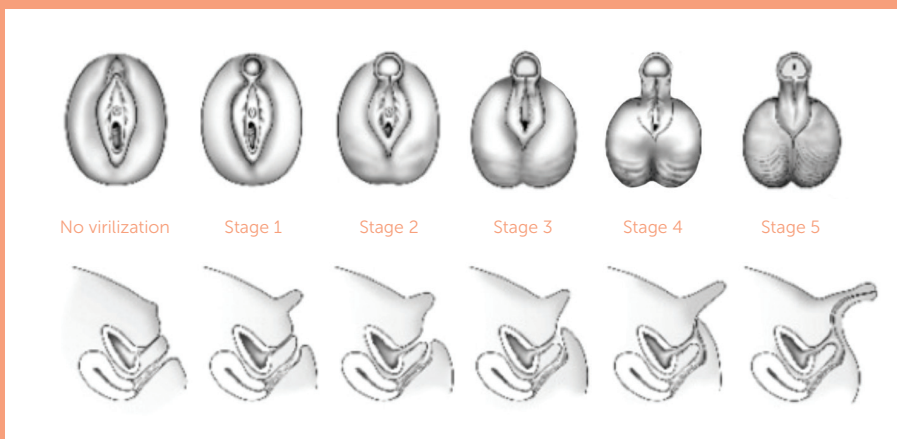
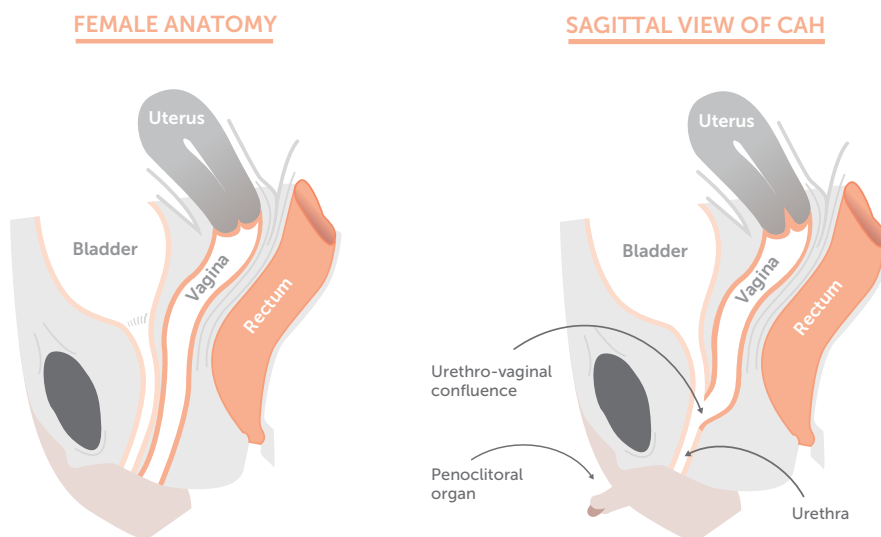


Figure 6

Patients with CAH require life-long medications, such as glucocorticoids with or without mineralocorticoids, and follow-up at specialist centers. Proper treatment prevents adrenal crisis and further virilization and enables normal growth and development [46]. However, certain features of this condition such as short final adult height, subfertility, adrenomedullary insufficiency, obesity, and insulin resistance cannot be completely overcome by glucocorticoid treatment [45]. Moreover, as CAH is in most cases characterized by a confluence of the vagina and the urethra, feminizing genitoplasty is often performed. The vaginal cavity can join the posterior wall of the urethra at any level between the bladder neck (high urogenital sinus) and the very distal urethra (low urogenital sinus) (*Figure 7*). Usually, the higher the sinus, the smaller the vaginal cavity [39]. In vaginoplasty, the vaginal cavity is opened to the perineum and the labia majora are reconstructed as separate structures [39]. In cases with severe clitoris hypertrophy, a nerve-sparing clitoral reduction (with preservation of the erogenous neurovascular bundle) usually is performed as well [47].

Figure 7



Unfortunately, there is a serious lack of data to provide adequate guidance as to the best timing and surgical approach. In recent years, ethicists and patient support groups have come forward to call a moratorium on any genital surgery in infancy, arguing that patients should be able to give informed consent before undergoing such procedures. However, consequences of this policy to patients and families have not been properly addressed either. Because the nature and timing of these feminizing genital procedures remain extremely controversial topics, they will be explored in more depth and detail later.

Classical CAH is currently the only DSD amenable to prenatal diagnosis and intervention. Because of the autosomal recessive nature, it is possible to test the developing genetic off-

spring of a known carrier or affected individual. In such cases, mothers may be prescribed the synthetic cortisol, dexamethasone, which prevents virilization of the external genitalia by influencing the negative feedback system and shutting down the excess production of adrenal androgens. It is as yet unclear whether or not treatment with dexamethasone prevents behavioral masculinization (e.g. preferences for boys' toys, rough-and-active play) which is often seen in CAH girls [7,48]. It is also possible that synthetic steroid administration may have detrimental effects on developing brain structures such as the hypothalamus [17]. Further studies are needed to determine if this is a desirable intervention [49,50].

Defects in 46, XX sex differentiation not associated with androgen defects occasionally occur in association with malformations of the intestine and urinary tracts. These can involve persistence of a primitive cloaca and may be accompanied by renal failure. Unlike other forms of 46, XX virilization, the internal genital ducts are often affected. The most common form of 46,XX DSD without associated androgen effects is Mayer-Rokitansky-Küster-Hauser syndrome (MRKH). Women with MRKH have normal functioning ovaries but an absent or rudimentary uterus and a short vagina resulting from failed embryonic development of the Müllerian duct. MRKH may be isolated (type I) but it is more frequently associated with renal, vertebral, and, to a lesser extent, auditory and cardiac defects (MRKH type II or MURCS association) [51]. Surgical and non-surgical enlargement procedures for the absent or short vagina exist, each with advantages and disadvantages [52]. The low incidence of side-effects, with the major psychological benefit of the woman being in control, would make non-surgical vaginal dilation therapy a logical first choice, with surgery reserved for those women unable to achieve adequate vaginal length via dilators. However, the few good long-term outcomes studies to date, claiming success rates in the range of 80%, do not always consider compliance or sexual function [47]. In general, vaginal dilation protocols (e.g. frequency of dilation, maintenance dilation), patient selection criteria and outcome parameters (e.g. what is success?) are lacking, adding to the controversy around this genital treatment (see *infra* for more details).

1.2.2 46, XY DSD

For male sexual differentiation to proceed normally, the testes need to make sufficient amounts of the hormones AMH (to suppress female internal sex duct development) and testosterone (to promote male internal sex duct development). Testosterone must be converted into the potent hormone DHT, which masculinizes indifferent external genitalia into a fully formed penis and scrotum [21]. The External Masculinization Score (EMS) was developed to assess the degree of undervirilization in an individual with 46, XY DSD. The score is based on the presence or absence of a micropenis (stretched penile length < 2.5 cm at birth), and bifid scrotum, the location of the urethral meatus and the position of the testes (Table 2) [53]. The Internal Masculinization Score (IMS) provides useful information about the internal anatomy and can be used to complement

the information gained from the EMS. These scores cannot replace a detailed description of the clinical examination, but might provide an indication of which newborns warrant a thorough endocrine evaluation for male undermasculinization (EMS < 11) [53,54].

TABLE 2

The masculinization score based on points allocated to a variety of anatomical features (adapted from [53]).

The External Masculinization Score (EMS) (total score 12) is based on external genital features and the IMS (total score 10) on internal sexual organs. In its present format, the EMS can only be zero if the testes are documented to be absent (instead of abdominal) in combination with a micropenis, perineal hypospadias and a bifid scrotum. Consequently, the minimum EMS on initial inspection cannot be <1 out of 12.

FEATURE	SCORE FOR YES/NO OR CONDITION	FEATURE	SCORE FOR YES/NO OR CONDITION
EMS		IMS	
<i>Scrotal fusion</i>	3/0	<i>Uterus</i>	0/3
<i>Micropenis</i>	0/3	<i>Fallopian tube</i> <i>(right and left score each)</i>	0/2
<i>Urethral meatus</i>		<i>Epididymis</i> <i>(right and left score each)</i>	2/0
<i>Normal</i>	3	<i>Vas deferens</i> <i>(right and left score each)</i>	2/0
<i>Glandular</i>	2		
<i>Penile</i>	1		
<i>Perineal</i>	0		
<i>Right and left gonad</i> <i>(score for each)</i>			
<i>Scrotal</i>	1.5		
<i>Inguinal</i>	1		
<i>Abdominal</i>	0.5		
<i>Absent</i>	0		

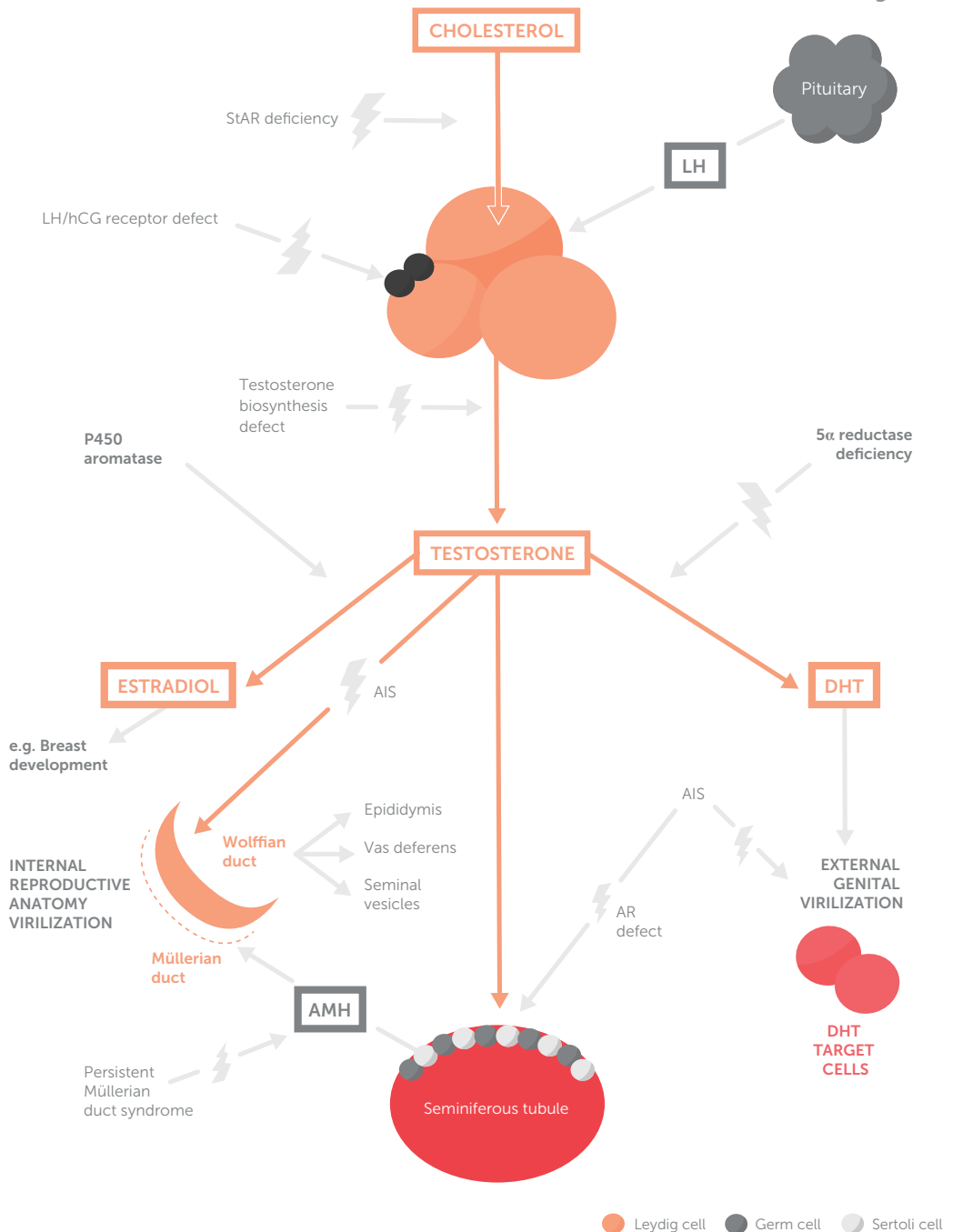


Figure 8. Schematic representation of the pathogenic mechanisms in undervirilization syndromes

In general, hormones can only exert their influences on specific tissues where functioning receptor cells are present. Errors in androgen biosynthesis or receptor availability lead to a disrupted sex differentiation (Figure 8, adapted from [24]).

1.2.2.1 Problems with testis differentiation: testicular dysgenesis

38

Errors in the action of certain transcription factors (such as SRY, DAX-1, SOX9), result in the absent or incomplete differentiation of the bipotential gonad into a testis, leading to a deficiency of Sertoli and Leydig cells. These cells are however necessary to produce AMH, testosterone, or DHT in sufficient amounts to support male sex differentiation. In some cases, the hormone deficiencies are incomplete and babies with 46, XY are born with: 1) testes (because of the presence of the SRY gene) 2) partial development of the internal female sex ducts (because the testes did not produce enough AMH to suppress the development of these structures) 3) partial development of the internal male sex ducts (because the testes did not produce enough testosterone to completely support the development of these structures) and 4) ambiguous external genitalia (because DHT was not produced in sufficient amounts to masculinize the external genitalia) [21].

46,XY gonadal dysgenesis is a DSD due to absent or incomplete testes differentiation, causing a (partial) lack of the Sertoli and Leydig cells. Affected individuals can respond to androgens, however, the abnormal testes are incapable of producing (sufficient amounts of) androgens. The phenotype and gonadal differentiation pattern of a patient with gonadal dysgenesis can be anywhere on the axis connecting the two opposite poles of normal male and female development⁸ [24].

Complete gonadal dysgenesis (Swyer syndrome) is characterized by streak gonads that did not fully differentiate on the pathway to becoming testes and as a consequence, do not produce testicular hormones. These babies will develop internal female ducts in the absence of AMH, no internal male sex ducts in the absence of testosterone and female external genitalia in the absence of DHT. Vaginal length is predicted to be in the normal ranges. Pubic and axillary hair development at puberty is normal, but there is a lack of or poor breast development [55]. Streak gonads are removed due to high risk of malignancy, and hormone replacement therapy (with both estrogen and progestogen components) is initiated to stimulate uterine and breast growth and the onset of menstruation [55].

In partial gonadal dysgenesis, (*Figure 9*) (bilateral dysgenetic testes) and mixed gonadal dysgenesis (an abnormal testis on one side and a streak gonad on the other side) the incomplete formed testes do not produce enough AMH or testosterone to result in male-typical reproductive structures. Some of the female internal reproductive structures are usually retained [56]. The karyotype is usually 46,XY or a varying degree of 45,X/46,XY mosaicism and genital appearance is usually ambiguous.

1.2.2.2 46,XY Undervirilization

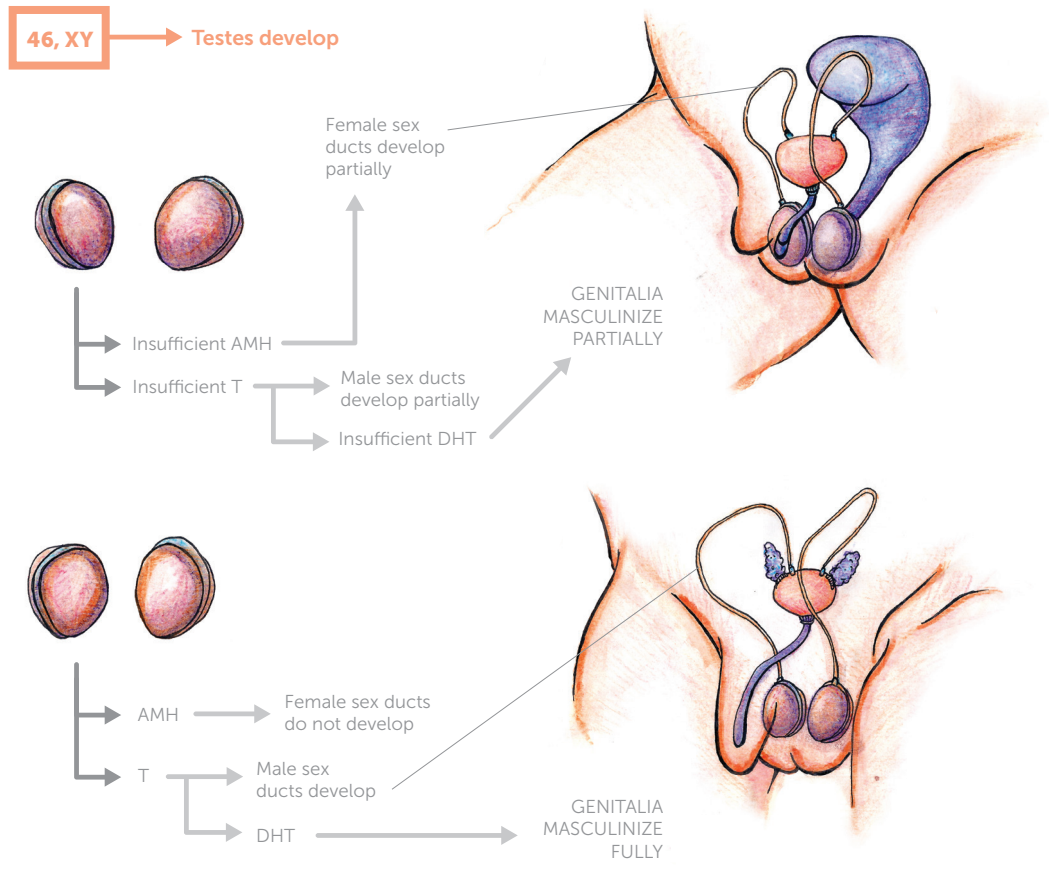
In 46, XY undervirilization syndromes, affected individuals have well-differentiated bilateral (intra-abdominal, inguinal or scrotal) testes, but enzyme deficiencies have disrupted the androgen biosynthesis or action (*Figure 8*).

⁸ Diagnostic work-ups usually reveal a 46, XY karyotype, but the karyotype can contain structural or numerical anomalies of the sex chromosomes, e.g. mosaicism for a Y bearing cell line eventually only detectable in the gonad and not in peripheral blood [24].

Figure 9. 46,XY DSD due to partial gonadal dysgenesis.

In partial gonadal dysgenesis (top panel), the testes are incompletely formed and do not produce enough AMH or testosterone (T). This hormonal environment may result in a situation where both Wolffian and Müllerian internal structures remain partially developed and the external genitalia are ambiguous. Typical male differentiation is displayed in the bottom panel (adapted from [21]).

Figure 9



A. Disorders in androgen biosynthesis

Some enzyme deficiencies only affect the testosterone synthesis, such as 17β hydroxysteroid dehydrogenase deficiency-3 (17β-HSD-3) and 5α reductase deficiency-2 (5αRD-2). In 17β-HSD-3 the fault lies with impaired ability to convert androstenedione to testosterone. Patients with the disorder have testes and normally developed Wolffian ducts derivatives ; however, they show severe to complete undervirilization of the external genitalia, often with normal appearing clitoris and labia majora [22]. Individuals with 17β-HSD-3 are primarily raised as

females and do not present with symptoms until the onset of puberty, at which time virilization occurs. Such characteristics include increased muscle mass and hair growth, lowering of the voice, and growth of the penis (though it is unlikely to reach normal male size) [17]. Deficiency of 5 α reductase-2, which normally converts T into DHT, results in a deficiency of DHT, and an undervirilization of the external genitalia [23]. The result is a newborn 46,XY male with functioning testes, normally formed male internal reproductive structures, a penis that resembles a clitoris, and a scrotum that resembles labia majora [17]. In cases where undervirilization is complete, the diagnosis may be missed and the child is assigned to the female gender and unambiguously raised as a girl [57]. However, because secondary sexual development at puberty is dependent on testosterone, and DHT that has been converted by an 5 α -reductase isoenzyme (e.g. type 1, not expressed in fetal life), individuals with 5 α -RD-2 will virilize in adolescence [58,59].

Some other biosynthetic defects can affect both glucocorticoids and androgens [23] (Figure 4). These include cholesterol side-chain cleavage deficiency, 17 α hydroxylase/17, 20 lyase deficiency and 3 β - hydroxysteroid dehydrogenase deficiency-2 (3 β HSD-2). These conditions are all autosomal recessive and very rare [60] (Figure 4).

In steroidogenic tissues, such as the adrenal cortex, testis, ovary and placenta, the initial and rate-limiting step in the pathway leading from cholesterol to steroid hormones is the cleavage of the side chain of cholesterol to yield pregnenolone. This reaction, known as cholesterol side-chain cleavage, is catalysed by a specific cytochrome P450, and by the steroidogenic acute regulatory (StAR) protein. (Figure 4) [61]. Individuals with a cholesterol side-chain cleavage deficiency are, in general, phenotypic females irrespective of gonadal sex or, sometimes, have slightly virilized external genitalia with or without cryptorchidism, underdeveloped internal male organs and an enlarged adrenal cortex, engorged with cholesterol and cholesterol esters [61]. Individuals with 17 α hydroxylase deficiency, and thus experiencing difficulties with the conversion of pregnenolone into 17 α -hydroxypregnenolone, have a phenotype similar to 46,XX or 46,XY complete gonadal dysgenesis, with the presence of systemic hypertension and absent or sparse pubic hair in post-pubertal patients. 46,XY Patients with isolated 17,20-lyase deficiency, whom cannot convert 17 α -hydroxypregnenolone into dehydroepiandrosterone (DHEA), present with ambiguous genitalia with micropenis, perineal hypospadias and cryptorchidism. Gynecomastia can occur at puberty [61]. 46,XY patients with 3 β -hydroxysteroid dehydrogenase (3 β -HSD) type II deficiency, who have trouble converting DHEA in androstenedione, present with ambiguous external genitalia, characterized by micropenis, perineal hypospadias, bifid scrotum and a blind vaginal pouch that may or may not be associated with salt loss [61]. Individuals without salt wasting show clinical features in common with the deficiencies of 17 β -HSD-3 and 5 α -RD-2.

B. Disorders in androgen action

To respond to masculinizing hormones, functioning androgen receptors (AR) must be present. Although testicular hormones are adequately produced by the testes, absent or malfunctioning androgen receptors (complete or partial androgen insensitivity syndrome, respectively,) result in an unambiguous external female phenotype in the former and an ambiguous phenotype

in the latter (due to the partial ability to respond to DHT) (*Figure 10*). Wolffian duct structures are absent or hypoplastic (due to the inability to respond to testosterone) and Müllerian duct structures are also absent (due to the AMH action) [17] (*Figure 8*). Because the external genitalia are completely feminine in appearance, all newborns with complete androgen insensitivity syndrome (CAIS) are assigned the female gender and raised as girls. In addition, feminizing puberty partially progresses as testosterone is converted to estrogen by P450 aromatase action, thereby promoting spontaneous breast development, though axillary and pubic hair are sparse [24]. As such, the diagnosis of CAIS is usually not made until (late) adolescence when the individual fails to menstruate. Appearance of external genitalia in partial androgen insensitivity (PAIS) is highly variable, with the genital tubercle being intermediate between a clitoris and a penis and the labioscrotal folds often only partially fused with frequent perineal hypospadias. Individuals with PAIS experience breast development at puberty, often resulting in pronounced gynecomastia in boys, as well as minimal axillary and pubic hair growth.

C. Luteinizing Hormone receptor defects

Defects in testosterone biosynthesis due to homozygous mutations in the gene for the LH receptor, resulting in Leydig cell hypoplasia or agenesis, have also been described [23]. In 46,XY DSD due to Leydig cell hypoplasia, there is a failure of intrauterine and pubertal virilization due to the scarcity of interstitial Leydig cells to secrete testosterone. Leydig cells are stimulated by both hormones, chorionic gonadotrophin (CG) and luteinizing hormone (LH), which act by binding and activating a common receptor (LHCGR) located in the cell membrane (*Figure 8*) [61]. Investigation will show high LH levels associated with low testosterone levels that fail to rise with hCG stimulation. The typical phenotype due to the complete form of Leydig cell hypoplasia is female external genitalia, undescended testes slightly smaller than normal with relatively preserved seminiferous tubules and absence of mature Leydig cells, presence of epididymides and vasa deferentia and absence of uterus and fallopian tubes [61]. As in CAIS, some degree of vaginal shortening is expected as a result of the action of AMH; in contrast to CAIS, there should be normal pubic and axillary hair growth [55]. The phenotype in the partial form of Leydig cell hypoplasia is heterogenous [61]. Most patients have predominantly male external genitalia with micropenis and/or hypospadias, and cryptorchidic or scrotal testes. During puberty, partial virilization occurs and testicular size is normal or only slightly reduced, while penile growth is significantly impaired [61].

D. AMH receptor defects

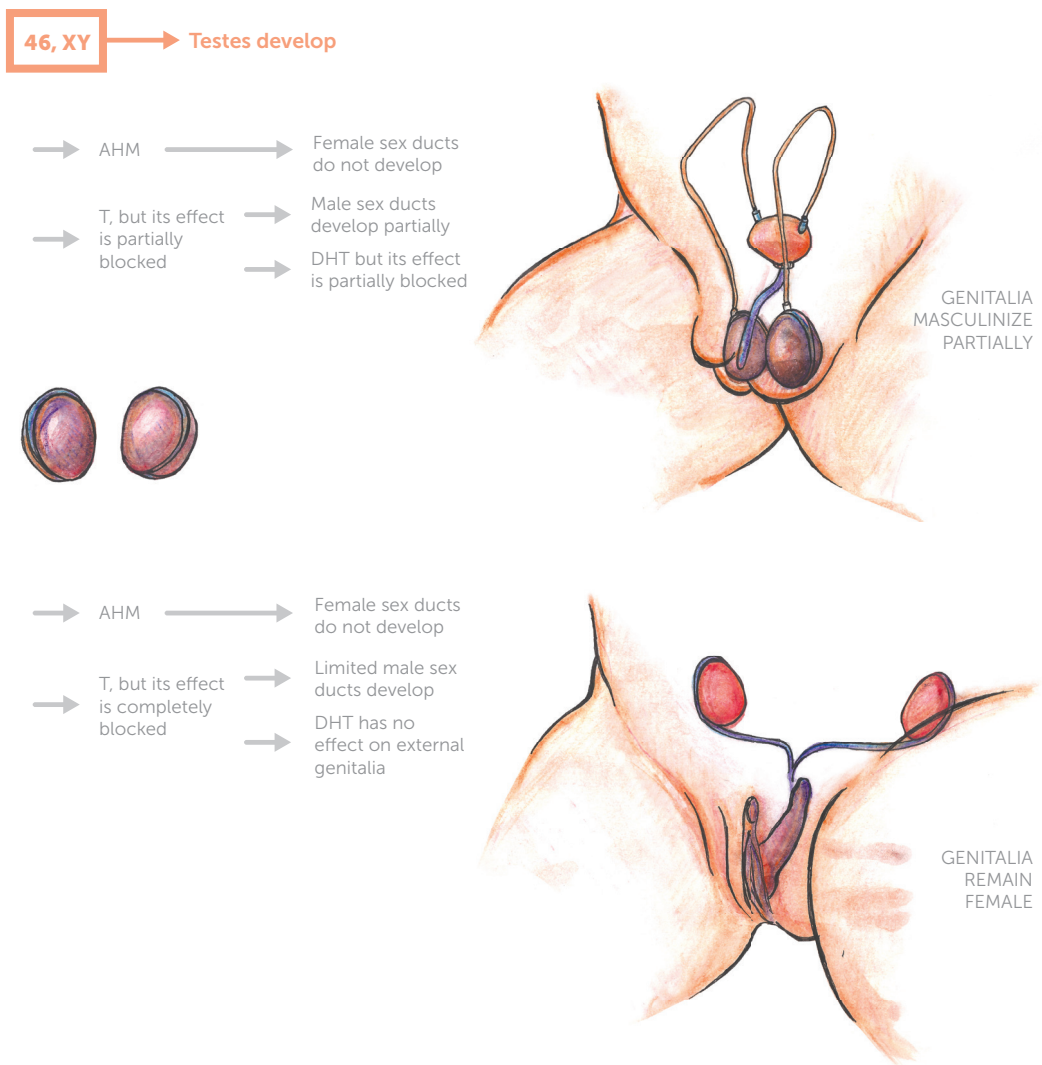
Deficiencies in AMH production or a resistance to its action due to receptor mutations will result in an 46, XY individual with internal and external male genital duct structures with the retention of Müllerian duct structures (Persistent Müllerian duct syndrome), often in combination with cryptorchidism [62, 63].

Figure 10. Sex differentiation in partial and complete androgen insensitivity syndrome.

In PAIS (top panel) and CAIS (lower panel), testosterone is produced, but due to a mutation in the androgen receptor gene, its effect is partially or completely blunted. Therefore, the external genitalia appear ambiguous (in PAIS) or female (in CAIS), but no internal female structures remain because the action of AMH is

unimpeded. The testes are structurally normal during fetal development and at birth, but remain in the abdomen, or more frequently in the inguinal channel because androgens are needed to complete the second phase of the testicular descent [21].

Figure 10



The new DSD classification also includes disorders of undermasculinization not further specified. At least part of them are due to environmental factors (endocrine disruptors¹⁰), affecting androgen production or causing an excess in estrogen production in boys, and their incidence in many Western countries is rising (for an overview see [24,64-66])¹¹. In hypospadias, the urethral opening is positioned on the ventral surface of the penis or on the scrotum or even on the perineum, resulting from an incomplete fusion of the urethral folds [24]. Hypospadias is a common congenital penile defect with an average of 1 in 250–350 male births [67].

In the condition of micropenis, the stretched penile length is at or below 2.5 SD of the population mean, adjusted for age [68]. In a newborn, stretched penile length is ≤ 2.5 cm [69]. The penis has fully differentiated from the bipotential genital structures but is very small, possibly caused by undervirilization during the second stage of androgen release in gestation. Syndromes often associated with micropenis include hypogonadotrophic hypogonadism and vanished testes syndrome. An example of the former is Kallmann's syndrome, characterized by secondary hypogonadism – inadequate gonadotropin-releasing hormone due to hypothalamic or pituitary dysfunction (and thus absent spontaneous puberty) with testicular failure, and a defective sense of smell [70]). In the latter, there is a bilateral absence of testes in a genotypically and phenotypically normal male. Absence of müllerian-derived tissue implies that functional testicular tissue was present in the fetus, but disappeared after 14 weeks of gestation [71]. Individuals with micropenis have been assigned as male and female, largely depending on circumstantial factors (i.e., policy of medical staff, parental wishes, cultural prescriptions).

Severe genital structural abnormalities can also occur despite normal male prenatal sex chromosome activity, testicular development, and androgen activity [72]. Cloacal, bladder or classic exstrophy – in which the lower abdominal organs such as bladder and intestines are exposed instead of sealed in the abdominal wall – are characterized by severe inadequacy or absence of genitalia [73]. Before 1959, survival was apparently nil; with vast improvements in neonatal medical and surgical care in the last 30 years approximately 90% or more babies who are born with these defects survive into adulthood [73]. Clinical success demands addressing the inadequate or absent penis in males.¹²

¹⁰ An endocrine disrupter (ED) is any exogenous substance that causes adverse health effects in an intact organism or its progeny, secondary to changes in endocrine function. Such substances can act through many mechanisms, which may be dose-dependent, such as agonist or antagonistic action at the receptor and post-receptor level, and interference with synthesis, transport and metabolism. EDs may simultaneously affect more than one hormonal system [64].

¹¹ In 2001, Skakkebaek et al. put forth the hypothesis that some male reproductive disorders were interlinked and originated from a disturbed testicular development in utero. This hypothesis was called the testicular dysgenesis syndrome (TDS). The TDS hypothesis was based on clinical, epidemiological and basic scientific evidence for a fetal origin of testis cancer, the well-established link between genital malformations in newborn boys and adult reproductive disorders, and on observations from experimental animal studies and wildlife. Together, this existing evidence suggested that the prenatal period may be the most vulnerable phase in which impairment of testis differentiation may result in permanent adverse effects. Such impairment of testis development could be caused by genetic disorders or polymorphisms, environmental exposure, lifestyle, intrauterine growth disorders or all these factors in combination [65, 66].

¹² Cloacal exstrophy is rare; it occurs in approximately 1 in 400,000 live births with about a 2:1 male:female ratio. Because the penis is seriously inadequate or absent, clinical recommendations for the past 25 years have included sex assignment of biological males at birth to females socially, legally, and surgically through neonatal bilateral gonadectomies and surgical feminizing genitoplasty [73].

In addition to 46, XX DSD and 46, XY DSD other types of DSD include sex chromosomal DSD and ovotesticular DSD. Sex chromosomal DSD refers to conditions with an atypical number of sex chromosomes. Complex karyotypes exist in which different cells from the same individual have different karyotypes (mosaicism), for instance 45X/46,XY (indicating that some cell lines are 45,X and others are 46,XY). This situation may result in gonadal differentiation defects, such as the formation of a streak gonad or testicular dysgenesis, or the gonad may remain largely in an undifferentiated stage. Individuals with either of these karyotypes may have ambiguous genitalia and thus such a mosaic karyotype may be a cause of DSD [74].

Other examples of sex chromosomal DSD are Klinefelter (47, XXY) and Turner (45,X0). Klinefelter patients (incidence 1 :1000) have an extra X chromosome (47,XXY; [75]) and present as tall males with small, dysgenetic testes, and often exhibit a delayed puberty. Their testes become increasingly fibrous over time and do not contain sperm [16]. Turner patients typically lack one X chromosome (1:2500 live female births [76]), and they appear as females with short stature and have a delayed puberty, lack of menses, and a variety of congenital malformations including heart and kidney defects. The ovaries are underdeveloped and composed essentially of fibrous tissue with a very premature loss of oocytes, which results in infertility and low levels of estrogens already during childhood or in early adult life. Genital ambiguity is not an associated feature in both Klinefelter and Turner syndrome [16,77].

Ovotesticular DSD is defined by the presence of both ovarian and testicular tissue in the gonads. The karyotype can be 46,XX, 46, XY or some other sex chromosomal constitution. Development of the internal and external genital structures is highly variable from one person to another [16,55]. In 46, XX testicular DSD, genotypically female individuals develop as males, i.e. the gonads develop varying degrees of testicular tissue and may produce testosterone, leading to virilization of external genitalia. The occurring testis development is likely due to a translocation of SRY to the X chromosome or one of the autosomes [67]. In a minority of cases (10%), no such SRY translocation can be detected (SRY⁻ XX testicular DSD). A limited number of gene mutations and copy number variations have been associated with this phenomenon (e.g. SOX9 duplication, R-spondin 1 (RSPO1) mutations)(for an overview see [67]). Possibly, XX ovotesticular and XX testicular DSD represent different variants of a common mechanism, in which the testis differentiation pathway is activated independent of SRY (for a discussion, see [67]).

1.3 Quest for a 'true' and 'best sex': Management of genital ambiguity and gender assignment

Genital atypia has its written origin in the ancient Greek myth of Hermaphroditus, whose male body was merged by the gods with the female body of the nymph Salmacis. Although this figure found no counterpart in the human world, the idea of one body exhibiting two sexes, able to couple with either sex, raised over the past centuries curiosity and host of anxieties, because of its implications for the binary model of sex as unequivocally male or female [29, 30]. Dreger [78,79] and Foucault [80] have focused on the late 19th and early 20th centuries – a time when the social order was threatened by war and by women's demands for the vote and a greater role in public life – as the beginning of the modern preoccupation with demarcating two sexes; biologically, socially and psychologically [10].^{13,14}

The concept of gender becomes complicated when the commonplace distinction between one's anatomy and one's identity is made, in that sex is considered by many to be anatomical (i.e. genitals, gonads, chromosomes) and *gender* is considered a social category (i.e. the subsequently developing sense and presentation of self as a sexed individual). We tend to infer a child's gender from its genital sex at birth, and subsequently interpret its behaviors as 'feminine' or 'masculine' [84]. As children age, the reverse process occurs. Because we are unfamiliar with a child's genital apparatus, we infer a child's sex from its behavior. In a culture that is heteronormative, there is the presumption that boys and girls will grow up to desire each other. Judith Butler calls this set of linear and causal assumptions of sexual identity development the heterosexual matrix [85,86] (*Figure 11*).

Figure 11. Butler's Heterosexual Matrix [85,86].

Western culture beliefs are based on the assumption that anatomical sex causes gender development which, in turn, causes sexual desire. In this sense, one is assumed to be 'anatomically' hard wired to develop a gender identity (i.e. the sense of self as being male or female) and gender role behavior (i.e. behavior

that is culturally associated with gender) that correlate with one's birth genitalia. In addition, the model assumes heterosexuality, that one will be naturally attracted to individuals whose genitals are different from their own and that penile-vaginal intercourse functions as the exclusive heterosexual act [84].

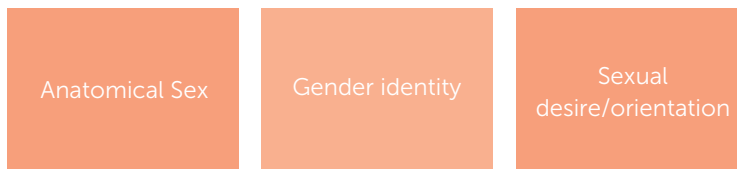
¹³ Identification of the 'true sex' became over the centuries important, as many civil and religious codes regarding marriage and property ownership differed significantly for males and females [80, 81]

¹⁴ Kessler and McKenna summarize them as follows [83]:

1. There are only two genders
2. Gender is invariant
3. Genitals are the essential sign of gender
4. Any exceptions to the two genders are not to be taken seriously
5. There are no transfers from one gender to another except ceremonial ones
6. Everyone must be classified as a member of one gender or the other
7. The female/male dichotomy is a natural one
8. Membership in one gender or the other is natural

Figure 11

46



By the middle of the twentieth century, the birth of a baby with ambiguous genitals had come to be labelled a medical and social emergency, and anguished parents and physicians considered it essential to assign the infant definitely as male or female and to minimize any discordance between somatic traits and gender assignment [29]. Interventions enabled the individual to fit into the binary model of sex and avoid possible social stigmatization and alienation [84]. The central issue became then how to best intervene. Urologists were inclined to resolve contradictions of sex through corrective surgery. Endocrinologists, by contrast, tried to apply theories of hormone secretions to treat intersexuality with the administration of hormones [29].

There was also vigorous debate over the extent to which the biological/anatomical sex could be overruled by socialization processes and the extent to which the psyche should be considered in treatment decisions¹⁵. People were often unaware of their chromosomal and hormonal (gonadal) status and ethical questions regarding a gonadal definition of 'true' sex multiplied. Until then, whether an individual had ovaries or testes, determined if he was 'really' male or female¹⁶. However, does the presence of testes make one a real man? The quest for 'best' sex became based on an assessment of one's likely gender identity [87], or sense of self as being male or female. Psychological testing became part of sex determination, based on the premise that an *optimal* personality integration can be guaranteed when there is congruity between external genitalia, the sex of rearing and the patient's psychological sense of wellbeing as male or female [88].

¹⁵ One of the crucial topics within this literature remains the unresolved debate on nature versus nurture and the question of whether and how early children learn gender roles versus the influence of genes and hormones on the development of behavior, gender identity, and sexual orientation.

¹⁶ In 1876, the German pathologist Theodore Klebs was the first to suggest a taxonomy based on the analysis of gonadal tissue and on whether an individual had ovaries or testes. He distinguished between pseudo- and true hermaphroditism. True hermaphrodites had both ovarian and testicular tissue in the same body. This simultaneous overlap of gonadal tissues may be represented in one gonad (e.g. one gonad with both testicular and ovarian parts) or may be presented separately in each gonad (e.g. one gonad is a testicle, the other is an ovary). True hermaphrodites more commonly have a 46, XX karyotype than 46, XY but may have either karyotype, and their external genitalia are typically ambiguous. In Klebs' system, pseudohermaphrodites have either ovarian or testicular tissue; these individuals were 'really' female or male, as indicated by their gonads, but their mixed external anatomy (genitals) obscured their sex [29, 83].

1.3.1 Optimal gender policy

Since the 1950's, clinicians have used a treatment protocol developed by John Money and his followers from the Johns Hopkins Medical School, based on his work on gender identity and role. These were, according to Money, not something individuals were born with, but something built up cumulatively over time. He suggested a small window of gender flexibility and opportunity (until eighteen months of age) before which gender should be assigned; otherwise children might risk 'psychological disturbance' [29]. Thorough clinical workups were important to identify the etiology, so that clinicians could determine a sex and select the optimal gender for the individuals and surgeons could modify the infant's body through surgical and hormonal treatment to conform to the assigned sex. This had to ensure that the child avoided physical developments incongruous with the assigned gender and was important with respect to future (hetero)sexual function (Table 3) [88, 89]. Money's research demonstrated that although it was critical to assess fully all the markers of biological sex –chromosomes, gonads, genitals and hormonal functioning- none of these sufficed alone or together to predict or explain gender. His theory of gender development, which suggested that sex of rearing was critically important for gender acquisition, filled this gap. He introduced psychological principles and advocated psychological support into the medical treatment of DSD and provided a link between the fields of psychology, endocrinology and surgery in gender assignment and treatment [29]. For roughly four decades, Money's recommended treatment was widely adopted and unchallenged, in part because it provided practitioners with a detailed guide for carrying out the treatment, one backed by empirical evidence, and because it was an innovative and more nuanced model of gender development [29].

TABLE 3

Parameters of the Optimal Gender Policy of Psychosocial and Medical Management. Based on [88, 89].

1. Reproductive potential (if attainable at all)
2. Good sexual function
3. Minimal medical procedures
4. An overall gender-appropriate appearance
5. A stable gender identity
6. Psychosocial well-being

¹⁷ A thorough history on the development of Money's model can be read in [29], but a short description is given here. Money was critical of the treatment practices of the 1950's, which were too based on the microscopic study of gonadal tissue. By reviewing the literature on so-called hermaphroditism for his dissertation, he found that neither anatomy alone, nor genetics or hormones could indicate the status of psychosexual differentiation and identity (Hermaphroditism: An inquiry into the nature of a Human Paradox, John Money, 1952). He did a comparative analysis of 248 published and unpublished case histories (from 1895 to 1951) and patient files, as well as an in-depth assessment of 10 living individuals classed a hermaphrodites. His first set of questions concerned the origin and determinants of one's 'libidinal inclination, sexual outlook and sexual behavior'. The second concerned the origins of the 'psychosexual role' (the social manifestation of sex differences or gender roles). On the first question, Money found that sex drive (or libido) was hormone dependent, whereas sexual orientation was not, bearing a strong relationship to 'teaching and the lessons of experience' (Money, 1952). His second finding was that so-called hermaphrodites generally fared well psychologically, with low incidences of mental illnesses. He argued that this finding suggested that the field of psychoanalysis had placed undue emphasis on psychosexual etiologies for mental disorders. Moreover, most hermaphrodites grew up to accept their sex of rearing, despite physiological contradictions. In general, those facing the greatest contradictions among their physical characteristics, psychosexual orientation and sex of rearing fared the worst. His emergent 1955-theory stated that the sex of rearing was a primary determinant of an individual's gender role and sexual orientation. To mitigate the possibility of severe contradictions between somatic sex traits and the sex of rearing, hormonal and surgical interventions had to be employed.

Although research on brain differentiation has not been used specifically in any classificatory or treatment schema for DSD [90], this research has also been at the center of debates about gender-identity formation. Structural sex differences – from the macroscopic to the ultramicroscopic level– have been observed in the adult brain, together with a large number of functional sex differences in a variety of brain regions, such as the sexually dimorphic nucleus of the preoptic area, the hypothalamic ventromedial nucleus, and the corpus callosum (for an overview, see [5,91]). Structural differences in the brain resulting from the interaction of genes, sex hormones, and developing brain cells are thought to be the basis of sex differences in e.g. gender identity, gender role behavior and sexual orientation [91]¹⁸. When Money published his gender socialization hypothesis in 1955, androgens were understood as the hormones responsible not only for masculinizing genitalia and for the pubertal development of secondary sex characteristics [92,93], but also for brain sexual differentiation and hence observed behavioral differences between male and female animals [94]¹⁹. This paradigm, often referred to as organization-activation theory, suggested that androgens directly (or via the local conversion into estradiol) organized the brain in early development and pubertal androgens would further activate the already organized brain, resulting in the expression of masculine behaviors. In the absence of exposure to androgens, the brain and resulting behavior would be feminine (*Figure 12*) [27, 95]. On the basis of subsequent work, Milton Diamond proposed that male or female human embryos begin with a predisposition for psychosexual development as either male or female; however, as development proceeds, the predisposition is limited by biological and cultural factors. He advanced this view in opposition to Money, which he characterized as arguing that humans were ‘psychosexual neutral’ at birth. Diamond saw gender as determined primarily by biology; the environment could only modify effects of an ‘inherent and previously organized soma’ [96] (p.160) on which it was superimposed [29].

Money however also built further on previous biological and hormonal work. In the 1960’s, Money and Ehrhardt reported masculinized gender role behavior (understood as a preference for boys toys and an active rough-and-tumble play style) in girls with congenital adrenal hyperplasia, subsequent to prenatal androgen exposure [97]. They concluded that the organization theory applied to humans only to some extent, since gender identity in these individuals was female, despite more masculine gender role behavior. In their 1972 book, *Man and Woman, Boy and Girl*, they further suggested that prenatal hormones proved important in

¹⁸ For instance, women have an increased risk of suffering from depression and most anxiety disorders. Morphometric studies have shown sexual dimorphism in several brain structures, such as the cingulate and ventrolateral prefrontal cortices (larger in women) and the medial temporal structures, including the amygdala (larger in men), to be implicated in emotional processing. Immunocytochemical studies of vasopressinergic neurons and corticotropin-releasing hormone (CRH) neurons in the human paraventricular nucleus have shown a larger amount of neurons in men compared to women. These physiological differences in the male and female brain, hypothesized to be programmed by sex steroids early in development, might have important implications for vulnerability in disorders associated with stress or mood [91].

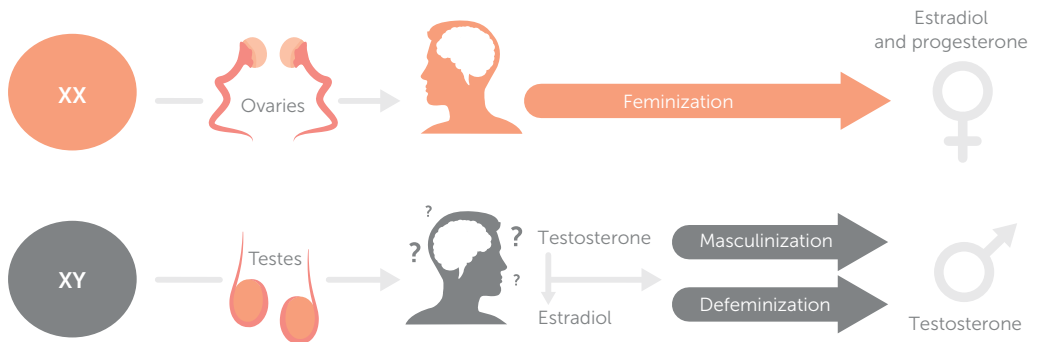
¹⁹ The two critical periods in human development when testosterone levels are known to be higher in boys than in girls are midpregnancy and the first three months after birth. These fetal and neonatal peaks of testosterone, together with functional changes in steroid receptors, are thought to program to a major degree the development of structures and circuits in a boy’s brain for the rest of his life. As sexual differentiation of the genitals takes place much earlier in development (i.e. in the first 2 months of pregnancy) than sexual differentiation of the brain (the second half of pregnancy), these two processes may be influenced independently. This means that in the event of ambiguous genitals at birth, the degree of masculinization of the genitals may not always reflect the degree of masculinization of the brain [91].

gender development, but they were not determinative. In that same book, Money also provided the first application of his theory to an individual without a DSD condition: a young boy, one of two identical twin boys, whose penis was accidentally destroyed during circumcision ('ablatio penis') and for whom he recommended a female reassignment [98-100]. The child's upbringing as a girl, transitioning to live as a male in his teens and enduring psychiatric distress was highly publicized, both in the popular media [101,102] and in psychiatric and pediatric medical journals, in particular by Diamond [103,104]. This case, known as the John/Joan case in the medical literature (and later identified as David Reimer) reanimated the long-standing nature versus nurture disputes regarding gender-identity formation and psychosexual development [29]. Most of the popular debate over the David Reimer case – also reflected in Colapinto's book title 'As nature made him' [102]- focused on the idea of a true, underlying sex, determined primarily by chromosomes and hormones that connected in a direct and predictable way with gender, and on the notion that DSD management protocols have been wrong because they were not based on the idea that biology determines gender [29]²⁰.

Figure 12. Twentieth-century linear view of sexual differentiation.

In this iconic model, based on the organizational/activational hypothesis, chromosomal sex determines gonadal sex, which determines brain sex. Feminization of the brain is the default process that occurs in the absence of high levels of gonadal steroids during a perinatal sensitive period. Masculinization and defeminization are separate hormonally driven processes that organize the neural substrate to promote male-typical behaviors while suppressing female-typical behaviors. The organized neural substrate is activated by adult gonadal steroids and required for sex-typical behaviors to be expressed [27].

Figure 12



²⁰ This case had failed, but it doesn't invalidate Money's other empirical research in DSD cases, nor does it follow that this case provides unequivocal support for Diamond's theory. As Karkazis [29] points out, most researchers still use a causal model of gender identity development that relies on a nature-nurture binarism. If nurture is demonstrated to be incorrect, it is assumed that nature must be the cause. This conclusion reaffirms the opposition between nature and nurture, more than it affirms or refutes claims about how gender identity develops.

Figure 13

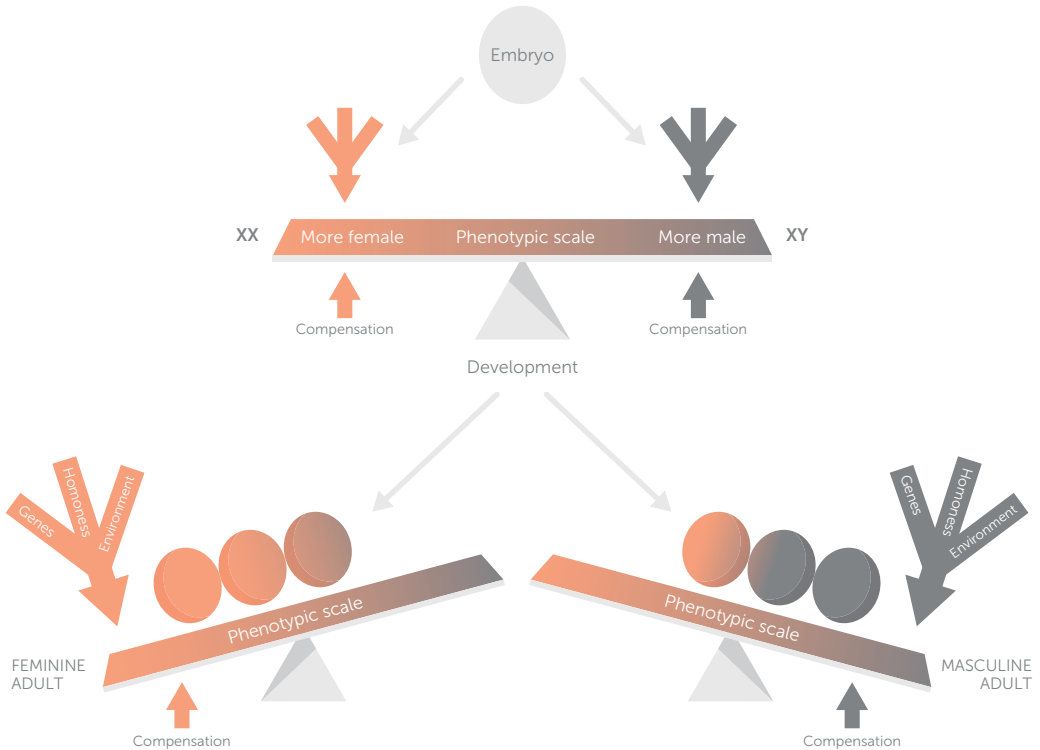


Figure 13. Redefining sexual differentiation.

In a twenty-first-century view of sexual differentiation of the brain, the importance of genetics and environment are incorporated along with the effects of hormones to provide a more nuanced portrayal of the types of variables that cause sex differences. Hormones, sex chromosome genes and sex-specific environments or influences have independent parallel differentiating effects that can interact with each other, often synergistically, resulting in a continuum of sex differences in the brain. However, there are also compensatory sex-specific variables that act to reduce sex differences rather than induce them. The result is that some aspects of male and female brain, behavior and physiology are unique, whereas others are highly similar. Two important aspects are not

illustrated here: 1) sex differences are pervasive throughout the brain and not restricted to reproductively relevant neural circuits, and 2) variability in the degree to which brain regions are masculinized or feminized in one individual results in a continuum of relative maleness or femaleness and thereby greatly increases the variance between individuals of the same sex in a population [5,27]. If gender identity is indeed the product of complex genetic, hormonal and environmental factors, it is plausible that sexual identity is not an all-or-nothing phenomenon, but rather represents a continuum from feeling male to feeling female, which would depend on the degree of genetic influences, prenatal concentrations of hormones and the environment in which the individual is raised [74].

1.4 Current issues

The resurgence of an interest in the role of pre- and postnatal hormones in sexual differentiation has forced the rethinking of the traditional model of gender assignment [5]. Curiously, the debate emanated from the sensationalistic case histories involving a gender change in individuals without DSD conditions (such as the John/Joan case) and evidence about gender-identity change in 46,XY individuals with cloacal exstrophy and severe phallic inadequacy, who were treated according to the treatment protocol for DSD [73,105,106]²¹. Money's model was challenged by researchers, such as Diamond and Reiner, targeting his belief that gender identity and sexual behavior at birth are not fixed but can be influenced by rearing. Their search for definitive biological markers of sex was based on the notion that prenatal androgen levels contribute to a masculine sexual differentiation of the brain and to subsequent gender difference. The extent to which androgens only masculinize gender role behavior or also masculinize gender identity remains a point of discussion. Researchers have to rely mainly on proxy measurements of the degree of prenatal androgen exposure, as it is difficult to reliably and accurately assess an infant's degree of androgens prior to birth. One proximate determinant is for instance the degree of genital virilization, which is thought to correspond to brain virilization. Whereas the relationship between the degree of genital masculinization and masculine play behavior is moderate [107,108], others found no relationship with gender identity [109,110]. Conceptual problems however arise by completely downplaying the role of socialization and relying exclusively on the explanatory power of biology – in casu androgen exposure- in the development of gender behavior and identity. The assumption of a neural and biological dimorphic body established early and being quite similar over time, across and within subjects is too simple, since recent research has shown brain plasticity and an ability of the nervous system to adapt to changing circumstances, as well as genes affecting behavior. Genes, or hormones do not act independently of their context to produce certain characteristics [15,17,22,89, 111-113] (Figure 13). Moreover, with a focus on biology, much less attention is paid to the world in which the child is born in, how parents react, the effects of possible peer rejection, education, race, class or culture. In sum, most studies do not model the interactive nature of biological and social effects, but underline too often the biological and social as distinct [29]. Though excellent progress has been made in understanding biological and environmental factors that contribute to healthy psychosexual development, it is still the case that variability in behavioral outcomes makes it difficult to be certain of optimal sex assignment (Table 4). The question seems then how to make the least bad choice [22]. Cautious and careful case-by-case management by multidisciplinary teams, balancing out all advantages and disadvantages and with parents fully involved in management decisions, is always indicated [17]. Gender assignment remains one of the most contentious areas in the field of DSD .

²¹ Reiners' work on cloacal, bladder or classic exstrophy was frequently cited in debates of gender assignment, although clinicians are adamant that these children do not have intersex conditions. Like Diamond, Reiner had also argued for a strong inborn bias for gender identity, depending on androgen exposure [29]. Although only half of the 46, XY individuals in his sample identified as male, he felt it would be a matter of time before the rest switched to live as men.

²² The uncertainty of how to deal with certain diagnoses was for instance reflected in the title of Mouriquand's article (2004): How to make the least bad choice in children with ambiguous genitalia.

TABLE 4

Gender assignment in 46, XX and 46,XY Disorders of Sex Development.

Syndrome (karyotype)	Prenatal T exposure	Assigned Gender	Gender Identity	Gender role behavior	Gender dysphoria and change	References
CAH (46,XX)	Y	Mostly F	F	Masculine	5% F → M	[7, 48, 114-119]
CAIS (46,XY)	N	F	F	Feminine	0% ^a	[113, 120-123]
PAIS (46,XY)	Y	Mostly F	As reared	Masculine	9.1% 5% F → M 4% M → F	[113, 120, 124, 125]
5 α RD-2 (46,XY)	Y	Both	M	Masculine	56-63% F → M	[126]
17 β HSD-3 (46,XY)	N	Mostly F	M	Masculine	39-64% F → M	[126]
Complete GD (46,XY)	N	Female	F	Feminine	0%	[17, 127]
Partial GD (mostly 46,XY)	Y	Both	As reared	Masculine	0% ^b M → F	[56, 128]
Micropenis (46,XY)	Y	Both	As reared	As reared	0% ^b M → F 0% ^c F → M	[120, 129]

Abbreviations: CAH= Congenital Adrenal Hyperplasia, CAIS= Complete Androgen Insensitivity Syndrome, PAIS= Partial Androgen Insensitivity Syndrome, 5 α RD-2= 5 α reductase deficiency-2, 17 β HSD-3= 17 β hydroxysteroid dehydrogenase deficiency-3, GD= Gonadal dysgenesis, Y=Yes, N= No, F= Female, M= Male ^a One case report has been described of gender change to male ^b No actual gender change but only gender dysphoria, ^c although satisfied with their gender identity, most had questioned their gender of rearing at some point.

The other particularly controversial field is genital treatment and its timing.

In October 2005, fifty international experts in such fields as pediatric endocrinology, pediatric urology, genetics and gender identity development were gathered in Chicago to revise the treatment guidelines for infants born with DSD. The meeting would not have happened without DSD activists' growing chorus of demands for changes in medical treatment practices. Beginning in the early 1990's, criticism on the traditional treatment paradigm- with its focus on rapid gender assignment, genital surgery and secrecy about the diagnosis- came from a number of adults

who had been treated as children and felt that they had suffered extraordinary and irrevocable harm. They pointed to the lack of complete and honest disclosure to parents about the child's anatomy and condition and to the child about its treatment history, to the rush to normalize atypical genitals by performing surgery and to the desire to erase gender atypicality and differences in the name of care [29]. By the year 2000, the topic had received extensive coverage in documentaries, newspapers, magazines, on television and even in novels (e.g. Eugenides' novel 'Middlesex'), with the field being in a deep crisis. Providing recognition and advising caution, the new guidelines stated that DSD conditions are not shameful and suggest that psychological care should be integral to medical treatment. Although these new guidelines encompass positive developments and incorporate important changes, they have been criticized as well for sustaining the assumption that physicians should intervene in controlling the 'sex of the body' [29]. While descriptions of the various genital treatment procedures, their advantages and disadvantages, risks and benefits along with the outcome literature are addressed in detail in subsequent chapters, we provide the reader with a short overview. The purpose of this overview is to engender in medical clinicians less familiar with genital reconstructive surgery or treatment a better understanding of the nuances of reconstructive procedures and how the various procedures may relate to the underlying anatomy of each DSD patient. In addition, we hope to fuel a discussion of the need for future development and research in the field.

1.5 Understanding and weighing genital treatment options

The areas of genital treatment currently under review within this doctoral thesis are:

Surgery for
ambiguous
genitalia

Treatment for
the absent or
short vagina

Masculinizing
genital
surgery

1. Genital surgery for ambiguous genitalia

Since John's Money's work, it has become routine to recommend feminizing genital surgery to all infants with ambiguous genitalia raised female - with congenital adrenal hyperplasia (CAH) being the most common cause of genital ambiguity. Surgical treatment of girls with CAH usually involves 1) clitoroplasty to reduce the clitoral size and improve the cosmetic appearance of the genitals, and 2) vaginoplasty, with the goal of exteriorizing the vagina and creating 2 separate

openings for the urethra and vagina, and to achieve an unobstructed, sex-typical manner for urination and to allow for vaginal-penile intercourse [175].

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Clitoral and vaginal surgery

Cosmetic surgery on the prominent clitoris has gone from simple amputation of the clitoris to techniques for recession (i.e. burying the clitoral shaft under the pubic bone without removing any erectile tissue) and nerve-sparing reduction (i.e. preserving the glans clitoris and neurovascular bundle running along the dorsal aspect of the clitoral shaft while removing most of the erectile tissue), with a focus presently on not only producing a normal cosmetic appearance but also at preserving (erotic) sensation and vascularity of the glans [134] and incorporating the preserved parts of the enlarged clitoris under a reconstructed clitoral hood [135]. There is much debate but little data on all aspects of clitoral surgery including the appropriate size and site for incisions on skin and crura, whether or not to anchor the clitoris to the bony pelvis, how much corporal tissue to remove as well as the requirement for reduction of the glans clitoris and what techniques best achieve this [175]. Most descriptions of clitoral reduction techniques usually report small series of patients with limited follow-up; there are no comparative studies of the short or long-term advantages of specific techniques [175].

State-of-the-art techniques for vaginoplasty, in which the vaginal cavity is opened to the pelvic floor allowing passage for menstruation, and later sexual activity, also have changed drastically over the years [132]. Flap vaginoplasty and vaginal pull-through techniques separating the urethra and vaginal components, have been replaced by total and partial urogenital sinus mobilization [136]. The former involves a 360° mobilization of the entire urogenital sinus, which is then brought to the perineum [137,138]. In the latter, dissection is avoided superior to the urethra under the pubic bone, a nerve-rich zone that contains the sphincteric musculature necessary for urinary continence [138].

In rare cases, the residual vaginal cavity is too small to be connected to the pelvic floor and a vaginal substitution appears necessary to bridge the gap [39]. A vaginoplasty with a skin graft substitution is particularly prone to contracture, making postoperative dilation necessary at least until a regular sexual relationship is established [47]. Many pediatric urologists and surgeons prefer therefore bowel vaginoplasty, as it is believed to obviate the need for postoperative dilation. However, this is a major surgical procedure that carries significant long-term complications, including mucous production, vaginal stenosis, vaginal prolapse, diversion colitis, bowel obstruction and rarely carcinoma [47]. Urinary incontinence and the need for re-operation for tampon use or intercourse remain postoperative concerns whatever technique is used [139].

Timing of surgery

Issues around timing of repairs are truly unsettled, although they have been conducted for decades [47,132,133]. The surgical challenge may be approached either separately (i.e., a 2-stage procedure, where the clitoroplasty is performed in infancy followed by vaginoplasty delayed

until near puberty) or as a 1-stage procedure (in which the clitoroplasty and vaginoplasty are performed in one setting in early childhood or infancy) (for an overview, see [39,132]).

Recent clinical practice guidelines published by the Endocrine Society suggest that:

1. for severely virilized (Prader stage ≥ 3) females, clitoral reconstruction be performed in infancy by an experienced surgeon [137,138]
2. for less severely virilized females (Prader stage < 3), clitoroplasty may be performed in adolescence, if necessary. Although a clitoris looks large on a small baby, the appearance relative to the rest of the genitals will change as the child grows older. Mild to moderate clitoral hypertrophy may also regress with medical therapy for CAH [142].

As a general rule, the more virilized the patient, the higher the vagina inserts in the common channel (urogenital sinus), which is technically more demanding for repair.

1. In patients with a low vaginal confluence, complete repair including vaginoplasty, perineal reconstruction, and clitoroplasty (if necessary) is recommended to be done simultaneously at an early age [138].
2. For individuals with a higher vaginal confluence, the timing is less certain, but most agree on deferring it to adolescence [137,140,141], with the exception in some severe CAH cases, in which early surgery is necessary to avoid urinary tract infections. Thus, even in cases where the urogenital sinus is long and vaginal entry high, vaginal surgery may be delayed until adolescence as, in most cases, menstruation can occur through the common urogenital sinus [175].

Advocates of surgery in infancy, maintain that the procedures are easier to perform and the results better in the young child [175]. In infants with severe virilization where clitoroplasty is being considered, the redundant clitoral skin can also be used as part of the vaginal reconstruction and gives the surgeon much more flexibility. In the neonatal period, the recent exposure to placental estrogens leads to more elastic vaginal tissue, facilitating vaginal reconstruction [138]. Other presumed values in seeking early surgery are reducing parental anxiety and easing acceptance of the child's congenital anomaly, avoiding stigmatization of a girl with masculinized genitals [144], and avoiding the psychological trauma of genital surgery during adolescence [138]. Some surveys completed by adult patients with CAH suggest that most women favor surgery before adolescence [182,183]. In addition, it has been shown that mothers of children for whom genitoplasty was delayed beyond 12 months experienced greater parenting stress than those whose children had surgery within the first year of life [188].

Those favoring later reconstructive surgery note that the decision more appropriately rests

with the patient rather than the family and that the surgical options for genital reconstruction will be preserved in the event that the initial sex assignment was incorrect and a sex change desired, or the patient does not desire genitoplasty [47,175]. It has also been suggested that a vagina is not necessary for a young girl prior to menarche or sexual intercourse [47]. Moreover, the implied surgical advantage of delayed reconstruction is that the risk of vaginal stenosis and the need for subsequent dilation is diminished, as well as the risk of repeat operations because of a narrow introitus and/or for more extensive reconstruction because of vaginal strictures or vaginal insufficiency [142,143].

Psychosexual function after clitoral and/or vaginal surgery

To date (and despite clinical practice guidelines), there have been no studies comparing early and delayed feminizing genitoplasty with regard to psychological and sexual outcomes [139] and the time span needed to conduct such studies, poses a methodological challenge [175]. Some studies suggest poor cosmetic and functional results of genitoplasty done in infancy [139,142,147,148,115,179] with a high re-intervention vaginoplasty rate in adulthood for stenosis [143,184]. Sexual QoL seems particularly impaired with regard to intercourse frequency, avoidance of sex, penetration difficulties and problems with orgasm [115,179], which the women with CAH attributed to their genital surgery. However, it is important to acknowledge that worse psychosexual function compared to controls might not be entirely related to surgical interventions since the null genotype alone (homozygous 21-hydroxylase mutation) has been associated with poorer long-term psychosexual outcomes regardless of having had surgery performed or not [189]. Furthermore, there is no information in regard to psychosocial and sexual outcomes of patients adequately supported and prepared for romantic and sexual relationships, e.g. with comprehensive sex education [174]. There are many confounds in the available reports on surgical interventions and psychosexual function, and it remains unclear why sexual lives of women with CAH differ compared to control groups in terms of timing of psychosexual milestones (delayed), sexual experiences (less), sexual activity and imagery (less), sexual motivation (less), partnership and marriage (less), and sexual self-image (less favorable) [190-192]. For instance, repeated genital exams and medical photography, treatment by clinicians experienced as disrespectful, or an atypical genital appearance might be particularly anxiety provoking for some adolescents, and uncertainty about masculinity/femininity, sexual adequacy, or sexual orientation and fear of rejection may lead to postponing initiating intimate relationships [193]. It is equally important to acknowledge that there are publications indicating that adult patients with CAH who had surgery early in life score similarly to those with other surgical and nonsurgical chronic medical conditions in quality of life, and physical and mental health tests [180,181].

Prospective long-term studies evaluating the results of modern feminizing genitoplasty techniques, including the nerve-sparing techniques, are needed as current evidence is based on outdated operations that are no longer used. Many authors, together with patient support groups, ethicists and DSD activists [8,31] have recommended a moratorium on genital surgery until better empirical evidence of risks and benefits are available [47,142, 145, 146] (Table 5). For women considering clitoral reduction surgery for dissatisfaction with cosmetic appearance,

sexual dysfunction or socially distressing erections, the surgical risk of damage to clitoral sensation and future orgasmic capacity is currently estimated at 25% [147,148]. All families should be counseled regarding the controversies and treatment options, including the watchful waiting approach.

TABLE 5 Risks and benefits of (early) feminizing surgery for ambiguous genitalia (adapted from [55]).

Benefits	Risks
Prevention of psychological distress from ambiguous genital appearance	Creation of psychological distress from undergoing childhood hospitalization, surgery and genital examination; possible lack of control over or consent for surgical interventions
Gender development in accordance with assigned sex of rearing	Gender development not in accordance with sex of rearing and irreversible surgery has been performed
Relief of parental anxiety	Damage to parent-child relationship
Stability in psychosexual development	Instability in psychosexual development Damage to sexual function
Good cosmetic outcomes 'Normal' female appearance	Poor cosmetic outcomes, surgical complications (including urethra-vaginal fistulae and vaginal stenosis) Few reports in the literature regarding overall female genital appearance, or the dimensions or positioning of the vagina, clitoris, labia and urethra
Vaginal introitus for adult penetrative sexual intercourse	Stenotic or fibrosed introitus causing dyspareunia
Vaginal passage for menstrual flow	Obstruction to menstrual flow from postsurgical scarring and fibrosis

2. Treatment for the absent or short vagina

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Controversies regarding types of genital treatment and their timing remain also unresolved in conditions involving vaginal hypoplasia, commonly diagnosed late, such as Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) or Complete Androgen Insensitivity Syndrome (CAIS), in which older girls/women need to decide whether they will opt for vaginal surgery or dilation to create a vagina and when it is optimal to proceed based on psychological readiness.

Surgical vaginoplasty is historically the cornerstone of treatment for vaginal hypoplasia and has been performed as early as the first half of the nineteenth century. Different techniques, including split-thickness skin grafts (e.g., McIndoe procedure [149], local flaps [150], bowel and peritoneal vaginoplasty (e.g., Davydov procedure [151]), or the use of a traction and pressure device (e.g., Vecchietti procedure [152]) have been proposed, each addressing difficulties encountered with previous methods, and yielding new barriers to overcome [52]. Non-surgical vaginal creation with the use of graduated vaginal dilators involving intermittent pressure on the vaginal introitus has first been proposed by Frank in 1938, but has not gained popularity for a long time. However, in view of the high complication rate associated with surgical vaginal creation [153], along with a societal trend towards preference of more conservative as well as cost-effective solutions for different medical problems, the non-surgical treatment option for MRKH is since 2002 recommended by the American College of Obstetricians and Gynecologists (ACOG) as first line therapy [154]. Meanwhile, advocacy groups of patients with DSD increasingly emphasized their right for self-determination and opposed to genital surgery. The idea of self-dilation as a first choice for women with CAIS and a short vagina was adopted by DSD experts, as well as the ACOG, in 2006 [185].

It seems that about an 80% success rate can be expected from any of the techniques, and using a more selective approach to surgery, it is estimated that only around 15% of patients who use the non-surgical approach will need to proceed to a surgical one [187]. Reasons for failure, however, need further clarification (e.g. age of the patient, sturdy or flat perineum). Moreover, it is not known if failed vaginal dilation therapy jeopardizes further surgical success outcomes, especially because in a number of these procedures ongoing vaginal dilation is required. In addition, if surgery is needed, there is a lack of evidence to inform physicians regarding the optimum surgical technique to use. Most series in the literature are by a proponent of a certain technique, reviewing the outcome of their series of cases, and concentrating mainly on immediate postoperative outcome. Long-term outcomes remain unknown. In addition, some follow-up on genital procedures is limited to assessments of patency or penetration without considering the quality of the sexual experiences. Papers refer to the vagina being 'satisfactory', without saying to whom it was satisfactory or by what means satisfaction was measured. These issues of practitioner-driven selection of intervention method versus patient-driven selection, and quality of sexual experience is highly relevant to the outcomes. In general, concise long-term comparison of treatment-specific and condition-specific outcomes (e.g. MRKH vs CAIS) and protocols for vaginal dilation, as well as recommendations ensuring therapeutic compliance remain largely unexplored, contributing to the controversies around the topic. In addition, the effect of adjunctive therapies used with surgery or vaginal dilation,

such as professional psychological or peer support, on psychosexual outcomes needs to be evaluated. Finally, as with all rare conditions sample sizes tend to be small, making statistical analysis difficult and subject to erroneous interpretations, a bundling of findings is necessary to draw reasonable conclusions and to enable an evidence-based ground for individual decision-making in women seeking care for vaginal hypoplasia.

3. Masculinizing genital surgery

The sex of rearing approach by Money and coworkers was also clearly influenced by Freudian psychoanalytic ideas. Like Freud, Money assumed that the presence or absence of the penis was of prime importance in psychosexual differentiation. Gender must be fixed before entry into the Freudian phallic stage, because children are then supposed to be very preoccupied with their genitalia and would notice penis presence or absence [6]. However, unlike Freud, who did not specify the size of the phallus as the main determinant of masculine development, Money thought it best to avoid problems of having a small penis in adulthood by assigning children with concurrent or anticipated small penis to the female gender [155]. Feminizing surgery was also considered more feasible compared to masculinizing surgery, i.e. it was easier to create a penetrative conduit than a penetrating organ.

The recent concern that has been raised regarding in utero brain masculinization and its effects on gender identity development, has resulted in more male sex assignments during the last decades, particularly in patients with less severe undervirilization [15,125,156]. Also, significant changes have been made in surgical techniques for masculinizing genitoplasty. The aims of male genitoplasty are in general (1) straightening of the penis so that full painless erection enabling satisfactory penetration can be achieved (with or without prosthesis); (2) hypospadias repair and urethroplasty enabling functional micturition (including urination from the standing position); (3) reconstruction of the tissues forming the ventral surface of the glans (glanuloplasty, repair of division of the corpus spongiosum and skin); and (4) reconstruction of the scrotum and orchiopexy [157]. These procedures (and mainly hypospadias repair) are frequently completed during the first year of life, because of presumed lower complication rates and better wound healing (for an overview, see [175]). However, despite significant advances in male genitoplasty procedures, there remain several questions to be answered. Will the reconstructed genitalia function normally and will they be well-adjusted when the patients grow up? What information can we provide about the functional and psychological outcomes in adulthood? The complications of these reconstructive techniques can take decades before becoming evident. Rapid pubertal growth can alter the final functional and cosmetic aspects of the corrected genitalia (e.g. the neourethra might fail to grow adequately during puberty causing new curvature) [169]. Moreover, psychosexual development is only completed after puberty, so the psychological and sexual function of patients who have undergone genital reconstruction can only be evaluated after puberty [169].

There is in general a paucity of data on the long-term effects of different male genital reconstruction techniques during childhood due to a lack of validated measurement tools and validated questionnaires, and high loss of patients during follow-up [169]. In addition, the varying standards of treatment (e.g. improved nursing practice adapted to children's needs) make direct comparisons of results difficult. Also, it is a challenge to perform high-quality research that is powerful enough to generate broad conclusions; a recent systematic review of the literature on hypospadias treatment from the last 20 years concluded that the current management of severe hypospadias is based on weak evidence, and even the definition of severe hypospadias is not the same between centers [194]. According to the available data, it seems that patients who have undergone masculinizing genital surgery (mainly hypospadias repair) are less satisfied with their urinary function in comparison with controls, and usually experience spraying, post-void dribbling and urinary stream deviation, symptoms that are more prominent in patients with a history of severe and proximal hypospadias [169]. A higher rate of avoiding sexual relationships is noted, as well as a higher prevalence of dissatisfaction about sexual function and a negative genital appraisal, in adulthood (for an overview, see [169, 195]). From the few studies specifically including male patients with a DSD diagnosis and hypospadias repair in childhood, the most frequent complaint is short penile length in comparison with the norm [124,170,177,178]. Virilization during puberty may be sufficient in some cases with DSD, however, severe micropenis and/or penile insufficiency often persist into adulthood, despite hormonal treatment, and may constitute a psychological burden for these patients. Are penis size and masculinity on the one hand, and masculinity and sexual wellbeing on the other hand really conflated? [6] Further controlled studies with direct interviews are needed to evaluate the functional and cosmetic outcomes after masculinizing surgery. The cosmetic aspect of the operation should not be underestimated, since over 70% of adults followed after hypospadias repair reported that appearance was as important as having a functionally appropriate phallus [176]. In addition, one may argue that patients with a DSD diagnosis have differential outcomes from genital surgery than their counterparts without a specific diagnosis and that long-term effects might differ in DSD conditions with different molecular backgrounds. In reality, and especially in cases with 46,XY gonadal dysgenesis and severe undervirilization, a specific molecular diagnosis is identified in only approximately 20% of cases [33,34]. Therefore, strict clinical inclusion criteria, with accurate descriptions of the specific genital situation (e.g. degree of hypospadias), are necessary to integrate these patients in clinical outcome studies [166]. One of the pitfalls of studies in men with DSD is that there is a great range of severity in genital anomalies which has confounded previous reports. Also, the effects of hormonal treatment on adult penile length in DSD patients should be further investigated [170]. Is postpubertal penile inadequacy predictable before or during puberty? Again, the importance of considering each DSD distinct from the others might prove critical for insights that go unnoticed otherwise. Lastly, phalloplasty is a relatively novel technique that is traditionally applied in female to male transsexuals with reassuring outcome results [171,172]. It might offer perspectives for DSD patients with a male gender identity, and a small penis. However, evidence-based data on the application and outcome of this technique on the long-term are lacking and highly needed, despite satisfactory psychological and cosmetic results in younger patients with congenital or secondary penile insufficiency [173]. Optimal protocols for phalloplasty and follow-up are actually non-existent and need to be established, with specific emphasis on the specific indications for this type of surgery (e.g. what are objective criteria to define postpubertal penile

inadequacy), optimal timing (for preparation of surgery, for performing surgery), possible complications on the short-and long-term and the need for re-intervention.

1.5.1 Why further study genital treatment practices in DSD?

The heated debate between DSD activists, scholars and clinicians centers on the appropriate response to physical sexual variation [158]. Primary points of discussion between these groups are whether or not most genital interventions in DSD are necessary for physiological or psychological health, or whether these procedures are primarily cosmetic or potentially physiologically and mentally harmful and alienating [84]. Crucial to the debate on the role of genital treatment, are however data on the long-term effects. Although the goal of genital treatment is an improvement of psychosexual and social outcomes, there is little long-term follow-up of these children into adult life to confirm that an improvement in these outcomes is actually achieved. Moreover, studies on DSD patients have been hampered by a widespread policy of non-disclosure, leaving patients unaware of their diagnosis, unable to access medical or peer support and unavailable for recruitment into outcome studies [130]. In addition, genital surgery has become so universal that it is difficult to recruit those patients who have not had surgery and their opinions remain mainly absent [131]. Beyond selection/recruitment bias and small sample sizes, outcome studies and evidence-based treatment of patients with DSD are also hampered by a missing independence of care provider and researcher, possibly leading to social desirability, and a lack of control groups and standardized instruments, reducing comparability between studies which employ different methodologies [120,166]. Lastly, there are also confounds inherent in the critiques of surgical intervention specific to the field of DSD, i.e., the rapid development/improvement of surgical techniques and the unfortunate delay between the intervention and assessment of outcome/functionality. Surgical techniques have largely changed by the time we see outcome data. In essence, as a field we are presented with potential moratoria based on practices that no longer exist. We risk throwing the baby out with the bathwater [165].

1.5.2 Further contributions of this thesis

The described problems show that the rareness of disorders of sex development, the heterogeneity of the clinical symptoms and variation in both surgical and medical treatments over time, requires more national and international cooperation on the long-term to increase sample sizes and to get high-quality outcome data [166]. The Belgian and Dutch-wide outcome studies, with the establishment of DSD patient registries, were designed to overcome at least some of the described problems, and to further drive multidisciplinary research and clinical quality improvement by fostering rapid translation and integration of standardized diagnostic and treatment protocols into ongoing clinical care of patients.

Before further discussing the concrete aims that we pursue and outline of this dissertation, a few words of caution are in order, which are already briefly touched upon. Psychosexual function and wellbeing may be affected by many variables, including physical and hormonal factors and body-image perception, genital interventions, emotional health, relationship quality, the environment, and cultural beliefs. Evaluating sexuality is a complex task in the 'normal' population but can be expected to be even more difficult in patients with a DSD. Not all individuals feel able to discuss sexual matters with their doctors [10,11] (or with researchers), so an absence of complaints (in medical records) may not mean that sexual experience is positive. Also, it remains difficult to separate psychosexual issues directly related to genital treatment from the underlying difficulties associated with other aspects of a DSD condition. Although individuals with DSD and their families face some of the same challenges as other chronic medical conditions (such as the intrusion of medical authority into their lives [6]), they differ in certain condition factors, such as the social stigma attached to having a DSD condition, and/or clinical management practices and attendant experiences, including medical photography and frequent genital examinations [6]. It can be questioned that too much emphasis is given to genitals and genital 'abnormality' in the context of DSD. Surgeons and clinicians have been criticized for labeling DSD and genital ambiguity as an emergency situation. Rather, it should be considered a *social* problem as genital ambiguity mainly installs social disruption and discomfort [84]. However, the ever popular reference to the "medical emergency" continually fails, in the extant literature, to acknowledge that genital ambiguity at birth invariably signals hormonal dysfunction which must be investigated immediately to avoid potentially life-threatening complications associated with some of the disorders, such as salt-wasting congenital adrenal hyperplasia. This is the crux of the emergency [165]. On the other hand, the attention given to genitals and treatment in DSD, may become a hook on which to hang all anxieties, including those which are probably most excruciating: the need to come to terms with the potential "loss" of a healthy (perfect) child [165]. A diagnosis of DSD in a child or adolescent is increasingly being understood as a traumatic event for parents, who report levels of posttraumatic stress symptoms, that are comparable to those reported by parents of children diagnosed with other disorders such as cancer [167]. Parent distress can be amplified by shock that DSD was even a possibility and never previously having heard of it; confusion and misconceptions about the origins of DSD; and the belief that maintaining secrecy about the condition is required to ensure their child's healthy psychosexual development [168]. In sum, with the presence of (any) birth defect or chronic disorder, the risk of a disturbed psycho-emotional and social development is increased, as parental anxiety, invasion of personal privacy, pain or physical discomfort, frequent visits to hospitals, early or late physical development (e.g. lack of pubic hair, primary amenorrhea) may all lead to feelings of being 'different' from one's peers [6]. Any differences in social and sexual dimensions (including the formation of close relationships and sexual function) found for these children (and adults) with DSD, would need to be explained within a biopsychosocial framework that could take account of the transactions with the social systems of hospital, school or work, family and friends, the type of condition and bodily presentation and/or pathology (e.g., hormonal deficiencies) and treatment demands (e.g., life-long medication and its side effects, the need for gonadectomy) [6]. Ultimately, a linear model in which psychosexual outcomes are hypothesized to be directly determined by biological (i.e. hormonal, genetic) factors and/or medical/surgical interventions proves to be an oversimplification that leaves substantial variability in endpoints unaccounted for, and (more) consideration should be given

to mediating and moderating social contextual factors and their potential import for clinical management [174].

Previous extensive social scientific work on DSD, with its focus on gaining a deeper and broader understanding of people's experiences, has made notable contributions, by including different actors i.e. clinicians [29,82,159], adults with DSD [29,84] and parents [29,160] and by using different methodologies i.e. interviews [29,82,84,160] and textual analysis [161-163]. There remains, however, a call for research using more 'objective' criteria to evaluate treatment outcomes (e.g. objective genital sensation measurements or validated standardized questionnaires). It is important to be very cautious about 'objectivity', given the implicit assumptions that may inform some of the 'objective' criteria for treatment success (e.g. 'normal' pudendal nerve latencies after clitoral surgery indicating 'normal' sensation, whereas sexual function is impaired) [10,164]. The routine inclusion of patients' accounts of outcomes remains essential. Therefore, we used a mixed-methods approach, combining the questionnaire approach designed for statistical analysis and allowing methodological comparability with other studies and control groups, with personalized qualitative interviews. Semi-structured interview formats were chosen to balance a structure imposed by the researchers with the need to allow participants to speak about what was relevant to them. By giving a voice to affected persons and combining this with more 'objective, quantitative' analyses, our hope is to provide a more balanced viewpoint in conceptualizing some of issues related to past, present and future genital treatment practices for patients with a DSD.

1.5.3 Thesis outline

The empirical part of this dissertation consists of three chapters (**Chapter 2, 4, 5**) that map psychosexual experiences after different genital treatment practices in patients with DSD and one chapter (**Chapter 3**) that maps self-perceived genital anatomy and sensitivity in women without DSD and genital treatment. Each empirical chapter consists of empirical studies that may be read as stand-alone research articles. The order of the empirical chapters takes the reader along a series of steps that largely mirror the thought processes of the multidisciplinary DSD teams of Ghent University Hospital, Belgium and Erasmus Medical Centre Rotterdam, the Netherlands. Both teams have for many years investigated the clinical, psychological and molecular genetic pathophysiology of genital development in a multidisciplinary approach and started their official structural collaboration in January 2007. This collaboration continues to offer an excellent platform for patient discussions and scientific research on a wider scale, also in the context of European research initiatives (EURO DSD), with the aim of ameliorating diagnosis, follow-up and treatment of DSD patients.

Chapter 2 reflects work conducted as part of a large scale Dutch multi-center clinical evaluation study on quality of life, sexuality, gender identity, treatment satisfaction, coping, psychosocial adjustment and problems associated with diagnoses and therapies in individuals with DSD (Study centers: Erasmus Medical Centre Rotterdam, VU Medical Centre Amsterdam,

UMC St Radboud Nijmegen, UMC Utrecht and UMC Groningen; coordinators Dr. Arianne Dessens and Dr. Sten Drop). Although there are several other criteria to evaluate treatment (e.g. health related quality of life, mental health), obviously, psychosexual aspects remain important outcome parameters in the context of DSD to improve clinical care. Therefore, my co-authors and I explore first cosmetic and functional outcomes and treatment satisfaction in three different etiological groups as medical and surgical care varies for these groups, i.e., women with congenital adrenal hyperplasia who had surgery for ambiguous genitalia (vaginoplasty and/or clitoroplasty) , women with vaginal hypoplasia, who had either vaginoplasty or vaginal dilation therapy to enlarge the vagina, and men with DSD who had hypospadias repair in childhood. The main goal of this work is to generate hypotheses for evidence based guidelines which should be tested in further studies, as until now, the scientific knowledge is not sufficient to generate a-priori hypotheses. This chapter constitutes a first attempt at showing variation regarding the relevance of cosmetic versus functional outcomes for psychosexual wellbeing in women and men with DSD. Moreover, the results suggest that patient reports may be valid for an objective assessment of cosmetic outcomes, and that invasive genital examinations may not be necessary for studies of outcomes.

The work presented in **Chapter 3** is conducted at Ghent University Hospital, Belgium as part of a different collaborative project (with Dr. Hoebeke and Mr Bronselaer), further assessing the genital rating concordance between clinicians and women without DSD and a history of genital treatment. In this chapter, the importance of self-perceived genital anatomy and sensitivity for female sexuality and wellbeing is further elucidated, by means of a large-scale validation study establishing norms for techniques of genital self-assessment. The data collected should provide a much needed comparison standard for assessments in the case of atypical genitalia.

Chapter 4 and 5, of which the studies are conducted at Ghent University Hospital, Belgium (coordinators: Dr. Martine Cools, Dr. Piet Hoebeke), further elaborate on typical treatment sequences and decisions for special genital and psychological interventions. **Chapter 4** first dissects the extant literature reporting outcomes for varied methods of vaginal creation methods for women with vaginal hypoplasia. The treatment algorithm developed within the context of the analysis possibly allows for better controlled, prospective and comparative studies, and may lead to vast improvements in patient experiences and outcomes. Further interviews with these women, in the context of a long-term prospective intervention study after vaginal dilation therapy, are highly informative as they suggest that psychological support services in their current form should be re-evaluated. In **Chapter 5**, my co-authors and I investigate the importance of penile size and satisfaction with genital appearance for sexual quality of life in male DSD patients with a micropenis. Male genitoplasty in its current form, with or without hormonal treatment to increase penile length, seems not able to replicate the complexity of penile anatomy and function and conducting phalloplasty procedures might improve physical and sexual outcomes. The subsequent report characterizes sexual quality of life outcomes with state-of-the-art phalloplasty procedures in a very specific cohort of male DSD patients ,which may lead to increased numbers of surgeries and more complete transition for those who wish to do so. This chapter however again highlights that - although the move to integrate behavioral and psychological health in clinical teams specializing in sex development is significant - it remains an empirical question whether the psychologist's role in this setting

delivers substantive therapeutic contributions, beyond managing support and information flow.

Finally, we summarize and discuss the empirical findings in a concluding **Chapter 6**, in which we also propose a broader perspective and future directions for research on psychosexual and social wellbeing in DSD patients.

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Severity of Virilization Is Associated with Cosmetic Appearance and Sexual Function in Women with Congenital Adrenal Hyperplasia:

2.1 A Cross-Sectional Study

ABSTRACT

Introduction. Women with the classical form of congenital adrenal hyperplasia (CAH) are born with different degrees of virilization of the external genitalia. Feminizing surgery is often performed in childhood to change the appearance of the genitalia and to enable penile–vaginal intercourse later in life. There are suggestions that this affects sexual functioning.

Aims. The aim is to study the anatomical, surgical, cosmetic, and psychosexual outcomes in women with CAH.

Methods. Forty women with CAH, aged over 15 years, from two referral centers for management of Disorders of Sex Development in the Netherlands were included. Physical and functional status were assessed by a gynecological interview and examination. Sexual functioning was assessed with the Female Sexual Function Index and Female Sexual Distress Scale—Revised scales and compared with a reference group.

Mean Outcome Measures. Surgery performed, anatomy, cosmetic score, sexual function and distress.

Results. Thirty-six of the 40 women had undergone feminizing surgery; 25 women (69%) underwent more than one operation. Resurgery was performed in seven of the 13 (54%) women who had had a single-stage procedure. Anatomical assessment showed reasonable outcomes. Multiple linear regression showed that only level of confluence had a significant effect on cosmetic outcome, the impact depending on the number of surgeries performed. Cosmetic evaluations did not differ between the women and the gynecologists. Only 20 women had experience of intercourse. Eight women reported dyspareunia; seven women reported urinary incontinence. The women's perceived sexual functioning was less satisfactory than in the reference group, and they reported more sexual distress.

Conclusion. The level of confluence was the major determinant for cosmetic outcome; the impact depended on the number of surgeries performed. Fifty-four percent of the women required resurgery after a single-stage procedure in childhood. Anatomical assessment showed reasonable outcomes. The women evaluated their sexual functioning and functional outcome less favorable than the reference group, and they experienced less often sexual intercourse.

Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from the deficiency of one of the five enzymes required for the synthesis of

cortisol in the adrenal cortex. About 90–95% of individuals with CAH have a mutation in the CYP21A2 gene, encoding the 21-hydroxylase enzyme [1]. There are two types of CAH: the

classical and a nonclassical form or late onset CAH. Genital ambiguity at birth is present only in the classical form, which can be subdivided in simple virilizing CAH (SV-CAH) when only a defect in cortisol biosynthesis is present and salt wasting CAH (SW-CAH) when the patient also shows a concurrent defect in aldosterone biosynthesis. Patients with the nonclassical form and untreated or insufficiently treated patients with the classical form have manifestations of androgen excess such as hirsutism, menstrual dysfunction, and acne [2]. The excessive amount of androgens circulating in the fetus probably also affects brain development in a masculine direction, leading to virilization of personality and cognitive, psychosocial, and psychosexual functioning [3,4]. Female patients with moderate or severe genital virilization may undergo feminizing surgery, e.g., clitoroplasty, vaginoplasty, and labioplasty, with the aim to create female appearing external genitalia and to enable sexual intercourse. Genital surgery is controversial as loss of sensitivity resulting in diminished sexual functioning has been reported [5–12]. Unfortunately, available data are conflicting because of confounding factors. Patient satisfaction with surgery is likely to be affected by many factors, such as the policy of nondisclosure and secrecy around the diagnosis, repeated genital examinations or being exhibited as a curiosity for medical photography, or inadequate professional support. These may all lead to a poor body image, a lack of self-confidence and general (sexual) unhappiness [29]. Further controlled studies with direct interviews are needed to evaluate the functional and cosmetic outcomes after feminizing surgery.

Aims

The aim is to study the long-term anatomical, surgical, cosmetic, and psychosexual outcomes of a large cohort of women with CAH.

Methods

Study Design

Cross-sectional study.

Patients

Eighty-nine patients with CAH (>15 years of age) were invited to participate in the study between 2007 and 2009. Participating centers were Erasmus MC Rotterdam (N = 53) and Radboud University Nijmegen MC, Nijmegen (N = 36), The Netherlands. The study was approved by the Medical Ethics Committees of both centers. Participants signed a written consent. Participants were free to refuse parts of the gynecological examination or the psychological assessment.

Procedure

The study consisted of two parts. Data on genital virilization at birth and genital surgery were collected retrospectively from medical files. Patients were invited to take part in a follow-up study consisting of a standardized gynecological examination, psychosocial assessment on sexual functioning, and an interview.

Outcome Measures

Surgery and Level of Confluence

A description of the urogenital sinus (UGS) was available in the medical records [13]. Therefore, the degree of virilization was classified by the level of confluence of the vagina into the UGS at birth. Three levels were distinguished: low, i.e., the junction of the vagina and urethra is near the perineum (N = 14); high, i.e., the junction is near the neck of the bladder (N = 8); and no confluence, i.e., clitoral hypertrophy only (N = 5). From 13 patients, we had no data on level of virilization.

Gynecological Examination

The standardized gynecological examination consisted of visual inspection (size of clitoris, labia majora, and labia minora; pigmentation; and meatus urethrae externus, hair growth, labial scarring, and perineal length), speculum examination (assessment of vagina, internal hair growth, granulation tissue, epithelial atrophy, and presence of a cervix), and pelvic examination (accessibility of the vagina by number of fingers, vaginal length, and width [measured by Hegar], strictures, pelvic floor tone, and vaginal discharge). The three gynecologists who performed the gynecological examination had not been involved previously in the care of these patients.

The gynecologist and the patient herself independently rated the general appearance and the appearance of different parts of the vulva (i.e., clitoris, labia majora, and minora) on a 1–10 scale (1 = extremely poor, 10 = excellent, <6 was considered insufficient). The cosmetic outcome score per patient was calculated as the mean of the gynecologists' or patient's scores for the different parts of the genitalia.

Psychosexual Assessment

Psychosexual functioning was assessed by the Dutch versions of the Female Sexual Function Index (FSFI) [14,15] and the Female Sexual Distress Scale—Revised (FSDS-R) [15,16]. The FSFI assesses sexual functioning by six key dimensions of female sexual function in the preceding 4 weeks: desire, subjective arousal, lubrication, orgasm, global emotional/relational satisfaction, and pain. The FSDS-R assesses perceived stress with respect to sexuality. The combined results of the FSFI and FSDS-R suggest the diagnosis of one or more sexual dysfunction(s) according to the Diagnostic and Statistical Manual of Mental Disorders (version four, text revision) (DSM-IV-TR) [17]. An FSFI score <26.55 combined

with a FSDS-R score >11 implies the existence of at least one sexual dysfunction according to the DSM-IV-TR [17]. As questions in the FSFI and FSDS-R relate mainly to the 4-week period before completing the surveys, and some items can only be filled out when having a partner (i.e., satisfaction domain of the FSFI), or when having intercourse (i.e., pain domain of the FSFI), a "valid" total FSFI score could only be calculated for a minority of the women. Therefore, we did not interpret zero responses ("no sexual activity in last 4 weeks") as extreme degrees of dysfunction but excluded these women from further analyses [18,19]. Patients' psychosexual scores were compared with data of a Dutch reference group of 108 healthy women with a mean age of 27.1 years (standard deviation 9.4) [15]. These authors had made up a reference group of women who were all engaged in heterosexual partner relationships and had reported they had no sexual dysfunctions. By making use of these inclusion criteria, the reference group is probably not representative for the Dutch female population. Analysis showed that the reference group is similar to our study group with respect to age ($P = 0.43$) and educational level ($P = 0.67$). On the FSFI and FSDS-R, the reference group did not report problems in psychosexual functioning. The psychological interview inquired about the ages sexual developmental milestones had been passed, such as age at first engagement in a romantic relationship, including kissing and touching the partner without sexual intercourse, and age at sexarche (i.e., first peno-vaginal intercourse).

Statistical Analysis

Univariate and backward stepwise linear regression analyses were used to identify factors associated with cosmetic outcome. Intercorrelated variables were evaluated for

the presence of confounding and/or effect modification in stratified analyses. Effect modification was twice identified: between "level of confluence," and "number of surgeries," and between "level of confluence," and "age at first surgery." We looked for a significant contribution of the interaction effects to the predictive ability of the model by adding the interaction effects to the main effects (backward stepwise linear regression analysis).

Comparisons between groups were assessed with descriptive statistics: the chi-square test for nominal/ordinal variables, Student's t-test for normally distributed continuous variables, and the Wilcoxon signed-rank test for paired variables with skewed distributions. Comparisons of continuous variables with skewed distributions were evaluated with the Mann–Whitney U-test (two groups) or the Kruskal–Wallis test (three or more groups).

A P value <0.05 (two sided) was considered a significant difference. As patients were free to refuse parts of the gynecological examination and the psychological assessment, number of participants may vary across analyses.

TABLE 1 Age and medical characteristics of nonresponders and participants.

Characteristics	Participant	Nonresponders	P values
Mean age (range)	29 (15-46)	30 (18-54)	
Type			
SW	32	37	0.75*
SV	6	9	0.88†
LO	2	3	
LOC			
High	8	10	
Low	14	15	
No	5	12	0.51‡
Unknown	13	12	
Mean number of surgeries (range)	1.8 (0-4)	1.5 (0-5)	0.15‡

We did not find statistical differences between the two groups.
 *Student's t-test - †Chi-square test - ‡Mann–Whitney U-test
 SW = salt wasting; SV = simple virilizing; LO = late onset; LOC = level of confluence

Results

Patient Group

Forty of the 89 invited women participated (response rate: 45%). The remaining 49 women either declined participation (45%), or could not be reached personally (i.e., by phone, e-mail, or post mail). Characteristics from the nonresponders and participants are depicted in Table 1. By inspection, it seems that the groups did not significantly differ in the medical variables.

Of the 40 participants, 38 fulfilled the criteria of 21 hydroxylase deficiency (32 had SW-CAH and six had SV-CAH) and two had 11 beta-hydroxylase deficiency. The median age at participation was 29 years (range 15–46).

Most patients with SV-CAH, and those with SW-CAH, had been diagnosed within the first year of life; only three SW-CAH and two SV-CAH patients were diagnosed after the age of 1 (mean age 3.3 and 4.0, respectively). Those with late onset CAH (N = 2) were diagnosed at a mean age of 12 years and were included because they attended the clinic with virilized genitalia; they both had clitoral hypertrophy. Main features of the 40 women are presented in Table 2. Height was below -2 standard deviation score (SDS) in 12 of the women, calculated on Dutch reference data for age 21 years [20]. Family history was positive for CAH in 13 patients, and parental consanguinity was present in three patients, all of whom had SW-CAH.

Surgical Procedures

Thirty-six of the 40 patients had undergone feminizing surgery of the external genitalia. Figure 1 gives an overview of the surgical procedures performed.

In 13 of those 36 patients, surgery consisted of a single-stage clitoroplasty and vagino-

plasty. The median age at surgery was 3 years (range 0–17 years). Seven patients (7/13, 54%) needed resurgery later in life. In 20 patients (median age 2 years, range 0–19), first surgery comprised only clitoroplasty. Additional vaginoplasty was performed in 16 patients (16/20, 80%) at the median age of 13 (range 4–22 years). Several patients (see Figure 1) had more than one additional surgical procedure.

In three patients (median age 11, range 2–16 years), first surgery comprised only

vaginoplasty.

One of these women requested additional clitoroplasty at the age of 17 even though clitoromegaly was only mild.

A redo-operation was performed in 25 of the 36 patients (69%). Eleven of these patients had their first surgery before the age of 13 months, and 14 patients had their first surgery between 13 months of age and 6 years.

In almost all cases (N = 32), clitoroplasty comprised reduction of the clitoris with

TABLE 2 Main features of the participants.

	Age (years)	BMI	Height (SDS)	Partner	CAH type	THERAPY		Menarche (years)
						Glucocorticoids	Mineralcorticoids	
1	36	23.4	-1.64	No	SW	Fc 62.5-62.5 ug	Fc 62.5-62.5 ug	No
2	37	28.3	-1.02	No	SV	Dexa 0.25 mg		No
3	28	23.9	-0.86	Yes	LO	Hc 10-5-5 mg		Yes
4	37	24.8	-0.40	Yes	SW	Hc 10-0-25 mg	Fc 62.5 ug	Yes
5	32	36.3	-0.71	No	SW	Hc 10-0-5 mg	Fc 62.5-94 ug	No
6	23	25.7	2.07	Yes	SW	Hc 15-0-20 mg	Fc 125-125 ug	Yes
7	29	26.3	-1.33	Yes	SW	Hc 7.5-5-2.5 mg	Fc 62.5-62.5 ug	Yes
8	22	27.8	-2.72	No	SW	Hc 10-10 mg	Fc 62.5-62.5 ug	No
9	38	32	-2.10	Yes	SW	Dexa 0.125-0.125 mg	Fc 125-125 ug	Yes
10	36	23.3	-1.17	No	SW	Dexa 0.25-0.25 mg	Fc 62.5 ug	No
11	18	25.4	-3.03	No	SW	Dexa 0.25-0.25 mg	Fc 62.5 ug	No
12	21	27	-1.64	No	SW	Hc 15-10 mg	Fc 30-30 ug	No
13	28	22.6	1.61	No	SW	Hc 5-5-15 mg	Fc 25-25 ug	No
14	22			No	SW	Hc 10-10 mg	Fc 50-50 ug	No
15	19	24.6	0.06	Yes	LO	Hc 10-10 mg		Yes
16	24			Yes	SW	Hc 10-5-10 mg	Fc 62.5-62.5 ug	Yes
17	30			Yes	SW	Hc 15-5-5 mg	Fc 62.5-62.5 ug	Yes
18	40	29.1	-0.40	Yes	SW	Dexa 0.50 mg	Fc 62.5 ug	Yes
19	40	25.3	-1.02	Yes	SW	Hc 10-10 mg	Fc 125 ug	Yes
20	26			Yes	SW	Hc 10-15 mg	Fc 62.5-62.5 ug	Yes
21	23			Yes	SW	Dexa 0.25-0.25 mg	Fc 45-45 ug	Yes
22	19	28.2	-1.17	No	SW	Dexa 5 mg	Fc 62.5 ug	No
23	34			Yes	SV	Hc 20-0-10 mg		Yes
24	44	29.3	-1.33	Yes	SV	Dexa 0.5 mg		Yes
25	24	35.5	-2.88	Yes	SW	Dexa 0.5-0.5 mg	Fc 100-100 ug	Yes
26	16	21.8	-0.94	No	SW	Hc 8-4-8 mg	Fc 62.5-62.5 ug	No
27	19			Yes	SV	Hc 10-10 mg		Yes
28	38	19.6	-2.10	No	SW	Hc 10-10 mg	Fc 100 ug	No
29	46	26.1	-3.34	Yes	SW	Hc 5-5-5 mg	Fc 62.5 ug	Yes
30	22	22.6	-2.72	Yes	SW	Hc 20 mg, Dexa 1.5 mg	Fc 100-50 ug	Yes
31	46	29.7	-1.17	Yes	SW	Hc 25 mg	Fc 62.5 ug	Yes
32	44	22.8	-0.86	Yes	SW	Hc 15-15 mg	Fc 62.5-62.5 ug	Yes
33	35	26.7	-2.72	No	SW	Hc 7.5-5-12.5mg	Fc 125-125 ug	No
34	18	20	-2.41	No	SV	Hc 12 mg, dexa 0.2 mg		No
35	19	22.6	-0.17	No	SV	Hc 10-10-10 mg		No
36	46	37.3	-3.88	No	SW	Hc 25 mg	Fc 62.5-62.5 ug	No
37	25	26	-1.95	No	SW	Hc 15-10 mg, Dexa 0.10 mg	Fc 40 ug	No
38	32	23.6	-1.10	Yes	SW	Hc 10-10 mg	Fc 62.5-62.5 ug	Yes
39	45	28.8	-2.10	Yes	SW	Hc 15-15 mg	Fc 75-75 ug	Yes
40	20	19.7	-4.34	No	SW	Hc 6-3-3 mg	Fc 62.5-62.5 ug	No

All visited the endocrinologist on a regular basis. Only one had hirsutism (patient number 30, Ferriman Gallway Score for hirsutism was 25). In general, the women were small, with 12 women below -2 SDS in height. SW = salt wasting; SV = simple virilizing; LO = late onset; Hc = hydrocortisone; Dexa = dexamethasone; Fc = fludrocortisone; SDS = standard deviation score; BMI = body mass index; CAH = congenital adrenal hyperplasia

preservation of the neurovascular bundle and glans. Two patients had a clitorrectomy: for one patient, that was the standard procedure at that time (42 years ago), the other patient underwent clitorrectomy because of persisting painful erections. The total number of surgical procedures in the patients assigned to the high confluence group (N = 8) was significantly higher than that in the patients assigned to the low confluence group (N = 14) or that in patients with no confluence (N = 5) (P = 0.004). As expected, the total number of clitoral or vaginal surgeries was higher in the SW group than the SV group but, given the small sample size, the difference did not reach statistical significance (P = 0.381 and P = 0.092, respectively).

Gynecological Examination

The results of the anatomical assessment during gynecological examination are presented in Table 3. Assessment data were available for 17 (Hegar examination) and 29 (speculum examination) women. Characteristics between patients who refused

gynecological examination compared with who did not were not different for CAH type (i.e., SW or SV), or number of surgeries (1.8 [1–4] vs. 1.8 [0–4]), but the groups did differ in age of attendance. The patients who participated were significantly older with a mean age of 32.6 years (18–46) compared with a mean age of 23.1 years (16–34) for those who did not participate (P = 0.03).

The clitoris was scored absent in two cases (due to clitorrectomy), small in five patients, normal in 15 patients, and enlarged in six patients. Visible labial scarring was present in 15 patients; only in one woman the scars were very pronounced. One patient had a vagina shorter than 6 cm after a pull-through procedure. In four patients, digital examination was possible with one finger only; they were virgins, i.e., had never had sexual intercourse. The Hegar width of the vagina was in the normal range in almost all patients; in only one woman it was smaller than 20 mm. Thirteen women refused speculum examination. Speculum examination was physically impossible in five patients. One

(Figure 1)

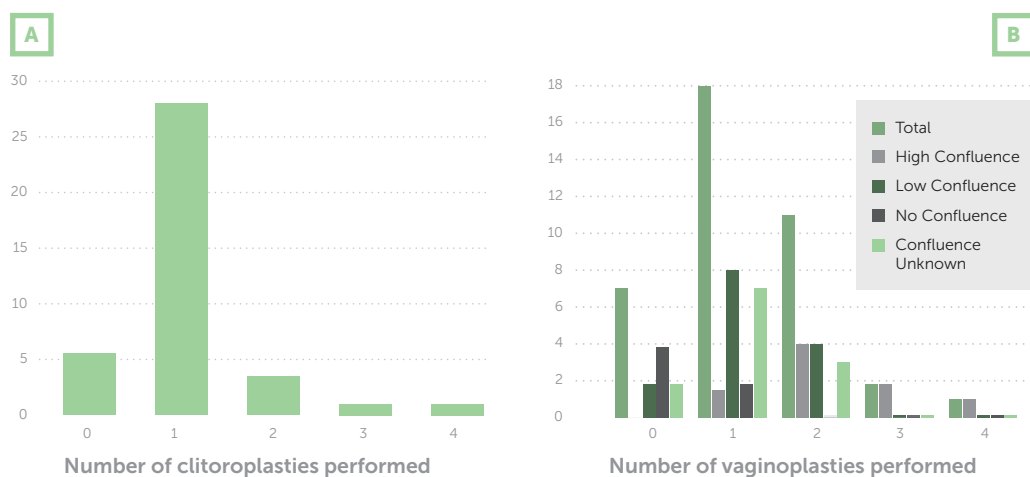


Figure 1 Numbers of clitorplasties and vaginoplasties performed in the total patient group (N = 40). (A) Number of clitorplasties performed. (B) Number of vaginoplasties performed and total number of vaginoplasties with breakdown by severity of virilization.

patient was diagnosed with vaginism, whereas another had recently undergone a vaginoplasty. Only two patients showed abnormalities (increased vaginal secretions and atrophy, respectively). Seven patients had vaginal strictures. Although variations in genital appearance were established during gynecological examination, appearance was in the normal range in the majority of women. Again, differences between the SW-CAH and SV-CAH groups did not reach statistical significance because of small sample size (see Table 3).

Cosmetic Ratings

Cosmetic results of surgical and medical treatment was evaluated in 28 patients. Both the patient and the gynecologist who did the examination of the patient scored cosmetic outcome for various parts of the external genitalia on a 10-point scale. The median total score of all parts was 7 for patients and 7 for gynecologists, which reflects overall satisfaction with cosmetic outcome ($P = 0.467$ for comparison of patients and gynecologists [$N = 27$ Wilcoxon signed-rank test]). Twenty-five percent (7/28) of the patients vs. 21% (6/28) of the gynecologists scored the cosmetic outcome as insufficient (i.e., a mean score <6).

Age at first surgery and level of confluence were significantly associated with the mean cosmetic outcome score (univariate analysis, $P = 0.021$ and $P < 0.01$, respectively [$N = 27$, Kruskal–Wallis test and one-way analysis of variance]). Stratified analyses revealed that number of operations and age at first surgery were effect modifiers of the association between level of confluence and cosmetic outcome.

Multiple regression analysis (Table 4) showed that after adjustment for the effect modifiers,

only level of confluence had a significant effect on cosmetic outcome. The adjusted impact of the level of confluence on cosmetic outcome is $1.055 - 0.987 \times$ number of surgeries. The adjusted R^2 of this model was 0.335.

Functional Assessment

Assessment of sexual function consisted of an interview with a gynecologist—as part of the gynecological checkup—and an interview and questionnaire assessment with a psychologist. The questionnaire results are shown in Table 5.

The gynecological interview was completed by 32 women. Twenty of the 32 (62.5%) women had experienced vaginal penetration (median 28.5 years, 19–46 years), and 12 (37.5%) women had not (median 33.5 years, 16–46 years). Two of the latter considered their vagina too narrow; two were embarrassed by the look of their body; two considered themselves too young (ages 16 and 19); three had sexual experiences in female homosexual relationships only, whereas three patients did not give a reason.

"I don't want to think about it [genitals]. I don't have a clue how it should look like normally, but I don't even look at it. If the doctor thinks it's ok, it is alright."

Eighty-three percent of women reported they were able to achieve orgasm. Eight women reported dyspareunia (8/33, 24%), all of whom had experienced vaginal penetration.

"I just can't have
easy sexual intercourse
with all guys.

Neither width nor length of the vagina correlated with dyspareunia (median Hegar width: 25.5 with dyspareunia vs. 26.0 without dyspareunia, $P = 0.86$; median length 10.0 cm vs. 10.0 cm, $P = 0.152$). Physical examination revealed vaginal strictures in two of the eight women who reported dyspareunia. Whereas five other patients with vaginal strictures did not report dyspareunia, two of them were virgins. Seven out of 33 women reported urinary incontinence (three stress incontinence, three urge incontinence, and one both). None of them had sought medical attention for the incontinence. They lost small amounts of urine and sometimes used panty liners for this. Two women reported incontinence that started after genital surgery.

All but three women filled in the FSFI questionnaire, and all but five women filled in the FSDS-R questionnaire. However, many questions remained unanswered. Twenty-five percent of the women (10/37) did not have sex regularly.

"Will it work? Does it
look pretty? Will he notice?
Because of your insecurity,
you just end up postponing
your sexuality.

Sexually experienced women with CAH had passed sexual milestones later than the Dutch reference sample (romantic engagement 17.7 years vs. 15.6 years, $P = 0.04$; sexarche 18.9 years vs. 18.3 years, $P = 0.36$). At the time of follow-up, half of the participant group (22/40) reported to be in a stable relationship.

TABLE 3 Anatomical assessment.

Outcome	SW (N = 32)	SV (N = 8)†	Total (N = 40)	P value*
Clitoris				0.918
Absent	2	0	2	
Small	4	1	5	
Normal	12	3	15	
Large	5	1	6	
Labia majora				#0.126
Normal	13	5	18	
Abnormal	11	0	11	
Scrotal effect	9		9	
Labia minora				0.393
Normal	9	3	12	
Abnormal	14	2	16	
Absent	5		5	
Small	5		5	
Labial scarring				0.502
Absent	10	3	15	
Present	13	2	15	
Satisfactory	6	0	6	
Neutral	6	2	8	
Not satisfactory †	0	1	1	
Vagina Length ‡				0.531
Short	1	0	1	
Normal	15	6	21	
Digital				
Examination				0.191
1 finger	4	0	4	
2 fingers	13	6	19	
Introitus (Hegar)				0.588
<15 mm	0	0	0	
15–20 mm	1	0	1	
20–25 mm	3	0	3	
25–30 mm	6	1	7	
>30 mm	4	2	6	
Speculum examination§				0.714
Physically impossible	4	1	5	
Normal	15	5	20	
Abnormal	2	0	2	
Stricture¶				0.147
Minimal	2	2	4	
Moderate	3	0	3	
Meatus urethrae externus				0.694
Normal	6	2	8	
Superficial	3	1	4	
Deep	14	2	16	

*Overall P value between SW and SV (chi-square test or # Fisher's exact test) †Includes patients with CYP11B1 deficiency, ‡Short = 0–6 cm, normal > 6 cm, §Physically impossible for the following reasons: virgin, recent operation, vaginism. Abnormal: too much floor, atrophy, ¶2–3 cm = minimal, 1–2 cm = moderate SW = salt wasting; SV = simple virilizing

A total FSFI score can be calculated for women who had sexual intercourse in the last 4 weeks; in our patient group, only 11 women had been sexually active during this period. The mean score of 29 (range 19.9–33.7) on the total FSFI did not differ significantly from the score of the Dutch reference group of 108 non-affected women with a partner. All but one had had feminizing surgery and had no confluence or low confluence of the vagina into the UGS at birth. However, when considering the separate FSFI domains, women with CAH had significantly lower functioning on the subscales of desire, arousal, lubrication but also pain compared with the reference group. No differences were found for satisfaction, or orgasm. On the FSDS-R, women with CAH indicated

In addition, no significant difference existed in perception of sexual function between SW and SV women as tested with Mann–Whitney U-tests.

TABLE 4

Multiple regression model for cosmetic appearance with mean gynecological score as dependent variable.

Multiple regression model for cosmetic appearance			
	B	Standard error	P value
Constant	4,631	1.278	0.002
Level of confluence	1.055	0.489	0.045
Number of surgeries	0.181	0.305	0.560
Age at first surgery	0.078	0.056	0.180
Level of confluence x number of surgeries	-0.987	0.539	0.084

Adjusted R²: 0.335

Only level of vaginal confluence had a significant effect on mean gynecological score. The adjusted impact of level of confluence depends on the number of surgical procedures performed.

to experience more sexual distress in comparison with the reference group (Table 5). Twenty-nine percent (10/35) had a score above the clinical cutoff of 11. When combining the (valid) FSFI and FSDS-R data, only one woman suffered from a sexual dysfunction, as defined in DSM-IV-TR. Kruskal–Wallis tests showed no significant differences between women with a high or low confluence level, or no confluence, possibly because of the small sample sizes.

TABLE 5

Mean scores (SD) on the different domains of the FSFI (range 0–6), total FSFI (range 0–36), FSDS-R (range 0–52) comparing CAH women and a non-affected reference group [18] (independent samples t-tests).

	Control	CAH	P value
Desire	4.0 (0.8) N = 108	3.5 (1.2) N = 37	0.017*
Arousal	5.3 (0.8) N = 108	4.4 (1.6) N = 31	0.004**
Lubrication	5.7 (1.0) N = 108	5.0 (1.1) N = 26	0.004**
Orgasm	5.1 (1.1) N = 108	4.6 (1.6) N = 26	0.131
Satisfaction	5.4 (0.8) N = 108	5.2 (1.0) N = 22	0.442
Pain	5.7 (0.8) N = 108	4.5 (1.7) N = 13	0.025*
Total FSFI	31.2 (3.9) N = 108	29.0 (4.2) N = 11	0.107
Total FSDS	5.1 (6.4) N = 108	8.8 (8.8) N = 35	0.02*

**P < 0.01; *P < 0.05

SD = standard deviation; FSFI = Female Sexual Function Index; FSDSR = Female Sexual Distress Scale–Revised; CAH = congenital adrenal hyperplasia

Discussion

We report on genital anatomy and ratings of cosmetic and functional outcome in women with CAH with and without feminizing surgery. We integrated gynecological and psychosexual outcomes with the aim to gain new insights in the long-term outcome of genital surgery in these women.

Level of virilization, assessed as level of confluence, proved to be the most important factor in cosmetic outcome; cosmetic appearance was judged as less favorable in case of a high vaginal confluence. In addition, patients with a high vaginal confluence underwent significantly more surgical procedures than the remainder of the women. Our regression model clearly showed that the adjusted impact of level of confluence on cosmetic outcome is modified by the number of surgical procedures. As shown in Table 4, the impact of the level of confluence on cosmetic

outcome is larger or smaller, depending on the number of surgeries performed. More than half of the patients who had single-stage surgery initially underwent additional procedures. Our results are in line with Nordenström et al. [21], who reported that surgery is more extensive in severely virilised patients, whereas other groups have reported either disappointing, or reasonably good outcomes after resurgery in puberty [6,15,16]. A practical advice is that parents should be informed on the fair chance of reoperation in adolescence.

In this study, patients and gynecologists both rated genital appearance as sufficient. In contrast, Wisniewski et al. [10] and Nordenström et al. [21] reported that patients were more negative than doctors. This might be due to a different composition of the group, or different approaches toward surgery. Female genital self-image, assessed using a four-point scale (FGSIS), was shown to be related to sexual function [22]. Although further research is needed, especially in patients born with genital anomalies like CAH, this scale might be useful in a clinical setting to create talking points that enhance patient–doctor communication and to better understand requests for additional surgery [22,23].

"I wasn't well prepared for surgery and they showed me afterwards how it looked like. I don't have to explain how shocking that was for a 12 year old."

Our findings probably underestimate the delay in experience of romantic and sexual encounters because there was a considerable

number of virgins and a considerable number of non-responders.

Comparisons using the FSFI scores were limited to women who were sexually active in the last 4 weeks, having a partner, and having penile–vaginal intercourse as described by Brotto [18]. Only one (1/11) of the women suffered from sexual dysfunction according to DSM-IV-TR criteria [17]. We suspect that the real number is considerably higher. Women with CAH achieved sexual milestones later than Dutch reference women, and a substantial part never had been engaged in a sexual relationship. Women with CAH experienced a significantly less satisfactory sexual functioning (desire, arousal, lubrication, and pain) and experienced more sexual distress compared with a Dutch reference group of healthy females. These data are in line with findings from Wisniewski et al. [10] and Gastaud et al. [7]. In our study, 24% of the CAH women reported dyspareunia (deep and superficial). In a large Dutch study, 5.4% of 2,024 healthy females reported dyspareunia, whereas 29.6% sometimes experienced pain during intercourse [24]. In females who have undergone vaginal surgery, dyspareunia might be related to vaginal stenosis [25], but in our study, only two of the eight patients who reported dyspareunia had vaginal strictures. Eighty-three percent reported they were able to achieve orgasm, although with more difficulty compared with healthy reference women.

"Why can't I get a proper orgasm just like any other woman? This is an injustice"

Other authors [6,21] have reported that the

clitoral sensitivity was affected in nearly all the women who had had surgery. These findings indicate that clitoral surgery may affect genital sensitivity. However, additional factors are likely to play a role as well, for example, degree of virilization and psychological factors. They are likely to be interrelated and little is known about their effects on outcome. For example, women with CAH reported high satisfaction levels. One possible explanation, suggested by Minto et al., is that living with CAH has contributed to low expectations of sexual functioning, that is, the women might have felt that sexual difficulties were to be expected and that they should not be dissatisfied [26]. Additionally, the paternalistic attitude of physicians and past practice of secrecy relating to Disorders of Sex Development (DSD), especially experienced by the older women in this study, might have resulted in inadequate information and lack of opportunity for discussion. Alternatively, infrequent sexual contact, associated with sexual dissatisfaction, might indicate a withdrawal from sexual intercourse and a relief from facing problems of sexual difficulties [27].

"They took almost my whole clitoris away. This should have happened differently, I wanted to have more information. I did want to keep it."

This study has drawbacks that need to be addressed. First, the study has a cross-sectional design, and part of the data have been retrieved retrospectively from medical files. Therefore, the study was limited by information available in these files. Second,

55% of the CAH women who had been under medical treatment in childhood, adolescence, and adulthood in our hospitals did not participate in the follow-up study. Most refused to participate, and in some cases, we were unable to contact them. We did not find significant differences, demographical and medical, in characteristics between responders and non-responders. However, we cannot exclude the possibility that the non-responders may have worse functioning than the participants. Women may not want to participate because participation meant a confrontation with a painful and distressing aspect of their condition, i.e., sexual functioning. Women who participated in the gynecological examination were significantly older compared with those who did not. We cannot explain this difference, but assume that women, as they become older, for medical purposes have undergone several gynecological examinations before and got familiar with this type of examination. Familiarity probably makes them feel more comfortable to participate in a gynecological examination with a research goal. Third, to measure sexual functioning, we selected the FSFI and FSFS-R. These scales are considered as first choice screening tools because they have excellent psychometric qualities, are easy to administer, and are available in many languages [15,19]. Their utility has been demonstrated in diverse conditions, for example, after vaginoplasty in females with Mayer–Rokitansky–Küster–Hauser Syndrome [28]. However, the FSFI will artificially inflate scores toward the sexual dysfunction pole in females who are not sexually active or who did not experience vaginal penetration in the 4 weeks prior to the test [18]. The results in our study revealed that only 55% of the women had a partner. The Dutch reference group only included women who had a sexual partner. In order to improve applicability of the scales in patient groups,

the scales need adaptation. Additional data in different patient and reference populations including females suffering from different types of somatic, emotional, and sexual problems should be collected.

Clinical Implications

We showed that cosmetic appearance and functional outcomes are associated with the degree of virilization at birth and that the impact of level of confluence on cosmetic outcome depends on the number of surgical procedures performed. These data might be used in the discussion whether or not to treat pregnant women at risk of carrying a child with CAH with dexamethasone. Incidence of reported dyspareunia is high in women with and without vaginal strictures, stenosis, or other visible anomalies. Parents and patients need to be informed extensively about the multiple aspects that contribute to outcome after feminizing surgery. They need to be informed that there will be a fair chance that reoperations will be necessary in adolescence. Despite their sexual problems, only a few women reported sexual problems to a gynecologist or psychologist, or had sought help from a sexologist. We would like to make a plea for assessing sexual well-being at follow-up visits and to discuss sexuality and work toward acceptance of the genital anatomy that may always remain different from the perceived norm. Ultimately, referral to a sexologist may be needed.

Conclusions

The level of confluence appeared to be the major determinant for cosmetic outcome, and the impact depends on the number of surgical procedures performed. The outcome of corrective genital surgery is positive with respect to genital appearance but less

favorable with respect to sexual functioning. Vaginoplasties carried out to improve sexual function should only be performed after consulting a multidisciplinary DSD team and after ample vaginal examination and counseling. We would advocate that surgeons inform and discuss these aspects with parents and patients so they can make a balanced decision.

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Long-Term Psychosexual and Anatomical Outcome after Vaginal Dilation or Vaginoplasty:

2.2 A Comparative Study

ABSTRACT

Introduction. In patients with disorders of sex development requiring creation of a neovagina, a number of techniques are available, including surgical vaginoplasty and self-dilation therapy. Vaginal dilation therapy has been recommended as a first-line treatment because of its less invasive character and high success rate. However, no data exist on long-term psychosexual functioning after vaginal dilation as compared with that after vaginal surgery.

Aims. The aim of this study is to compare the psychosexual and anatomical outcome of women with congenital vaginal hypoplasia followed in the same clinical setting after vaginoplasty with that after vaginal dilation.

Methods. The sexual quality of life of 35 women at least 2 years after vaginoplasty (N = 15), vaginal dilation therapy (N = 8), or coital dilation/no treatment (N = 12) was investigated and compared with the Dutch test validation population (as control).

Mean Outcome Measures. Psychosexual functioning was assessed with the Female Sexual Function Index, the Female Sexual Distress Scale-Revised, and a semi-structured interview. A gynecological examination was performed to determine the anatomical outcome after both vaginal treatment regimens.

Results. After either treatment, 26% of these women had a shortened vaginal length of less than 6.6 cm, i.e., more than two standard deviations below the published mean value (9.6 ± 1.5 cm). Irrespective of the treatment, 47% of the patients had (a) sexual dysfunction(s) and experienced sexual distress. However, after vaginoplasty, patients reported significantly more problems with lubrication ($P = 0.025$) than after self-dilation therapy.

Conclusion. Both psychological and physical factors are predisposing for sexual difficulties. To optimize psychosexual comfort, the clinical management of women with vaginal hypoplasia needs to be multidisciplinary and individually tailored. With high success rates reported, vaginal dilation should remain the cornerstone of treatment.

Key Words. Vaginal Hypoplasia; Vaginal Agenesis; Disorders of Sex Development; Vaginoplasty; Vaginal Dilation; Psychosexual Functioning; Neovagina

Introduction

Vaginal hypoplasia or vaginal aplasia is an uncommon congenital anomaly with an estimated incidence of 1:5000 to 1:10000 live female births; it involves the complete

or partial absence of the vagina, uterus, or both [1,2]. Implicated etiologies are Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, Complete Androgen Insensitivity

Syndrome (CAIS), and certain other disorders of sex development (DSD) [3]. Although healthcare providers agree on the importance of the construction of a good functional vaginal substitute that is durable, requires a minimum of post-operative maintenance manipulation, and provides long-term sexual satisfaction, there is substantial disagreement as to which technique best accomplishes these goals [4,5].

Specific surgical vaginoplasty procedures, including split-thickness skin grafts (e.g., McIndoe procedure [6]), local flaps [7], bowel and peritoneal vaginoplasty (e.g., Davydov procedure [8]), or the use of a traction and pressure device (e.g., Vecchietti procedure [9]) can be complex, and the timing of surgery remains controversial. Complications, such as scarring, vaginal stenosis, vaginal prolapse, dry vagina, or excessive vaginal discharge have been described [10]. Therefore, the American College of Obstetricians and Gynecologists recommends a nonsurgical treatment option as first-line therapy—with the use of graduated vaginal dilators involving intermittent pressure on the vaginal introitus (Frank or Ingram method [11,12])—due to the absence of surgical risk and preservation of vaginal tissue [13]. However, while both approaches yield high anatomical success rates [14,15]—defined as an adequate vaginal depth between 5 and 10 cm [2,16]—functional results remain unclear. Functional outcomes refer to sexual functioning, but studies are difficult to compare due to the heterogeneity of reports. Some state these outcomes as satisfactory, adequate, or unsatisfactory [17], whereas others make use of standardized sexual function tools [15,16,18–20] and a more detailed assessment of psychosexual well-being [21], including the effects of this lifelong condition on fertility and bodily integrity [22,23].

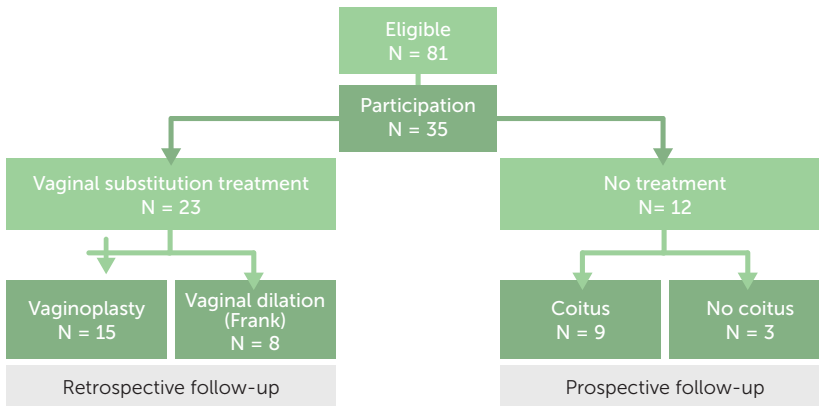
Aims

While most studies evaluate a specific treatment (either surgical or nonsurgical) to create a neovagina, the primary aim of this retrospective study is to compare in a standardized manner the psychosexual functioning—and the relationship with psychological adjustment—of these women seen in the same clinical setting after vaginoplasty with that after vaginal dilation. This approach may lead to evidence-based practice guidelines and further clinical implications for the management of women with vaginal hypoplasia or vaginal aplasia to optimize their psychosexual and psychosocial comfort.

Methods

Participants and Procedure

The study was conducted as a long-term follow-up audit of DSD patients referred for management of vaginal agenesis to the University Hospital Ghent, Belgium; Erasmus Medical Center Rotterdam, the Netherlands; or Radboud University Nijmegen Medical Center, the Netherlands. Randomization to the two vaginal substitution treatments was not conducted when these patients initially received care, because operative vaginoplasty was in these institutions the standard procedure in the past. Exclusion criteria were: age <18 years and >60 years, recent diagnosis (<6 months), gonadal dysgenesis (because of the heterogeneous clinical picture), and intellectual disability. After exclusion, 57 eligible participants were contacted in Rotterdam and Nijmegen, 24 participants in Ghent, inviting them to attend a clinic visit with a gynecologist and psychologist, who were not previously involved in the care of these women.

Figure 1**Figure 1** Study design.

Twenty-four patients in Rotterdam and Nijmegen (42%) and 11 patients in Ghent participated (46%) between February 2007 and January 2010. A flowchart of the study design can be found in Figure 1. All patients gave written informed consent, and the study was approved by the Medical Ethics Committee of the different institutions. Each research participant was asked to complete standardized questionnaires assessing psychosexual functioning and was invited for a gynecological check-up.

Assessment of Psychosexual Functioning

A sexual dysfunction, according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth edition, text revision) (DSM-IV-TR), is diagnosed by increased sexual distress and decreased sexual function. Sexual distress was assessed by the Female Sexual Distress Scale-Revised (FSDS-R) [24], validated for the Dutch-speaking population [25]. Sexual function was assessed by the Female Sexual Function Index (FSFI) questionnaire [26] (Dutch translation with excellent psychometric properties) [25]. This short 19-item questionnaire assesses adult female sexual quality of life in the

4-week period before completing the survey [27,28], and its score is unbiased regarding age, education, and economic status. The items are assigned to six separate domains of female sexual function: desire, arousal, orgasm, sexual pain, vaginal lubrication, and global sexual and relationship satisfaction. All items in the FSFI have a five-point basic response scale (1–5) denoting variations in frequency, intensity or degree of satisfaction. In addition, some items carry a zero-category coding for “no sexual activity” or “did not attempt intercourse” in the last 4-week period. Instead of interpreting zero answers as extreme degrees of dysfunction [29], women were also asked how they were sexually functioning on the six domains beyond the 4-week period (adjusted FSFI). In case women had not had a sexual partner, the domain score for satisfaction was solely based on item 16. However, the original FSFI scores were used when comparing women with vaginal agenesis to the test validation population and clinical cutoff scores [30]. Additionally, a semi-structured interview delivered in-depth information about psychosexual and psychosocial adjustment.

Gynecological Evaluation

The gynecological evaluation consisted of a (i) medical–somatic anamnesis and

(ii) a gynecological exam including visual inspection (clitoral size, labia majora, labia minora, pigmentation, meatus urethrae externus, hair growth, labial scarring, and perineum length), speculum examination (assessment vagina, internal hair growth, granulated tissue, atrophy, and cervix), and pelvic examination (accessibility by number of fingers, vaginal length and width [Hegar], strictures, pelvic floor tone, and vaginal discharge). Vaginal length, defined as the distance from the posterior fourchette to the most proximal part of the blind-ending vagina, was compared with normal reference values previously established [29]. Both patients and gynecologists scored the cosmetic appearance of the external genitalia (vagina, clitoris labia majora, and labia minora) on a rating scale (going from 1 = extremely poor to 10 = excellent). In addition, an adapted version of the body image scale [31] was used to assess patient satisfaction with the external genitalia and total body image (based on 31 sex-specific and nonsex-specific body characteristics) (scale 1 = very satisfied to 5 = very dissatisfied). Medical notes were reviewed to confirm the diagnosis and treatment procedures.

Statistical Analysis

Differences between proportions were tested by chi-square tests or Fisher exact tests, as appropriate. The Mann–Whitney U-test was used to compare sexual functioning in women after vaginoplasty with that after vaginal dilation. Student's t-tests were used to compare women with vaginal agenesis with the test validation population (as control). Spearman correlations were used to assess associations; the Wilcoxon signed-rank test for intergroup comparisons. $P < 0.05$ was considered statistically significant. Two-tailed statistical tests were chosen to reduce the risk of type I errors. Sensitivity and specificity

were further analyzed through the receiver operating characteristic (ROC) curve. Analysis was carried out by the statistical software package SPSS 19.0 (SPSS Inc., Chicago, IL, USA), and the authors received help from a statistical expert.

TABLE 1 Treatment details and diagnoses.

		DIAGNOSIS		
		Disorder of androgen action or synthesis*	MRKH	Total
None	No coitus	3	0	3
	Coitus	9	0	9
Dilators	Frank method	8	0	8
Surgery	Intestinal [†]	2	0	2
	Skin grafts	4	7	11
	Vecchietti	2	0	2
Total		28	7	35

*Nineteen women had a diagnosis of Complete Androgen Insensitivity Syndrome (CAIS). Other diagnoses comprised 17 β 3 hydroxysteroid dehydrogenase deficiency in four, Leydig cell hypoplasia in three, and 5 α reductase deficiency and 17,20 lyase deficiency each in one woman. [†]In one woman the Vecchietti failed and she then had an intestinal vaginoplasty. MRKH = Mayer–Rokitansky–Küster–Hauser

Results

The median age of the 35 participants was 26 years (18–48 years); 21 participants (60%) were in a stable relationship. The various treatment regimens are summarized in Table 1. Operative vaginoplasty was, in our institutions, the standard procedure in the past. The choice of surgical procedure relied greatly on the surgeon's preference and experience. In the last decade, clinical practice has changed, and women are offered a choice between dilation therapy and surgery, with a suggestion to start with dilation first. Six out of 15 (40%) of the vaginoplasty patients had tried dilation therapy before having surgery but failed to reach sufficient vaginal length. Fourteen out of 15 women who had undergone vaginoplasty followed a postoperative dilation program (mean 3.7 months, range 1–12 months) to

maintain their vaginal patency. Psychosexual counseling has only become a vast part of any of the treatment regimens in the last decade. Mean duration of follow-up for the 23 medically treated patients was 6 years (0.5–23 years). Twelve patients received no treatment, because health providers and/or more likely patients themselves judged this was not necessary (yet). Nine of them were sexually active at the time of examination. It is likely that these women increased their vaginal length by regular coitus alone. Because this can be seen as a natural dilation method and because of the small numbers, these women were considered as part of the dilation group in the next analyses. The other three women who had no treatment were the youngest ($M = 18.7$ years, standard deviation [SD] = 0.6) and did not yet engage in coitus. Because this group is too limited, they were not considered as a separate group but were only included in analyses when the total group of women with vaginal agenesis was considered, irrespective of treatment. The individual diagnoses of the participants are summarized in Table 1. Except for

MRKH, all diagnoses were confirmed by gene mutation analyses. All 28 women with a disorder of androgen action or synthesis received bilateral gonadectomy. Twenty out of 28 women were on regular hormone replacement therapy (HRT), one woman refused this, and seven women were not compliant with this treatment.

Anatomical Outcome

Only 27 out of 35 women participated in the gynecological check-up (Table 2). Four out of eight women did not participate because they lacked the time to do so. Four other women refused because of repeated and shameful examination of the genitalia, including medical photography, experienced in the past. Only two women with MRKH participated.

Vaginal Length

Overall mean (\pm SD) vaginal length was 8.5 cm (± 2.5), which was significantly shorter than

TABLE 2 Anatomical outcome grouped according to type of intervention for the vagina.

	None—no coitus	None—dilation by coitus	Dilators	Surgery	St data
N	3	9	8	15	50
Median age (yrs)	19 (18–19)	28 (20–48)	24 (18–36)	29 (20–42)	
Follow-up (yrs)	NA	NA	5 (0.5–17)	6 (2–23)	
Vag length (cm)	7.3 (3.7) (N = 3)	8.9 (2.6) (N = 9)	7.3 (1.3) (N = 6)	9.1 (2.7) (N = 9)	9.6 (N = 50)
Complications	None	None	None	Moderate strictures (1–2 cm): N = 2; internal hair growth and vaginal prolapse: N = 1	
Cosmesis					
Patient	7.0 (0.9)	7.3 (1.2)	7.7 (1.0)	7.0 (2.1)	
Gynecologist	8.5 (1.3)	8.1 (0.5)	8.4 (1.1)	6.9 (1.7)	
Satisfaction					
Genitals	3.3 (0.3)	2.7 (0.7)	2.5 (0.4)	2.8 (0.7)	
Body	2.7 (0.1)	2.3 (0.5)	2.4 (0.3)	2.5 (0.6)	

Data shown as mean (standard deviation), the standardization data for vaginal length were based on [32].

Variables: follow-up since last treatment, complications at follow-up, cosmetic appearance of the genitalia according to the patient and gynecologist (scale 1–10), patient satisfaction with genital and total body image (scale 1–5) Used abbreviations: St data = standardization data; vag = vaginal; yrs = years; NA = not appropriate

the published mean value (9.6 ± 1.5 cm) ($P = 0.027$). The mean vaginal length of women (9.1 ± 2.7 cm) who had surgery did not differ from the reference value and was on average greater than in women who had no treatment (8.5 ± 2.8 cm) or followed a medical vaginal dilation program (7.3 ± 1.3 cm), although no significant differences were found (Table 2). Coital dilation led to a mean vaginal length of 8.9 cm (± 2.6), compared with 7.3 cm (± 1.3) when dilators were used (not significant [ns], $P = 0.21$). Seven out of 27 (26%) of the women had a shortened vaginal length of less than 6.6 cm, i.e., more than two standard deviations below the mean, irrespective of treatment [32] (22% after vaginoplasty, 20% after vaginal dilation). Two out of the three women, who had no treatment, had a short vagina. Women with a short vaginal length, in both treatment groups alike, had a higher incidence of sexual dysfunction compared with those with a normal vaginal length (75% vs. 14%, respectively); however, because of the small numbers, this did not reach statistical significance ($P = 0.088$). No significant association was found between vaginal length and having had intercourse in the last 4 weeks (8.2 cm vs. 8.7 cm, $P = 0.723$). Significant correlations were found between vaginal length and arousal ($R = 0.471$, $P = 0.015$) and between vaginal length and orgasm ($R = 0.409$, $P = 0.047$). Because the vaginal length of only two women with MRKH could be measured ($M = 8$ cm), no meaningful comparison with the 25 women with a disorder in androgen action or synthesis could be made ($M = 8.5$ cm). Specific data for the 19 women with CAIS are provided in Table 4. Overall mean (range) vaginal length was 7.8 cm (4.5–12 cm), which was significantly shorter than the published mean value (9.6 ± 1.5 cm) ($P = 0.004$). Five out of 17 had a shortened vaginal length of less than 6.6 cm, irrespective of treatment. The four women, who underwent surgery, had

on average a larger vaginal length (8.8 ± 2.9 cm) than the 12 women who dilated coitally (8.1 ± 2.2 cm) or with dilators (7.3 ± 1.4 cm), although not significant.

Complications at Follow-Up

At gynecological examination, three out of nine women (30%) in the vaginoplasty group displayed complications. No resurgery was required at the time of follow-up. However, six out of 15 women had had multiple operations in the past because of vaginal insufficiency or complications (strictures, excessive mucus production). Median time between the first and second surgery was 1.5 years (2 months–10 years). No meaningful comparison of the complication rate after different types of surgery could be made because of the small numbers.

Cosmetic Outcome, Genital, and Body Image Satisfaction

The patient and gynecologist scored different parts of the external genitalia (vagina, clitoris, labia majora, and labia minora) on a 10-point scale (Table 2). Gynecologists, in contrast with patients themselves, scored the genital appearance of women who had surgery significantly lower than women who dilated (regular coitus and Frank dilation combined) ($M = 6.86$ vs. 8.2, $P = 0.01$).

Participants were also asked to rate satisfaction with their genital and total body image on a 1–5 scale, with higher scores indicating more dissatisfaction. Women who had surgery reported more dissatisfaction with their genital and total body image than women who dilated (regular coitus and Frank dilation combined) ($M = 2.78$ vs. 2.6, $P = 0.642$ for genitals; $M = 2.47$ vs. 2.31, $P = 0.650$ for total body), but no statistical difference was reached. A positive association was

found between genital and total body image satisfaction ($R_s = 0.409$, $P = 0.015$).

Psychosexual Outcome

Five women out of 35 (14%) had not been sexually active within 4 weeks before completing the surveys; two of them had undergone vaginal surgery and three did not have treatment. Sexual activity could include caressing, foreplay, masturbation, and/or vaginal intercourse. A further 13 women (37%) specifically had no penile-vaginal intercourse (four women did not have treatment, four women had undergone vaginal surgery, and five women had used dilators). Reasons for having no intercourse were varied: two women reported this was physically impossible, three women were still virgin, and one woman was involved in a homosexual relationship; in seven women, no specific reasons were given.

No difference in prevalence of sexual

difficulties was found between women who also participated in the gynecological examination and those who only filled out psychological questionnaires ($P = 0.596$, ns).

"There was no sex at all, not even masturbation after the operation. Everything related to your vagina was dirty, no fun."

FSFI

As a group, and irrespective of treatment, participants fall below the cutoff score of 26.55 on the total FSFI score when compared with the Dutch test validation population, which implies they are significantly at risk for sexual difficulties [25] (Table 3). Sixty-five percent (11/17) of the participants had a total FSFI score below the cutoff score. Lower

TABLE 3 Psychosexual outcome grouped according to type of intervention for the vagina.

	St data* (N = 108)	Total patient data (N = 35)	No coitus (N = 3)
FSFI total	31.2 (3.9)	21.3 (9.6)† N = 17	6.2 (NA) N = 1
Adjusted total FSFI		24.2 (5.0) N = 22	24.8 (NA) N = 1
Desire	4.0 (0.8)	3.5 (1.0)† N = 35	3.4 (0.4) N = 3
Adjusted desire		3.6 (1.0) N = 32	3.6 (0.0) N = 2
Arousal	5.3 (0.8)	3.4 (1.8)† N = 34	3.0 (2.8) N = 3
Adjusted arousal		4.5 (1.1) N = 31	4.5 (1.3) N = 2
Lubrication	5.7 (1.0)	3.7 (2.0)† N = 33	2.2 (2.8) N = 3
Adjusted lubrication		4.2 (1.6) N = 31	3.3 (3.0) N = 2
Orgasm	5.1 (1.1)	3.9 (1.8)† N = 32	2.8 (4.0) N = 2
Adjusted orgasm		4.4 (1.3) N = 29	5.6 (NA) N = 1
Satisfaction	5.4 (0.8)	4.5 (1.5)† N = 23	3.2 (NA) N = 1
Adjusted satisfaction		4.5 (1.1) N = 32	3.6 (1.7) N = 2
Pain	5.7 (0.8)	2.9 (2.6)† N = 27	0.0 (0.0) N = 3
Adjusted pain		3.6 (2.4) N = 24	0.0 (0.0) N = 2
FSDS-R distress	5.1 (6.4)	12.2 (10.3)† N = 33	7.7 (1.2) N = 3

Data shown as mean (standard deviation, adjusted scores go beyond a 4-week period). *Standardization data for FSFI and FSDS-R were used from [23] †Different from the standardization data, $P < 0.01$, ‡Different from the dilators group, $P < 0.05$, §Different from the surgery group, $P < 0.05$

scores were evident in all of the subscales equally: desire, arousal, lubrication, orgasm, satisfaction, and pain. On the basis of a clinical cutoff score of 26.55 or less, we determined that 100% of cases in the study sample (N = 6/6) were correctly classified as not sexually dysfunctional and 72.7% (N = 8/11) were correctly classified as sexually dysfunctional. The area under the ROC curve—as a combined measure of sensitivity and specificity—was 0.864, 95% confidence interval [0.686, 1]; which indicated the ability of the FSFI instrument to correctly demonstrate the presence or absence of sexual problems in this study sample. Women who had undergone treatment (surgery or vaginal dilators) did not have better FSFI indicators of sexual function than those who were untreated (regular coitus). When the adjusted FSFI was used, significantly more problems with lubrication were reported after vaginoplasty than after vaginal dilation/coitus (P = 0.025) (Table 3, right panel). Within the vaginal dilation group,

no significant differences were observed between the women who followed the Frank dilation program and women who had regular coitus, except for desire (Table 3). Women who had a lower FSFI score were significantly more dissatisfied with their genital appearance (R = -0.553, P = 0.021). No differences were found between MRKH patients and patients with a disorder of androgen action or synthesis on both the original FSFI and adjusted FSFI. Within the CAIS group, all but two women were sexually active. A further five women did not have sexual intercourse. In five out of nine women in whom the total FSFI score could be calculated, a score below the clinical cutoff of 26.55 was found, indicating that they are at risk for developing a sexual dysfunction (Table 4).

FSDS-R

Both treatment groups had a mean score above the cutoff value of 11 on the FSDS-R

		Dilation by coitus (N = 9)	Dilators (N = 8)
21.9 (9.5)† N = 8	22.7 (9.3)† N = 8	19.2 (4.9) N = 2	23.8 (10.5) N = 6
23.9 (5.7) N = 11	24.6 (4.8) N = 10	27.6 (4.8) N = 5	21.6 (2.5) N = 5
3.8 (1.2)† N = 15	3.3 (0.9)† N = 17	2.8 (0.8)† N = 8	3.8 (0.6) N = 9
3.9 (1.2) N = 14	3.3 (0.9) N = 16	3.8 (0.6) N = 8	2.8 (0.8) N = 8
3.9 (1.9)† N = 14	4.3 (1.5)† N = 17	4.3 (1.0) N = 8	4.3 (2.0) N = 9
4.3 (1.3) N = 13	4.6 (1.0) N = 16	4.8 (1.2) N = 8	4.3 (1.1) N = 8
3.0 (2.2)† N = 14	4.5 (1.6)† N = 17	4.7 (1.4) N = 8	4.3 (1.8) N = 9
3.5 (1.8) N = 13	4.8 (1.1)§ N = 16	4.8 (0.9) N = 8	4.8 (1.3) N = 8
3.6 (1.7)† N = 14	4.3 (1.7)† N = 16	4.3 (1.6) N = 8	4.3 (2.0) N = 8
4.0 (1.3) N = 13	4.6 (1.4) N = 15	4.9 (1.0) N = 7	4.3 (1.6) N = 8
4.6 (1.4)† N = 10	4.5 (1.7)† N = 12	4.4 (1.8) N = 4	4.5 (1.7) N = 8
4.5 (1.2) N = 14	4.6 (1.0) N = 16	4.9 (1.0) N = 8	4.4 (1.0) N = 8
3.3 (2.7)† N = 3	3.2 (2.4)† N = 11	2.1 (2.5) N = 5	4.2 (2.2) N = 6
4.1 (2.2) N = 12	3.7 (2.3) N = 10	5.0 (0.7) N = 5	2.4 (2.5) N = 5
13.9 (12.1)† N = 14	11.5 (9.5)† N = 16	9.4 (8.4) N = 7	13.1 (10.5) N = 9

and experienced significantly more sexual distress than the control group (Table 3). No significant difference was found between the vaginoplasty and dilation group (57% vs. 50%, $P = 0.667$). Within the CAIS group, 10/18

TABLE 4

Functional and anatomical outcome within the CAIS and MRKH group.

	CAIS	MRKH
Desire	3.3 (0.9) (N = 19)	3.9 (0.8) (N = 7)
Arousal	3.7 (1.8) (N = 19)	4.5 (1.2) (N = 6)
Lubrication	3.7 (2.1) (N = 19)	3.1 (2.1) (N = 7)
Orgasm	3.8 (1.9) (N = 17)	3.6 (1.4) (N = 7)
Satisfaction	4.1 (1.8) (N = 11)	4.8 (1.3) (N = 6)
Pain	2.3 (2.5) (N = 15)	4.9 (1.6) (N = 7)
Total FSFI	20.7 (10.6) (N = 9)	25.0 (8.3) (N = 5)
FSDS-R	12.8 (9.6) (N = 18)	11.7 (11.9) (N = 6)
Vaginal length	7.8 (2.2) (N = 17)	8.0 (2.8) (N = 2)

Data shown as mean (standard deviation) Used abbreviations: Female Sexual Function Index (six domains of the FSFI, range 0–6) and total FSFI (combined scores of the six domain, 2–36); FSDS-R = Female Sexual Distress Scale-Revised (0–52)

women had a score above 11 on the FSDS-R, which indicates that they experience sexual distress (Table 4).

A significant but not clinically relevant association was found between sexual distress and satisfaction with genital appearance ($R = 0.389$, $P = 0.025$) but not with total body image satisfaction ($R = 0.165$, $P = 0.360$).

"My vagina
is definitely not
my best friend"

Combined Score

A score below 26.55 on the FSFI together with a score above 11 on the FSDS-R implies a sexual dysfunction according to the DSM-IV-TR [30]. In general, 47% of the women (8/17 of whom the total original FSFI and

FSDS-R score could be determined) had a sexual dysfunction vs. 6.5% of the Dutch test validation population ($P < 0.001$). There was no statistically significant difference between the different treatment groups (43% [3/7] after vaginoplasty, 50% [4/8] after vaginal dilation/ coitus, $P = 0.595$).

Psychosexual Counseling

Forty-two percent (13/31) of the women with vaginal hypoplasia received psychosexual counseling before or during either treatment. Only half of the women who attended counseling (7/13) thought this was useful. Some were already psychologically well adjusted and needed little in the way of counseling. Others had specific issues that they felt needed to be explored more such as feelings about infertility and other diagnosis related obstacles. Interestingly, 83% of the women within the dilation group were satisfied with the usefulness of the psychological care they received, compared with only 20% of the women within the vaginoplasty group ($P = 0.048$).

"How can she know...
it's impossible that she
understands what I am
going through."

The influence of specific patient characteristics on the obtained results was further explored. Women involved in a current relationship experienced less dyspareunia than women who had no partner (4.0 vs. 1.5, $P = 0.014$). Women above the median age of 26 years had more problems with lubrication (2.8 vs. 4.4, $P = 0.027$). No associations were found between HRT use

and sexual counseling on the one hand, and the prevalence of sexual problems on the other hand.

Discussion

Our study findings show that vaginal hypoplasia or vaginal aplasia, despite treatment, is associated with compromised sexual wellness (difficult lubrication and dyspareunia), as was found in previous studies [14,15,18,33–36]. Eighty-six percent of our sample was sexually active, but only 49% had vaginal intercourse. Although a problematic sexual functioning was reported in both treatment groups, women who had undergone vaginal surgery had more complications at follow-up and experienced on average more sexual problems, specifically with respect to self-reported lubrication. This difference was not influenced by the underlying diagnosis, nor by compliance with estrogen therapy. Age was however positively correlated with lubrication problems, and women who had had vaginal surgery were older than the Frank dilation group (presumably reflecting a change in clinical practice).

"I have sort of a vagina now, but it is not a real vagina. Every time when we have sex I think 'this is all so artificial!'"

Other suggested interfering factors are the type of vaginoplasty procedure and the lack of cervical mucus [27]. Lubrication during intercourse is thought to be the

result of several processes including transudation of plasma through the vaginal epithelium, secretions from the uterus, and the vestibular and Bartholin's glands [1]. Although the vaginal lining may be normal in the neovagina created by dilators and the Vecchiatti and Davydov techniques—in contrast to other surgical procedures—it is not known whether the blood supply of the neovagina and its capacity to produce the transudate is adequate. The lack of vestibular and Bartholin's glands, which are a source of lubricating secretions during arousal, may also be relevant. Whether or not these glands are present in women with vaginal hypoplasia should be the topic of future studies [1].

"I really thought that this operation would solve all my problems. But that was only the beginning... my psychological status only got worse."

Vaginal dilation has been put forward as a first-choice treatment, because it is a patient-driven technique that is easy to perform, cost-effective, safe, and can be highly successful [2,5,13,37]. Sixty-seven percent of the Frank dilation patients in this study acquired a normal-sized vagina within 3–12 months. It also obviates the need for postsurgery dilation therapy, which was required in 93% of women who underwent surgery. Moreover, six out of 15 women (40%) in the vaginoplasty group needed resurgery, showing that these procedures carry significant long-term complications, including increased mucus production, vaginal prolapse, and strictures. The women who had had vaginal surgery acknowledged that it was not the "quick fix" (and also less emotionally involved)

procedure that it initially appeared to be.

However, success of dilation therapy as a first-line treatment depends on a large time investment and motivation of the patient. Forty percent of the vaginoplasty patients had tried dilation therapy first but without success. The reported problems can be summarized as persistent discomfort and pain or lack of privacy; the regimen was regarded as shameful and “distasteful” [38], or reinforced a feeling of being different. The profound emotional impact of this diagnosis inevitably evokes feelings of depression, anger, and loss of self-esteem. A poor organization of the therapy with little psychological input at that time may also reflect the lack of enthusiasm for the dilation technique; moreover, most of these patients were young (range 14–17 years). Roberts et al. [39] found that patients younger than 18 years at the start of dilation treatment had a statistically significant dilation failure rate. Our study confirms previous reports that the compliance and patient satisfaction are generally low in vaginal dilation programs [40]. Every unsuccessful attempt will decrease the motivation of the young patient and lead to emotional instability, which highlights that adequate sexual and psychological support is an integral part of the management [10].

The description of long-term outcome taking into account different pathogenesis of vaginal hypoplasia is difficult because of several DSD enclosed. However, we provided specific data for 19 women with CAIS, allowing to further examine the effects of androgen deficiency on sexual function. Androgens are thought to influence sexual function in females by their affects on sexual motivation and desire [40]. When compared with the MRKH and the Dutch control group, desire and arousal scores in the CAIS group were lower, but 79% and 84% of the CAIS

sample yielded scores within normal limits for desire and arousal, respectively. Vaginal hypoplasia and various psychological factors undoubtedly also impact sexual functioning in women with CAIS [40].

We recognize several weaknesses of this study. First, there was a potential selection bias, because participants in this study were recruited exclusively from a clinical sample. Further studies should also recruit from other samples such as peer-support groups. Additionally, data on nonresponders should be gathered. Fewer than half of the eligible women approached actually participated in the study, indicating that physical aspects of female sexuality are still a very sensitive subject. Second, due to the rarity of the condition, the actual number of patients did not lend itself to robust regression analyses. Because the sample of patients who followed a vaginal dilation program was rather small to draw definite conclusions, we included patients who created a sufficient vagina by coitus alone in this group. Although coitus can be considered as a form of dilation (with

"There was a time when for me the purpose of sex was just to keep the vagina open, to keep it dilated. That feels very double. It's like a pornstar saying 'Sex is my job, but I don't enjoy it!'"

the penis as only dilator size) this might have influenced the results. Meanwhile, it has been demonstrated that the dimensions of the neovaginal increase at coitus is comparable in magnitude with the normal vagina. In young women with an understanding and

cooperative sexual partner, the possibility of coital dilation should be taken into consideration as one of the available therapeutic procedures. Additionally, those women who had undergone treatments for vaginal hypoplasia had similar sexual function scores to women who had not undergone any treatment. It is likely that those offered treatment for vaginal hypoplasia were a group with more severe vaginal hypoplasia, so no definite conclusions can be made on the impact of vaginal hypoplasia treatment on the incidence of sexual difficulty. These results do suggest, however, that any treatment for vaginal hypoplasia may be of limited usefulness without concomitant psychological expertise to address other aspects of self-perception.

"Women have scars from giving birth. In contrast, I have scars because I cannot. Every time you see yourself naked in the mirror, you notice that scar, reminding you of the operation and your syndrome. Every day again, despite the fact you are used to it."

Third, because randomization to the two treatments was not conducted, we measured several important confounders, such as age, HRT, genital appearance, satisfaction with total body image, and psychosexual counseling, which could influence sexual functioning. However, the long-term assessment of vaginal reconstruction methods remains difficult, and complications may be troublesome many years after the primary procedure. Patient satisfaction will

be influenced as well by the procedure as the clinical (e.g., hormonal treatments) and psychosocial implications (e.g., infertility) of the underlying condition. Lastly, this was a retrospective study with a cross-sectional design, which does not permit interpretation of causal relationships. No information was available on vaginal length or psychosexual functioning and expectations of the participants before treatment. Prospective, longitudinal studies with a focus on diagnosis-related success rates (e.g., CAIS cases with distal third vaginal remnant vs. cases with vaginal aplasia or MRKH) should be undertaken. Comparison with normative data from other gynecological conditions may also be worthwhile.

Conclusion

The findings in this study have implications for clinical management as they suggest that long-term psychosexual outcome after vaginal dilation is at least equivalent to that of vaginoplasty. It appears reasonable to consider self-dilation as the first therapeutic procedure. However, if it wants to reach a high success rate, gradual self-dilation has to be supported by an expert multidisciplinary team that integrates endocrinology, gynecology, sexology, and clinical psychology expertise. Failed dilation therapy for neovaginal creation does not preclude subsequent surgical reconstruction. Equal priority should be given to quality of life outcomes, including psychosexual treatments, as is currently given to the traditional clinical concerns such as anatomical outcome [40]. Psychological counseling as both a primary and adjuvant treatment has a clear role in discussing any aspects of this lifelong condition. Further studies must clarify the multiple obstacles for women in different age groups and life stages

and emphasize objective outcomes in a prospective way using validated questionnaires for patients and partners, in addition to clinical examinations and patient interviews.

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2.3 Long-Term Outcomes in Males with Disorders of Sex Development

ABSTRACT

Introduction. Indications that the prenatal action of testosterone in the brain is an important determinant of gender development and improved reconstructive techniques have caused a shift in male gender assignments in patients with 46,XY disorders of sex development. We report long-term outcome data on psychosexual development and sexual function of these individuals in a cross-sectional study.

Materials and Methods. Physical status of 14 men with a mean age of 25 years with disorders of sex development was assessed by a structured interview and physical examination. Psychosexual outcome was evaluated by questionnaires and compared to a control group of 46 healthy, age matched men.

Results. A total of 13 men underwent 1 to 6 (mean 2) genital surgeries. Mean age at first surgery was 2.7 years. Mean penile length was 6.6 cm. All men reported erections and were able to experience orgasms. Ejaculatory dysfunction was reported by 7 men. Mean penile length was 7.9 cm in patients who were able to achieve penetrative intercourse and 4.9 cm in those who were not. Meatus was glanular in 5 patients, coronal in 7 and at the distal shaft in 1. Compared to controls, men with disorders of sex development were less satisfied with the appearance of the penis and scrotum but not with the total body image. These patients reported decreased sexual desire and activities.

Conclusion. Outcome in this group of men with disorders of sex development was poor regarding penile length, ejaculation, satisfaction with external genitalia and frequency of sexual activity. Other aspects, such as overall body image and psychosexual functioning, showed no difference from controls.

Key Words. body image; disorders of sex development; follow-up studies; sex reassignment surgery; urologic surgical procedures, male

Introduction

Disorders of sex development (DSD) are defined as congenital conditions involving atypical development of chromosomal, gonadal or anatomical sex [1]. The underlying chromosomal constitution of infants with markedly ambiguous genitalia may

be 46,XY, 46,XX or a mosaic pattern. Of patients with DSD of sex development and 46,XY hypovirilization syndromes a specific diagnosis can be made in only 20% [2]. Improved reconstructive techniques and observations of gender dysphoria and a wish for a gender role change in patients with 46,XY hypovirilization raised as girls resulted

in more male sex assignments in the last decades, particularly in patients with less severe hypovirilization [1,3-7]. The aim of masculinizing surgery in patients with DSD is to improve cosmesis and function of the external genitalia, to enable sexual intercourse and to avoid stigmatization. Therefore, it is important to assess the functional and sexual outcomes of these patients. There have been a limited number of outcomes studies in males with DSD, including those with an undefined 46,XY condition [5,8-12]. However, studies with combined data on urological and in-depth psychological examination in relation to surgical history are scarce. We investigated the long-term physical, functional and psychosexual outcomes in males with DSD in a cross-sectional study.

Methods

A total of 37 males with DSD older than 14 years identified at 2 university hospitals between 2007 and 2009, were invited to participate. Of these individuals, 14 (37%) participated, including 9 from Erasmus MC Rotterdam and 5 from Radboud University Nijmegen Medical Center. Inclusion was based on diagnosis of DSD and phenotype (i.e. proximal hypospadias and unilateral/bilateral cryptorchidism). The study was approved by the medical ethics committees of both centers. All participants were informed about the study and signed a written consent form. Participant responses to the Male Sexual Health Questionnaire (MSHQ) were compared with those of a control group of 46 male students with a median age of 21.5 years (range 18 to 36) who volunteered to participate in the study.

Data on genital appearance at birth and genital surgeries were retrospectively collected from the medical files. Subsequently, par-

ticipants underwent a urological examination, hormonal analysis and psychological assessment between 2007 and 2009. LH, FSH and serum testosterone levels were determined as described previously [13].

Surgeries were divided in hypospadias repair and additional procedures. Patients were grouped based on diagnosis. Cases without a molecular diagnosis were classified as undefined 46,XY DSD.

Standardized urological examination consisted of visual inspection (general impression, testes, localization and shape of meatus, penile curvature, distortion, penoscrotal transposition) and measurements (testis volume, penile circumference, stretched penile length, self-measured degree of curvature). The examiners had not been involved in the medical care of these patients.

Psychosexual functioning and satisfaction with genital image were assessed by questionnaires and a semistructured interview administered by psychologists not involved in the care of the patients. The MSHQ is a validated, self-administered instrument for assessing problems in the primary domains of erection, ejaculation and sexual satisfaction in men [14]. Aspects of sexual functioning and problems, as well as satisfaction with (surgical) treatment and impact of treatment on psychosexual functioning were addressed in the interview. Satisfaction with body appearance and appearance of the external genitalia was assessed using a 5-point Likert scale [15].

Comparisons between groups were done using the chi-square test for categorical variables and Student t-test for continuous variables. MSHQ scores were compared using a Mann-Whitney U test (not normally distributed). A p value of less than 0.05 was considered significant.

Results

Participants

Of the 37 men invited to participate, 14 agreed (response rate 37%). Mean age was 25 years (range 14 to 32). There were no significant differences between participants and nonresponders regarding age ($p=0.81$), diagnosis ($p=0.5$) or number of hypospadias repairs ($p=0.97$).

Characteristics of the participants are presented in the Appendix. One patient with 45,X/46,XY DSD who presented with bilateral cryptorchidism without hypospadias at age 8 months was excluded from the functional and psychosexual analyses. The others had been diagnosed at birth with hypospadias and cryptorchidism. Family history was positive in 3 patients and consanguinity in 2. Based on Dutch reference data for age 21 years, height was below -2 SD in 5 men and borderline (1.98 SD) in 1 man [16].

Of the 6 men with undefined 46,XY DSD, 1 had a positive family history of proximal hypospadias. This patient was diagnosed with morbid obesity (body mass index 44 kg/m²), hypergonadotropic hypogonadism and small testes. Semen analysis revealed azoospermia. Medical history consisted of unilateral testicular torsion, utricular cyst and epididymitis. Hormonal analysis, including human chorionic gonadotropin, adrenocorticotropic hormone and gonadotropin-releasing hormone tests, was normal. Genetic analysis of the androgen receptor was negative.

One man with undefined 46,XY DSD was suspected of having a 5 α -reductase deficiency. Sequencing of the SRD5A2 gene did not demonstrate any abnormalities, but enzyme function was impaired in fibroblasts in vitro. In the remaining 4 patients with undefined 46,XY DSD, testosterone synthesis

disorders were excluded, and sequencing of the androgen receptor gene did not show any abnormalities.

Surgeries and Urological Examinations

A total of 13 men underwent hypospadias correction involving a mean of 2 surgeries (range 1 to 6). Mean age at first surgery was 2.7 years (range 3 months to 6 years). The undefined 46,XY DSD group differed from the other diagnostic groups with respect to a larger variation in age at first surgery. No other differences between groups were found. The groups were too small to assign statistical significance. One man with undefined 46,XY DSD had undergone 6 surgical procedures for hypospadias repair. One patient in the mixed gonadal dysgenesis (GD) group did not have hypospadias. Repeat surgery was needed in another patient with mixed GD at age 17. The other surgeries consisted of hypospadias repair in 2 planned sessions.

Additional procedures are listed in [Table 1](#). Both patients with partial androgen insensitivity syndrome (PAIS) had undergone gynecomastia correction, of whom 1 needed correction of recurrence after 1.5 years. Gonadectomy was performed in 4 patients. In the ovotesticular DSD group, all patients had a histologically confirmed ovotestis. One of these patients had undergone gonadectomy on the right and orchiopexy on the left side plus biopsy. In 2 patients a streak gonad was found, both of whom had a mosaic chromosomal constitution. Histological review of the gonadal tissue did not reveal signs of malignancy. The results of the urological examination are listed in the supplementary table. Mean penile length was 6.6 cm (range 4.2 to 10.5), which was below -2.5 SD. Four men had a curvature of more than 10 to 60 degrees during erection. The meatus was glanular in 5 patients, coronal in 7 and on the distal shaft in 1.

Functional Assessment

All men reported erections and were able to experience an orgasm. Abnormal ejaculation was present in 7 men, of whom 3 were on androgen replacement. Two patients experienced dry ejaculations most of the time and 1 had dry ejaculations half of the time. Two men complained about the small amount of ejaculate (a couple of droplets), and 2 experienced weak ejaculation. The 8 men who reported achieving penetrative intercourse had a mean penile length of 7.9 cm, which was significantly greater than in the 4 not achieving penetrative intercourse (4.9 cm, $p=0.028$).

Serum LH, FSH and testosterone measurements demonstrated hypergonadotropic hypogonadism in the 3 patients with mixed GD (LH 18.7, 22.3 and 27.3 IU/L, FSH 46.6, 66.0 and 54.4 IU/L and testosterone 7.0, 4.2 and 2.7 nmol/L, respectively). All of these patients were on testosterone replacement therapy (Sustanon® 250 or testosterone undecanoate) after gonadectomy and thus had signs of under treatment. The remaining patient (with ovotesticular DSD)

who was on testosterone replacement after gonadectomy, had slightly increased FSH values (11.1 IU/L) but normal LH (1.15 IU/L) and testosterone values (19.5 nmol/L). The two patients with PAIS had high levels of LH (19.8 and 12.4 IU/L) and testosterone (63.7 and 28.7 nmol/L). The 6 men with undefined DSD had normal male values (2 patients) or increased FSH values and normal LH and testosterone levels (4). There was no relationship between libido and testosterone values ($p=0.892$).

Men with sufficient urine volume (greater than 100 cc) during flow measurement (8 patients) showed a mean maximum flow rate of 20.6 ml per second. One patient had a plateau curve and the others had a normal curve.

Men with DSD were significantly less satisfied with the appearance ($p<0.001$), color ($p<0.001$), thickness ($p=0.03$) and size (flaccid $p<0.001$ and erect $p<0.001$) of the penis, as well as the scrotum ($p<0.001$) and size of the testes ($p<0.001$) compared to the control group. Participants were dissatisfied regarding penile size (small), scrotum (asym-

TABLE 1 Surgical procedures.

	PAIS	Mixed GD	Ovotesticular DSD	Undefined 46,XY DSD	All Pts
Mean yrs age at first hypospadias repair (range)	3.3 (1.5–5.0)	3 (2.5–3.5)	3.2 (2.0–5.0)	2.3 (0.3–6)	2.7 (0.3–6.0)
Mean No. hypospadias repairs (range)	1 (1–1)	1.3 (0–2)	2 (1–3)	2.5 (1–6)	1.9 (0–6)
No. additional procedures:					
Inguinal herniorrhaphy	2	1	2	2	7
Orchiopexy	2	1	2	2	7
Penoscrotal transpositioning	2	0	0	0	2
Gynecomastia correction	3	0	0	0	3
Gonadectomy	0	2	2	0	4
Fistula repair	1	0	0	2	3
Utricle excision	0	0	1	1	2
Totals	10	4	7	7	28

Used abbreviations: PAIS= Partial Androgen Insensitivity Syndrome; Mixed GD= Mixed Gonadal Dysgenesis; DSD= Disorders of Sex Development; Pts= Patients; yrs= years

metry) and testes (too small). Satisfaction with the amount or appearance of pubic hair did not differ between participants and controls. There was also no difference in satisfaction with secondary sex characteristics (voice, body hair, facial hair, breasts, hips and Adam's apple, $p=0.489$) and nonsexual characteristic body parts ($p=0.267$) or total body image between participants and controls ($p=0.098$). Six of the 10 men who answered the question, perceived that their sexual development was negatively influenced by their genital appearance. Only 3 men felt they were sexually hampered, especially regarding penile size.

Psychological Assessment

Detailed psychosexual functioning was assessed in 11 participants. One adolescent (14 years) had no sexual experience, and 1 man (19 years) refused to complete the MSHQ. Mean age at first coitus was 18 years (range 15 to 23).

Frequency of sexual activity differed significantly between patients and controls. Of the controls 76% had been involved in sexual activities more than 6 times in the month preceding the study, compared to 18% of the patients ($p<0.001$, Table 2). One man (18 years) never had sex due to the absence of sexual desire and arousal, difficulties with erection and orgasm, and lack of a partner. Another man tried to avoid sex as much as possible but gave no further explanation. These statements suggest that both men might be asexual. Others reported difficulties with erection and orgasm (1 patient), low arousal (1 patient) and having no partner (1 patient). The distress related to the frequency of sexual activity did not differ significantly between patients and controls. The same held true for the proportion of men involved in a steady relationship and satisfaction

with sexual relationship. Ten out of 11 men had a heterosexual orientation and 1 had a homosexual orientation. No subject reported gender dysphoria. Men with DSD reported on average more difficulties than men without DSD, although the difference did not reach significance, except regarding frequency of desire to have sex and problems with firmness of the erection (Table 2).

TABLE 2 Male Sexual Health Questionnaire results.

	Controls	Pts with DSD	p-value
Sexual frequency/mo:			
No. 0 (%)	0 (0)	3 (27)	
No. 1–6 (%)	11 (24)	6 (55)	
No. > 6-almost daily (%)	35 (76)	2 (18)	
Mean \pm SD frequency	4.0 \pm 1.0	2.6 \pm 1.4	0.002*
Mean \pm SD distress	1.6 \pm 0.9	1.8 \pm 1.3	0.900
Partner:			
No. with partner (%)	21 (46)	5 (45)	0.805
Mean \pm SD satisfaction†	4.4 \pm 1.0	4.4 \pm 0.8	0.610
Mean \pm SD desire:			
Frequency	3.9 \pm 0.6	3.3 \pm 0.9	0.016*
Level	3.8 \pm 0.7	3.4 \pm 0.9	0.121
Distress	2.0 \pm 0.8	1.9 \pm 1.0	0.534
Mean \pm SD erection:			
Frequency	4.7 \pm 0.6	4.2 \pm 1.2	0.155
Frequency of maintaining erection	4.6 \pm 0.6	4.2 \pm 1.3	0.465
Firmness of erection	4.7 \pm 0.6	3.8 \pm 1.2	0.006*
Distress	1.4 \pm 1.1	1.3 \pm 0.6	0.988
Mean \pm SD ejaculation:			
Frequency	4.8 \pm 0.5	3.7 \pm 1.8	0.052
Frequency dry orgasm	1.2 \pm 0.6	1.5 \pm 1.2	0.342
Frequency delayed ejaculation	1.5 \pm 0.7	1.2 \pm 0.9	0.222
Force	4.7 \pm 0.6	3.8 \pm 2.1	0.395
Vol	4.8 \pm 0.5	4.2 \pm 2.2	0.583
Pain	1.2 \pm 0.5	1.4 \pm 1.6	0.394
Distress	1.2 \pm 0.6	1.3 \pm 0.6	0.786

* $p<0.05$ (2-tailed Mann-Whitney U test). † Based on 5 items (overall sexual relationship, quality of sex life, frequency of sexual activity with partner, communication about sex with partner and affection during sex).

Discussion

This study evaluates the long-term outcome in males with DSD. We found that mean penile length of postpubertal patients with DSD was below -2 SD and that penile

length is correlated to the ability to achieve penetrative intercourse. Moreover, abnormal ejaculations are common. The incidence of male gender assignment is increasing due to the awareness of prenatal testosterone effect on gender development, improved surgical techniques and change in attitudes toward tolerance of genital anomalies [1,5,6,12]. Generally, males with DSD need extensive genital surgery. The severity of hypospadias is correlated with adult penile length [17]. In our study, all but 1 patient had a history of hypospadias repair. The patient without hypospadias repair presented with an undescended testis and slight scrotal asymmetry, which triggered chromosomal analysis that revealed 45,X/46,XY mosaic DSD.

Mean penile length was below -2.5 SD. Mean adult penile length is 13.3 cm (SD 1.6) [18]. Reilly and Woodhouse reported the absence of a relationship between sexual functioning and penile length and the ability of men with a microphallus to achieve satisfactory sexual intercourse [19]. In our study the men who were able to achieve penetrative intercourse had a significantly greater mean penile length than those who were unable to do so. Phalloplasty might be an option for men who fail to achieve penetrative intercourse and are dissatisfied with this. However, there is little experience with the procedure, and long-term results are lacking [20].

Men with DSD were less satisfied than controls with penile appearance, color, size and girth. This finding is in line with other studies demonstrating that small penile size is a major cause of dissatisfaction [9,21]. Sircili et al found that penile length is not significantly related to satisfaction with surgical results [11]. Patients in our study were significantly more dissatisfied with their genital image compared to controls, and

those with a shorter penile length were the most dissatisfied. Interestingly, satisfaction with secondary sex characteristics and more neutral body parts did not differ significantly. This finding suggests that genital image and acceptance need special attention during psychosexual counseling of boys with DSD.

Our study confirms that males with DSD in general experience erections and orgasms. However, half of our study population reported abnormal ejaculation, as described previously [22,23]. Schönbucher et al reported an increased incidence of sexual dysfunction and an overall low sexual quality of life in males with 46,XY DSD [24]. In our study, equivalent numbers of men with DSD and controls were involved in a steady relationship, and satisfaction with the partner and the sexual relationship did not differ between these groups. Men with DSD tended to be less sexually active and reported more erectile problems. However, no significant differences were found in terms of distress or dissatisfaction. The frequency of desire was significantly decreased in men with DSD, but not the intensity. Finally, sexual orientation was heterosexual in all but 1 patient, which is in line with previous studies [9,24].

Our study has some limitations that need to be addressed. First, the study had a cross-sectional design, and some of the data were retrospectively retrieved from medical files. In addition, 61% of the men with DSD declined participation for unknown reasons. Therefore, our data might not be representative of the total group. Furthermore, sexual functioning was measured with the MSHQ, which inquires about sexual problems in the prior 4 weeks only and was designed to assess sexual problems in males. Regrettably, there are no validated questionnaires focusing on sexual impairment due to DSD. Lastly, the power of statistical analyses was

limited due to the small sample size and, therefore, associations might not have reached significant differences.

In conclusion, the outcome in this group of men with DSD was poor regarding penile length, ejaculation, satisfaction with external genitalia and frequency of sexual activity. Other aspects such as overall body image and psychosexual functioning showed no difference from controls.

APPENDIX

Patient Characteristics.

Karyotype	Diagnosis	Mutation Found	Family History
1 46 XY	PAIS	AR ⁺	Positive
2 46 XY	PAIS	AR ⁺	Positive
3 45X/46XY	mixed GD (streak)	no	Negative
4 45X/46XY	mixed GD (streak)	no	Negative
5 45X/46XY	mixed GD (streak)	no	Negative
6 46 XX	ovotesticular DSD	SR ^Y sequences	Negative
7 46 XX	ovotesticular DSD	no	Negative
8 46 XX/46 XY	ovotesticular DSD	no	Negative
9 46 XY	Undefined 46 XY DSD	no	Negative
10 46 XY	Undefined 46 XY DSD	no	Positive
11 46 XY	Undefined 46 XY DSD	no	Negative
12 46 XY	Undefined 46 XY DSD	no	Negative
13 46 XY	Undefined 46 XY DSD	no	Negative
14 46 XY	Undefined 46 XY DSD	no	Negative

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SUPPLEMENTARY TABLE

Physical examination results.

	Height (SDS)	BMI	Hair growth	position testis	Volume testis (ml) left/right	circumference penis (cm)
1	-1.55	23	feminine	inguinal	10/15	-
2	0.05	23	absent	scrotal	15/20	6
3	-3.39	27	male	scrotal	8/20	-
4	-3.67	20	feminine	scrotal	0/8	8.5
5	-1.98	27	male	scrotal prostheses	10	-
6	-2.97	25	male	absent	0/<1	-
7	-2.12	18	male	scrotal prostheses	10	9.2
8	-	-	feminine	scrotal	12/8	-
9	-2.40	20	male	scrotal	10/0	-
10	-0.28	44	male	scrotal	8	9
11	-0.99	28	male	scrotal	10	8
12	-1.20	27	male	high scrotal	8/25	9.5
13	0.01	24	male	scrotal	10	12.5
14	0.15	21	feminine	scrotal	30/35	10

Stretched penile length (cm)	Curvature penis	Distortion penis	Meatus	Shape meatus	Penoscrotal transposition
4.2	non	non	coronary	irregular	no
5	non	non	coronary	irregular	no
5.4	45° ventral	non	coronary	irregular	yes
7	30° lateral	30° left	coronary	irregular	no
10.5	non	non	top glans	vertical slit-shaped	no
7	non	non	distal shaft	vertical slit-shaped	no
9.7	10° dorsal	non	top glans	vertical slit-shaped	no
-	-	-	-	-	-
8	10° ventral	non	low glandular	irregular	no
5	non	10° left	midglandular	irregular	yes
6	non	non	midglandular	vertical slit-shaped	no
5	20° dorsal	non	coronary	horizontal	no
6	60° ventral	non	low glandular	irregular	no
7.5	non	40° right	top glans	vertical slit-shaped	no



CHAPTER 3

Self-perceived genital anatomy and sensitivity in women without DSD and genital surgery

I was worried about vaginas. I was worried about what we think about vaginas, and even more worried that we don't think about them... There's so much darkness and secrecy surrounding them—like the Bermuda Triangle. Nobody ever reports back from there.

Eve Ensler – The Vagina Monologues

Based on:

Bronselaer, G*, Callens, N*, De Sutter, P., De Cuypere, G., T'Sjoen, G., Cools, M., Hoebeke, P. Self-Assessment of Genital Anatomy and Sexual Function in women (SAGAS-F): Validation within a Belgian, Dutch-Speaking Population, J Sex Med, 2013, in press.

*Joint first authorship

Self-Assessment of Genital Anatomy and Sexual Function within a Belgian, Dutch-Speaking Female Population:

3.1 A Validation Study

ABSTRACT

Introduction. Data on self-perceived genital anatomy and sensitivity should be part of the long-term follow-up of genitoplasty procedures. However, no normative data, based on a large sample, exist to date.

Aims. Validation of the Self-Assessment of Genital Anatomy and Sexual Function, Female version (SAGAS-F) questionnaire within a Belgian, Dutch-speaking female population.

Methods. Seven hundred forty-nine women with no history of genital surgery (aged 18–69 years, median 25 years) completed an Internet-based survey of whom 21 women underwent a gynecological examination as to correlate self-reported genital sensitivity assessed in an experimental setting.

Mean Outcome Measures. The SAGAS-F enables women to rate the sexual pleasure, discomfort, intensity of orgasm, and effort required for achieving orgasm in specified areas around the clitoris and within the vagina, as well as genital appearance. The latter was similarly evaluated by an experienced gynecologist, and women were asked to functionally rate the anatomical areas pointed out with a vaginal swab.

Results. Sexual pleasure and orgasm were strongest, and effort to attain orgasm and discomfort was lowest when stimulating the clitoris and sides of the clitoris ($P < .05$). Vaginal sensitivity increased with increasing vaginal depth, but overall orgasmic sensitivity was lower as compared with the clitoris. Functional scores on the SAGAS-F and during gynecological examination corresponded highly on most anatomical areas ($P < .05$). Gynecologist's ratings corresponded highly with the women's ratings for vaginal size (90%) but not for clitoral size (48%).

Conclusion. Replication of the original pilot study results support the validity of the questionnaire. The SAGAS-F discriminates reasonably well between various genital areas in terms of erotic sensitivity. The clitoris itself appeared to be the most sensitive, consistent with maximum nerve density in this area. Surgery to the clitoris could disrupt neurological pathways and compromise erotic sensation and pleasure.

Key Words. Self-Assessment; Genital Anatomy; Genital Sensitivity; Sexual Function

Introduction

There is a consensus between multidisciplinary teams treating disorders of sex development (DSD) that surgical genitoplasty procedures in

females should be minimized and performed if possible according to the patients' needs and with the patients' consent, mainly in puberty and adulthood. Additionally, previous studies have shown that up to 80% required

further procedures to permit sexual function [1,2]. The long-term outcome of (childhood) genital surgery on sexual function in adulthood has been recently investigated extensively, with both positive and negative psychosocial and psychosexual outcomes [3–11]. However, only few reports considered systematic assessment of genital sensitivity and sexual function, whereas the latter, and particularly the experience of orgasm, appears to be closely related to sensitivity [12–14]. Genital surgery risks disruption of nerves and blood vessels, which may impair sensation to the genital area and affect future capacity for sexual pleasure [15,16]. On the other hand, it was argued that subjects may have normal objective-evoked responses or thermal/vibratory genital sensation in a laboratory setting, yet have little or no perceived sensation to sexual stimulation or capacity for orgasm in a real-life situation [17]. Moreover, although the provider (surgeon) may be pleased with the clinical outcome (such as cosmesis, structural and anatomical integrity, or coital capacity of the vagina), equal priority should be given to erotic sensitivity and orgasmic capacity, as judged by the patient. Discrepancies between physiological and subjective erotic responses are well documented in women [18]. Therefore, assessment of self-reported genital sensation and comparison between patients with and without a history of genital surgery is highly needed, but no normative data, based on a large sample, exist to date.

Aims

Tools are needed to systematically assess the effects of surgical genital modification on sexual sensitivity and orgasmic capacity, as reported by the patient, and to assess sensitivity of the human genitalia for relevant sexual stimulation in contrast to vibratory and

hot/cold sensory input. The Self-Assessment of Genital Anatomy and Sexual Function, Female version (SAGAS-F) was originally designed to obtain a woman's perception of what her genitals look like and to map her experience of cutaneous sensitivity, sexual pleasure, discomfort/pain, and orgasm across specific areas of her genital region [19]. The primary objective of the present study is to validate this questionnaire in a sample of Belgian, Dutch-speaking women and specifically to investigate whether a large population of women without genital surgeries can discriminate between various genital areas in terms of erotic function.

Methods

Participants and Procedure

Respondents were recruited by means of leaflets that were randomly distributed at railway stations in Flanders to ensure participation of native Dutch speakers between January 2010 and May 2012. The leaflet explained that Ghent University was conducting a study on women's sexuality and provided a URL for more information about the study. Each woman was invited to fill out an Internet-based questionnaire and was instructed in a cover sheet that by completing the questionnaire, she gave informed consent. Participants' privacy and confidentiality were protected by the use of a secured, anonymous database. We ensured that each response represented a unique individual participant.

To be included in this study, the women needed to be older than 18 years of age and sexually active in the last year. Quality control was assured by repetitive questions. Women with gross inconsistencies on these check questions were excluded from analysis. For

the gynecological examination, women were recruited through the same information leaflet between December 2012 and April 2013 but were also asked to leave contact information. Two weeks after filling out the questionnaires, these women were invited to the University Hospital Ghent for the gynecological examination. Ethics approval was granted by the joint university and hospital ethics committee (EC2009/629).

Measures

Biographic Questionnaire

Relevant medical and demographic data were obtained. Additionally, the gender of their sexual partner(s) was assessed in a closed format ("my sexual partner[s] is [are] male, female, or both male and female").

Assessment of Genital Anatomy and Sensitivity

The original version of the SAGAS-F [12] was

translated into Dutch by two independent persons. Consensus between the translators was sought in case of inconsistency. The final version was back translated by a native English speaker and did not lead to substantial loss of information. In the original SAGAS-F, the participants are asked to select one of several options of appearance, size and position of clitoris, vagina, and labia minora and majora. In addition, they rated on five-point Likert scales the sexual pleasure, discomfort/ pain, orgasmic intensity, and effort for achieving orgasm for several graphically and verbally demarcated areas at and around the external genitalia, vagina, and anus (e.g., "sexual touch/stimulation of the area above the clitoris [area A] by a partner or yourself has produced sexual pleasure": 1, none; 2, mild; 3, moderate; 4, strong; 5, very strong) (Figure 1).

Gynecological Examination

Women were placed in the lithotomy position. An experienced female gyne-

Figure 1

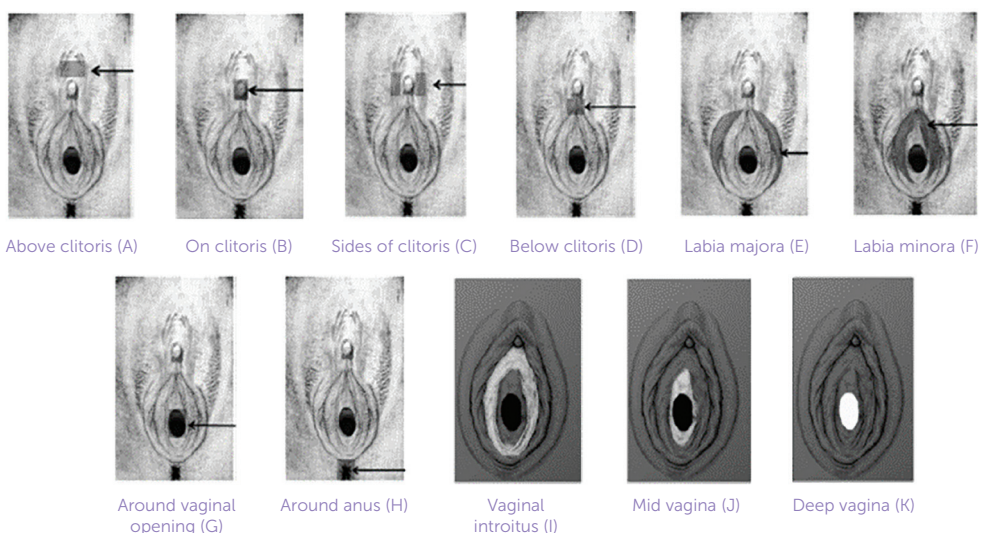


Figure 1. External genital areas (A–H) and vaginal areas (I–K)

cologist (P.D.S.) rated one of the same options of genital appearance and size as the women had rated before in the SAGAS-F questionnaire. A moistened cotton swab was used to designate the different anatomical areas for which women rated on five-point Likert scales the sexual pleasure, discomfort/pain, orgasmic intensity, and effort for achieving orgasm when imagined being stimulated by themselves or a partner. The time lapse between filling in the SAGAS-F and gynecological examination was 2 weeks.

Statistics

As Kolmogorov–Smirnov tests and normal probability plots indicated that the data approximated a normal distribution, anatomical locations were compared for ratings of sexual pleasure, discomfort/pain, orgasmic intensity, and effort for achieving orgasm using a repeated measures ANOVA. These were followed by all possible pairwise group comparisons by paired t-tests using Bonferroni corrections for multiple comparisons. Nonparametric Wilcoxon paired t-tests were used to compare the functional ratings on the SAGAS-F and the gynecological exam. Multiple regression analysis was used to identify factors associated with the genital sensitivity outcomes. We looked for a significant contribution of the interaction effects on the predictive ability of the model by adding the interaction effects to the main effects. Differences between proportions were tested by chi-squared tests or Fisher exact tests, as appropriate. $P < .05$ was considered statistically significant. Two-tailed statistical tests were chosen to reduce the risk of type I errors. Analysis was carried out by the statistical software package spss 20.0 (SPSS Inc., Chicago, IL, USA), and the authors received help from a statistical expert.

Results

Over a 10-month period, 728 women completed all applicable items. The median time needed to fill in the SAGAS-F was 18 minutes (range 5–652 minutes). Women were offered the possibility to fill in the questionnaire in different sessions. The participants consisted of women without a history of genital surgery and with a variable educational background. All women were sexually active (clitoral and/or vaginal sexual stimulation by self or a partner in the last 12 months). Detailed demographic data are provided in Table 1. As expected, there was a significant association between age and

TABLE 1 Demographics.

	Total group (n = 728)	Gynecological exam (n = 21)
Median age (years)	25 (18–69)	22 (20–55)
Partner (% yes)	54.8	67
Education (%)		
No education or primary school level	0.7	0.0
Lower secondary	3.2	0.0
Higher secondary school	32.8	42.9
Higher education short type	19.2	4.8
Higher education long type—university	44.1	52.4
Has a child (% yes)	35.2	14.3
Median number of children	2 (1–7)	2 (1–2)
Racial background (%)		
Caucasian	98.8	95.2
African	0.3	4.8
Asian	0.1	0.0
Arabic	0.1	0.0
Other (not specified)	0.7	0.0
Gender of actual sex partner(s) (%)		
Male	84.2	71.4
Female	2.3	9.5
Both	0.7	0.0
Neither	12.8	19.1

parity status, with 71% of the women above the median age of 25 years having children, compared with 1.3% of the women below the median age of 25 years (χ^2 (1, 728) =

390.47, $P < .001$). Women who took part in the gynecological examination had a median age of 22 years (20–55 years) and were a representative sample of the total group of participants in terms of the other demographic details (Table 1).













Genital Anatomy

Women's Responses

Women were asked to select the response option that best described their genital anatomy (for more details, see [19]). Table 2 gives an overview of the perceived size ratings of the clitoris, labia (majora and minora), and

vagina. For clitoral size, the majority chose moderate sized and raised (45.2%), and small and raised (43.4%). Regarding labial size, 68% of the sample chose average sized. For vaginal opening size options, up to 90% indicated that their vagina was adequate and deep enough for penetration. Significantly more women above the median of 25 years reported their vaginas to be very large as compared with women below the median age ($\chi^2(2, 728) = 26.44, 11 \text{ vs. } 2\%, P < .001$), as well as women who gave birth compared with nulliparous women ($\chi^2(2, 728) = 49.98, 14\% \text{ vs. } 2\%, P < .001$).

TABLE 2 Genital size ratings of the clitoris, vagina, and labia.

Clitoris		(%)	Vaginal size		(%)
Small disk with brighter color than the surrounding skin, not raised		4.3	Small dimple		0.4
Small and raised		43.4	Not large enough to even insert small dilator or finger or small tampon		0.5
Moderate sized and raised		45.2	Just large enough to insert finger or small object but not large enough to insert average-sized penis, regular tampon, or speculum		4.5
Large and slightly long		4	Adequate for sexual penetration		88.2
Large and raised		1.8	Very large		6.3
Larger and longer than average		0.7			
Large and very long		0.7			

Labia minora	(%)	Labia majora	(%)	Vaginal depth	(%)
Not able to locate them	1.1	Not able to locate them	0.001	Do not know if it is deep enough for intercourse with an average penis	5.9
Small	12.5	Small	4.5	Not deep enough for intercourse	1.8
Average sized	59.1	Average sized	76.6	Deep enough for intercourse	92.3
Large	23.9	Large	17		
Very large	3.4	Very large	1.6		

Gynecologist's Responses

The response options chosen by the gynecologist corresponded highly with those of the women for vaginal size and vaginal depth (>90%) but much less for labia minora and majora and clitoral size (Table 3). However, no systematic pattern was observed in terms of divergent answers (i.e., the gynecologist did not systematically rate the clitoris larger or smaller compared with the women and vice versa).

Genital Sensitivity

Overall Genital Sensitivity

For the sample as a whole, overall discrimination between the 11 genital regions (external and vaginal areas) was highly significant ($P < .001$) for ratings of sexual pleasure, discomfort/pain, orgasm intensity, and effort to achieve orgasm. Ranked by degree of "sexual pleasure," the area on the clitoris was highest followed by the other regions as outlined in Table 4, but not all Bonferroni corrected pair differences were significant. In the vaginal area, the deep

vagina was highest followed by midvagina and vaginal introitus. The rank order was similar for "orgasm intensity" (Table 4), both for the external and vaginal area, and for "orgasm effort" for the external area but not the vaginal area. There were also fewer significant pair differences. The likelihood of reaching an orgasm was highest when stimulating the clitoral area (Figure 2). Ninety-four percent of the women reported orgasm with clitoral stimulation (area B), followed by 75% when stimulating the sides of clitoris, and 64% below the clitoris. The region above the clitoris was reported to be orgasm sensitive in only 41% of the women. Sixty-one percent indicated that the area around the vaginal opening was orgasm sensitive. Stimulation of the labial area was reported to be orgasm sensitive in 41% of the women for the labia minora and in 27% for the labia majora. Only 18% of the women reported their anal area to be sensitive for achieving orgasm. For vaginal sensitivity, the likelihood of orgasm estimate increased with increasing vaginal depth: 49% for the vaginal introitus area, 61% for the midvagina, 70% for the deep vagina (Figure 3). "Discomfort/pain" was rated highest in the

TABLE 3 Ratings of genital anatomy by gynecologist and women (n = 21).

	Women	Gynecologist	N	Match (%)
Clitoral size	Average	Average	4	48
	Small	Small	6	
	Average	Small	6	
	Small	Average	5	
Vaginal size	Adequate for sexual penetration	Adequate for sexual penetration	18	90
	Very large	Very large	1	
	Adequate for sexual penetration	Very large	2	
Vaginal depth	Deep enough for intercourse	Deep enough for intercourse	20	95
	Don't know	Deep enough for intercourse	1	
	Average	Average	7	
Labia minora size	Average	Average	1	57
	Small	Small	1	
	Large	Large	4	
	Average	Large	1	
	Large	Average	3	
	Small	Average	1	
	Average	Small	4	
Labia majora size*	Average	Average	11	55
	Large	Average	2	
	Average	Large	3	
	Average	Small	4	

*Based on n = 20; information from one woman is missing.

external area around the anus, followed by clitoris, below clitoris, and around the vaginal opening. In the vaginal area, discomfort was rated highest in the deep vagina, followed by midvagina, and vaginal introitus (Table 4).

Clitoral and Vaginal Sensitivity

Ratings of "sexual pleasure" and "discomfort" were significantly higher for clitoral stimulation by partner than by self ($P < .001$). Ratings for "orgasm intensity" were significantly higher, and ratings for "orgasm effort" significantly lower for clitoral stimulation by self than by partner ($P < .001$) (Table 5). Women who perceived their clitoris to be small experienced significantly less sexual pleasure and less orgasm intensity when clitorally stimulated by a partner and self as compared with women who perceived their clitoris to be of average size (for sexual pleasure: $t(625) = -2.47, P = .014$ [partner] and $t(583) = -2.01, P = .044$ [self]; for orgasm intensity: $t(627) = -2.91, P = .004$ [partner] and $t(583) = -2.01, P = .045$ [self]). Alternatively, women who perceived their clitoris to be large experienced significantly more sexual pleasure, $t(59) = -2.34, P = .023$ and more orgasm intensity when self-stimulated as compared with women with a perceived small clitoris, $t(340) = -2.81, P = .045$ (Table 5). For vaginal sensitivity, scores for sexual pleasure, discomfort, orgasm intensity, and effort increased with increasing vaginal depth. There was a significant effect for perceived size of the vagina, with women with a large perceived vaginal size reporting more effort to achieve orgasm in the vaginal introitus area but less in the mid and deep vagina compared with women who perceived their vaginal size to be average or small (Table 5, $ES\ r = 0.3$ for introitus and 0.2 for mid and deep vagina). More discomfort was reported in the mid and deep vagina by women with a perceived smaller vaginal size ($ES\ r = 0.1$ and 0.2 , respectively). ANOVA analyses with

TABLE 4

The scoring, listed in sequence from highest to lowest rating, of the various domains by genital area.

Domain and area	Mean (SD)	Areas significantly different*
Sexual pleasure†		
External		
B Clitoris	4.1 (0.9)	A, C, D, E, F, G, H, I, J, K
C Sides of clitoris	3.4 (1.0)	A, B, D, E, F, H, I, K
G Around vaginal opening	3.4 (1.0)	A, B, D, E, F, H, I, K
D Below clitoris	3.0 (1.1)	A, B, C, E, F, G, H, J, K
F Labia minora	2.7 (1.0)	A, B, C, D, E, G, H, I, J, K
A Above clitoris	2.6 (1.1)	B, C, D, E, F, G, H, I, J, K
E Labia majora	2.4 (1.0)	A, B, C, D, F, G, H, I, J, K
H Around Anus	2.0 (1.2)	A, B, C, D, E, F, G, I, J, K
Vaginal		
K Deep vagina	3.6 (1.1)	A, B, C, D, E, F, G, H, I, J
J Mid vagina	3.4 (1.0)	A, B, D, E, F, H, I, K
I Vaginal introitus	2.9 (1.0)	A, B, C, E, F, G, H, J, K
Orgasm intensity†		
External		
B Clitoris	3.8 (1.1)	A, C, D, E, F, G, H, I, J, K
C Sides of clitoris	2.8 (1.3)	A, B, D, E, F, G, H, I, J
G Around vaginal opening	2.4 (1.3)	A, B, C, E, F, H, I, K
D Below clitoris	2.4 (1.3)	A, B, C, E, F, H, I, K
A Above clitoris	1.8 (1.1)	B, C, D, E, G, H, J, K
F Labia minora	1.8 (1.1)	B, C, D, E, G, H, I, J, K
E Labia majora	1.5 (0.9)	A, B, C, D, F, G, I, J, K
H Around anus	1.4 (0.9)	A, B, C, D, F, G, I, J, K
Vaginal		
K Deep vagina	2.8 (1.4)	A, B, D, E, F, G, H, I, J
J Mid vagina	2.4 (1.3)	A, B, C, E, F, H, I, K
I Vaginal introitus	2.0 (1.1)	B, C, D, E, F, G, H, J, K
Orgasm effort†		
External		
B Clitoris	3.0 (0.8) n = 682	E, F, H, A, I
C Sides of clitoris	2.8 (0.9) n = 544	E, F, H, A
D Below clitoris	2.7 (0.9) n = 463	
A Above clitoris	2.6 (0.9) n = 295	B, C
G Around vaginal opening	2.6 (1.0) n = 446	E, F, H
H Around anus	2.6 (1.0) n = 134	G, B, C, K
E Labia majora	2.5 (0.9) n = 194	G, B, C, K
F Labia minora	2.5 (0.9) n = 297	G, B, C, K
Vaginal		
I Vaginal introitus	3.3 (0.8) n = 359	J, K, B
K Deep vagina	2.8 (1.0) n = 512	I, E, F, H
J Mid vagina	2.7 (0.9) n = 447	I
Discomfort/pain†		
External		
H Around anus	1.6 (1.0)	A, C, D, E, F, G, I, J, K
B Clitoris	1.5 (0.8)	A, C, D, E, F, G, I, J
D Below clitoris	1.3 (0.7)	A, B, C, E, F, H
G Around vaginal opening	1.3 (0.7)	A, B, C, E, F, H, I
E Labia majora	1.2 (0.5)	B, D, F, G, H, I, J, K
A Above clitoris	1.1 (0.4)	B, D, F, G, H, I, J, K
F Labia minora	1.1 (0.4)	A, B, D, E, G, H, J, K
C Sides of clitoris	1.1 (0.4)	B, D, G, H, J, K
Vaginal		
K Deep vagina	1.4 (0.7)	A, C, E, F, H, I, J
J Mid vagina	1.3 (0.7)	A, B, C, E, F, H, I, K
I Vaginal introitus	1.2 (0.5)	A, B, E, G, H, J, K

*Significant Bonferroni corrected pair comparisons ($P < .05$), †1 = none, 5 = intense; †1 = very strong, 5 = very little, SD = standard deviation

Bonferroni corrections were not significant for orgasm intensity and sexual pleasure in the vaginal areas.

Genital Sensitivity During Gynecological Examination

The results of the gynecological examination are summarized in Table 6. The functional ratings on the original SAGAS-F corresponded well with the functional ratings during the gynecological examination for most anatomical areas, showing again the highest sexual pleasure and orgasm intensity in the clitoral region and around the vaginal opening, as well as in the deep vaginal area. However, orgasm intensity of the clitoris (area B) was rated significantly lower on the gynecological exam compared with the SAGAS-F rating ($Z = -2.06$, $P = .04$). Additionally, sexual pleasure in the region above clitoris (area A) was rated significantly higher ($Z = -2.18$, $P = .029$) and orgasm effort lower ($Z = -2.12$, $P = .034$) during gynecological examination as compared with the rating on the questionnaire (Table 6).

Influence of Participant Characteristics

Multiple regression analyses corrected for age and parity status showed significant effects of both characteristics as well as a significant interaction effect on genital sensitivity outcomes, although effective sizes were small (Table 7). With increasing age, less discomfort in the clitoral area and around the vaginal opening was reported, as well as more orgasm intensity in the labial and vaginal introitus areas. The effects of age were different in the groups of women with and without children (i.e., with increasing age, women without children experienced more sexual pleasure and orgasm intensity in the clitoral area and less effort to achieve orgasm in the labia minora area than women with children).

Discussion

Data collected on the SAGAS-F, in a sample of 749 Dutch-speaking Belgian women, proved

Figure 2

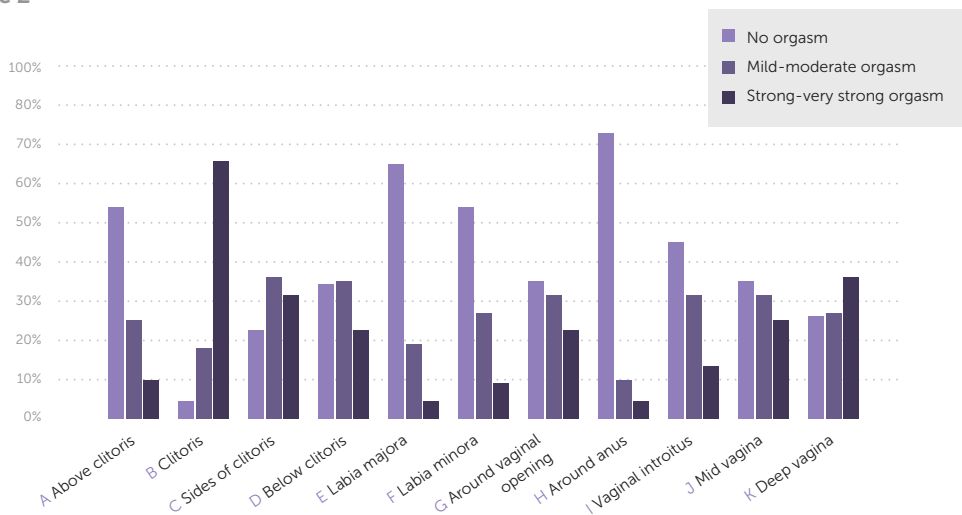


Figure 2. Likelihood of orgasm estimate and its intensity for each location

to be valid and reliable, adding to information about the utility of the scale as the results of the original pilot study by Schober and colleagues are replicated [19].

Genital Anatomy

Around 90% of women indicated their vaginal size and depth to be adequate for vaginal intercourse, and gynecologist's ratings matched those of the women in majority of cases (>90%). As in the original pilot study, only 43% of the women indicated a clitoral size that typically would be regarded as normal ("small and raised clitoris"), whereas a similar proportion selected the descriptor "moderate sized and raised" and a picture showing a clitoris that experts reported to be relatively large or larger than normal.

Figure 3

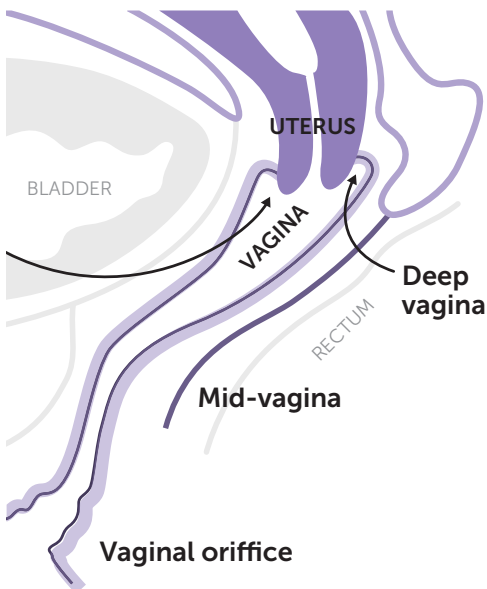


Figure 3. Sagittal view of vaginal area

This suggests that women may accept a larger clitoral size than commonly believed, which could imply a diminishing need for clitoral reduction for esthetic reasons in the

normal female population (i.e., without an underlying DSD condition) [19]. Perception of clitoral size seemed to influence the functional ratings (i.e., smaller perceived size was associated with less orgasm intensity and larger perceived size with higher orgasm intensity). In contrast with our findings, limited data suggest that clitoral size is not necessarily a criterion of responsiveness or related to sexual function [20,21]. Quantitative measurements should be undertaken to further elucidate the relationship. Clitoral length variability is three-fold greater than that of vaginal length and compared with its male homologue, penile length, at least as variable, which may be explained by the wider variation in exposure to prenatal androgens in women [22,23]. Although reports are available about the gross anatomy and diversity of the female genitalia (e.g., [24]), the further study of clitoral (and vaginal) neuroanatomy [22,25,26], as well as afferent pathways and sensory cortex projections, as it relates to sexual function, is crucial for our understanding of female sexuality and may aid the strategic design of female reconstructive surgery [27].

Genital Sensitivity

Scores indicated that orgasm intensity and sensitivity were perceived largest in the area of the clitoris (i.e., clitoral glans) and sides of the clitoris, as was only partly predicted [19,28,29], and that the area above the clitoris (i.e., vestibule of the vulva) did not seem to be perceived as the most sexually sensitive area. However, during the gynecological examination, women did indicate this last area to be highly sensitive, which might suggest that this specific genital area is somewhat undervalued in Flemish women's self-reported perception of genital sensitivity. Underlying this skin zone is the root of the clitoris and the location of the confluence of clitoral erectile bodies, which is supposed

TABLE 5

Clitoral sensitivity when stimulated by a partner or self in the last 12 months and according to perceived size (upper panel) and vaginal sensitivity according to perceived size (lower panel).

	Mean (SD)					
	Sexual pleasure ^a			Discomfort/pain ^a		
	Partner	Self		Partner	Self	
Clitoral sensitivity according to size						
Small	4.1 (0.8) n = 676	4.0 (0.8) ^a n = 630		1.4 (0.7) n = 676	1.1 (0.3) ^a n = 630	
Average	4.2 (0.8) n = 310	4.0 (0.8) ^a n = 288		1.3 (0.7) n = 310	1.1 (0.4) ^a n = 288	
Large	4.0 (0.8) n = 47	4.2 (0.8) n = 45		1.4 (0.5) n = 47	1.1 (0.3) ^a n = 45	
Vaginal sensitivity according to size						
Small	2.7 (0.9) n = 41	3.1 (1.2) n = 41	3.2 (1.4) n = 41	1.3 (0.7) n = 41	1.6 (1.1) n = 41	1.9 (1.1) n = 41
Average	2.9 (1.0) n = 641	3.5 (1.0) n = 641	3.6 (1.1) n = 641	1.2 (0.5) n = 641	1.3 (0.7) n = 641	1.3 (0.7) n = 641
Large	3.0 (1.0) n = 46	3.2 (1.2) n = 46	3.8 (1.2) n = 46	1.2 (0.5) n = 46	1.1 (0.4) n = 46	1.3 (0.8) n = 46

†1 = none, 5 = intense; †1 = very strong, 5 = very little. [†]In 87.7% (593/676) orgasm was reached when stimulated by the partner; in 92.5% (583/630) orgasm was reached when self-stimulated. ^aSignificant differences between the pairs (partner vs. self), $P < .05$. ^bSignificant differences between perceived large and small size ($P < .01$) and average and small size ($P < .01$). ^cSignificant differences between perceived large and small vaginal size, $P < .01$.

to be highly responsive to sexual stimulation [30,31]. Fetal clitoral studies have shown the greatest nerve density superior to and fanning out above the clitoris [29]. Consequently, as the clitoral area has the highest nerve density, it may not only be highly sensitive in terms of sexual pleasure but may also elucidate more pain/discomfort when stimulated (extensively), in accordance with underlying brain circuits that generate both pleasure and pain [32]. Moreover, Masters and Johnson observed that in the preorgastic arousal phase, the visible part of the clitoris retreats under the clitoral hood as to protect the clitoral glans from direct contact. Thus, in manipulating the clitoris, only a small margin between stimulation and irritation seems to exist [33]. For vaginal sensitivity, scores

for sexual pleasure, discomfort, orgasm intensity, and effort increased with increasing vaginal depth. Deep vaginal sensation scored the highest for erotic impact. Decreased orgasmic sensitivity was reported at the vaginal introitus site [19]. This is surprising, as the pleasurable area called the "G-spot" is supposed to be situated in the superficial vagina (i.e., the anterior vaginal wall) [34]. Objective measures (pathologic specimens, various imaging modalities, and biochemical markers) have not always provided consistent evidence for the existence of an anatomical site that could be related to this famed spot, but reliable reports exist [35]. Although the participants in the current study did not seem to report a unique "entity" within the anterior distal wall whose direct stimulation

Orgasm intensity ^a		Orgasm effort ^a if orgasm was reached ^b	
Partner	Self	Partner	Self
3.5 (1.2) n = 676	3.7 (1.1) ^a n = 630	2.8 (0.8) n = 593	3.2 (0.9) ^a n = 583
3.4 (1.3) n = 319	3.6 (1.2) ^a n = 297	2.7 (0.8) n = 273	3.3 (0.9) ^a n = 266
3.7 (1.2) n = 310	3.8 (1.0) n = 288	2.8 (0.7) n = 277	3.2 (0.9) ^a n = 274
3.5 (1.3) n = 47	4.1 (0.9) n = 45	2.8 (0.8) n = 43	3.3 (0.8) ^a n = 43

Orgasm intensity ^a			Orgasm effort ^a if orgasm was reached ^b		
Area I	Area J	Area K	Area I ^c	Area J ^d	Area K ^d
1.9 (1.0) n = 41	2.3 (1.3) n = 41	2.7 (1.4) n = 41	3.2 (0.9) n = 22	2.7 (0.7) n = 23	2.6 (0.9) n = 27
1.9 (1.1) n = 641	2.4 (1.3) n = 641	2.8 (1.4) n = 641	3.4 (0.8) n = 309	2.7 (0.9) n = 393	2.7 (1.0) n = 449
2.3 (1.3) n = 6	2.6 (1.3) n = 46	3.2 (1.4) n = 46	2.8 (0.8) n = 28	3.1 (0.9) n = 31	3.2 (1.1) n = 36

^aSignificant differences between perceived large and average size, P <.05 SD = standard deviation

leads to vaginal orgasm, the question of whether enough investigative modalities have been implemented in the search of the G-spot is certainly raised. Also, the role of the area surrounding the urethral opening (periurethral glans)—which has been shown to move towards the vagina during coitus—remains unclear in terms of vaginal orgasmic sensitivity [25]. On the other hand, studies on innervation and nerve distribution of the upper vagina, including apex and cervix, remain scarce [36]. Sensations evoked by deep vaginal (penetrative) stimulation are probably pressure related (e.g., stretch) rather than tactile [19]. However, other factors that have been, at least in part, related to deep vagino (cervical) responsiveness and orgasm intensity are greater thickness and/or length

of the urethrovaginal space [37] or better pelvic region muscle function [38] (as been described by Costa et al. [39]), which might differ in our validation sample. The individual variability in terms of orgasm sensitivity for each location was considerable, indicating that there are many sites of sexual sensation which differ in the kinds of orgasm they produce [40]. However, more women considered stimulation of the clitoral region—or in combination with stimulation of the vaginal region—necessary for reaching orgasm. Less women were exclusively vaginally oriented, and no women reached

orgasm without stimulating the clitoris and/or vagina. Scores for orgasmic sensitivity and intensity of the vagina at any depth were also less than scores for clitoral surfaces, which seems to be in line with studies where women rated surface orgasms (i.e., orgasms described as having originated on the surface of the genitalia) as more relaxing as well as more intense and localized compared with deep orgasms (i.e., orgasms described as having originated deep inside the body) [41]. Currently, the most common view is that all women's orgasms during intercourse are triggered by direct or indirect clitoral stimulation [33,42] (e.g., penile traction on the woman's labia minora pulling them across the clitoral glans) [33]. Because studies on human female cadavers reported an anatomic relationship between the urethra, distal vagina, and the surrounding erectile clitoral tissue, some authors suggested to use the term "clitoral complex," which is the location of female sexual activity, analogous to the penis in men [14]. Such an inclusive anatomical concept would also provide an answer to the somewhat artificial discussions on the precise trigger/ location of the orgasmic focus, that is clitoral vs. vaginal. However, our results do not fully support this

TABLE 6

Comparisons of genital sensitivity ratings on SAGAS-F and during gynecological examination (n = 21).

Mean (SD)	Sexual pleasure [†]		Discomfort/pain [†]	
	SAGAS-F	Gynecological exam	Partner	Self
A Above clitoris	2.7 (1.0)	3.1 (0.9)*	1.0 (0.0)	1.0 (0.0)
B Clitoris	4.0 (0.8)	3.8 (1.0)	1.2 (0.4)	1.4 (0.6)
C Sides of clitoris	3.2 (1.1)	2.7 (1.1)	1.0 (0.0)	1.0 (0.0)
D Below clitoris	3.0 (1.0)	2.2 (1.3)	1.2 (0.6)	1.7 (0.9)*
E Labia majora	2.1 (0.9)	2.0 (0.9)	1.1 (0.4)	1.1 (0.4)
F Labia minora	3.0 (1.0)	2.9 (1.2)	1.1 (0.5)	1.0 (0.0)
G Around vaginal opening	3.2 (0.8)	3.4 (1.0)	1.5 (0.8)	1.1 (0.4)
H Around anus	2.1 (1.0)	2.1 (0.8)	1.4 (0.6)	1.1 (0.7)
I Vaginal introitus	2.8 (0.9)	2.9 (1.0)	1.0 (0.0)	1.2 (0.5)
J Mid vagina	3.4 (0.8)	2.4 (1.0)*	1.4 (0.9)	1.1 (0.4)
K Deep vagina	3.4 (1.2)	3.0 (1.0)	1.3 (0.6)	1.3 (0.9)

*Significant differences between the pairs (SAGAS-F questionnaire vs. gynecological exam), $P < .05$, Wilcoxon paired t-tests, †1 = none, 5 = intense; †1 = very strong, 5 = very little, †Not enough valid cases to perform paired t-tests SAGAS-F = Self-Assessment of Genital Anatomy and Sexual Function, Female version

notion as women made a clear distinction between vaginal and clitoral regions in terms of the value of erotic sensation, which is also in line with the separable and distinct sensory cortical regions activated by vaginal and cervical vs. clitoral stimulation [43]. Ironically, Freud's distinction between vaginally and clitorally triggered orgasms may actually reflect a natural typology of women's orgasm induction but not—as he argued—the psychological maturity of women [44]. Although the specific mechanical and anatomical interplay are by no doubt of relevance in the further investigation of female orgasm (e.g., see [23,31]), this is beyond the scope of this study.

Limitations of the Study

We assessed the impact of certain demographic variables on the self-perceived genital sensitivity outcomes, such as age and parity status. However, genital sensation probably varies with phases of the menstrual cycle, differs between pre and postmenopausal women, and is influenced

by estrogen replacement therapy. A first major shortcoming of the present study is that menopausal status was not assessed thoroughly, limiting the validity of the findings. In previous studies, hypoestrogenic postmenopausal women were noted to have reduced vulvar and clitoral sensitivity to vibration, pressure, and light touch [30–32]. In our study, women above 50 years of age (presumably postmenopausal [45]) experienced significantly less sexual pleasure in the area of the clitoris and deep vagina ($P < .05$). A second limitation of the present study is that the cross-sectional design prohibits inferences about causality. Thirdly, participants were limited to provide responses to predetermined categories selected by the researcher. Therefore, we might have missed a broad range of information relating to women's own perception of sexual sensitivity and anatomy. Open questions should be available, as well as the response "no experience in this genital area." For instance, the anus as a sexual organ needs to be further investigated. Next, because of the multifactorial nature of the human sexual

Orgasm intensity ¹		Orgasm effort ¹ if orgasm was reached ²	
Partner	Self	Partner	Self
2.0 (1.4)	2.1 (1.4)	2.4 (0.9)	3.2 (1.0)*
3.7 (1.2)	2.8 (1.6)*	3.1 (0.9)	3.1 (1.0)
2.5 (1.4)	2.0 (1.3)	2.8 (0.8)	2.7 (1.1)
2.2 (1.3)	1.6 (1.2)	2.6 (0.8)	2.8 (1.3)
1.3 (0.8)	1.4 (0.9)	2.3 (1.5)	2.5 (1.0)§
1.8 (1.2)	2.0 (1.4)	2.3 (1.0)	3.0 (0.8)
2.0 (1.1)	2.5 (1.5)	2.5 (0.8)	2.6 (1.0)
1.2 (0.7)	1.2 (0.5)	4.0 (0.0)	1.7 (0.6)§
1.8 (1.2)	2.1 (1.3)	3.0 (0.9)	2.6 (0.9)
2.0 (1.2)	1.8 (1.0)	2.4 (1.1)	2.3 (1.0)
2.5 (1.4)	2.2 (1.4)	2.6 (1.0)	2.3 (1.3)

response, the type of sexual stimulation that triggers orgasm is very individualized for each respondent. In hopes of advancing understanding of female sexual experience and the evolutionary basis of female orgasm, further investigation of different types of orgasm is needed as women report their orgasms to

differ not only in intensity but also in location, phenomenology, and emotional components [42,46]. In general, other emotional, physiologic events, psy-chological, cultural, religious, medical (e.g., antidepressants), and social factors modulating female sexuality should be considered when assessing self-reported genital anatomy and sensation [15]. For instance, increased access to pornography and the rising popularity of female genital cosmetic surgery may enhance feelings of distress about genital appearance [24]. Despite extreme variability of the female genitalia on an individual level, further objective investigative measures of genital anatomy (e.g., clitoral size, distance between the clitoral glans and shaft relative to the vaginal opening, G-spot existence) demand further consideration. Only recently the clitoris has been found a much more complex and larger—largely internal or hidden— organ than commonly assumed [26], acknowledging that the visible external tip of the clitoris is not the only site of female

TABLE 7 Multiple regression analyses corrected for age, parity, and the interaction between both variables.

	Variable	Area	β	CI, P
Age	Discomfort	Clitoris	-0.11	[-0.01; -0.002], $P < .01$
		Vaginal opening	-0.12	[-0.011; -0.002], $P < .01$
	Orgasm intensity	Labia majora	0.17	[0.004; 0.009], $P < .01$
		Labia minora	0.15	[0.003; 0.009], $P < .01$
		Vaginal introitus	0.02	[0.002; 0.03], $P < .05$
Parity	Orgasm intensity	Clitoris	-0.40	[-0.68, -0.11], $P < .01$
	Orgasm effort	Vaginal introitus	0.35	[0.027; 0.67], $P < .01$
	Sexual pleasure	Labia minora	-0.32	[-0.584; -0.063], $P < .05$
		Around anus	-0.37	[-0.67; -0.062], $P < .01$
Age x parity	Sexual pleasure	Clitoris	0.02	[0.001; 0.031], $P < .05$
		Around anus	0.02	[0.003; 0.043], $P < .05$
	Orgasm intensity	Clitoris	0.03	[0.1; 0.05], $P < .01$
	Orgasm effort	Sides of clitoris	0.03	[0.007; 0.044], $P < .01$
		Labia minora	0.03	[0.006; 0.059], $P < .05$

Only significant results are reported, constant included in equation, standardized slope beta. Confidence interval (CI): 95% CI

sexual sensitivity and underlining that the clitoris cannot be conflated with the clitoral glans. Further quantitative genital sensation measures during sexual stimulation may be of added value, although assessment of any sensory pathway is complex, and sensation is a subjective personal experience [23]. Lastly, the sample consisted primarily of heterosexual, Caucasian women between 18 and 28 years, with a high educational background. Generalization of findings to other segments of the female population or women of other cultures is accordingly compromised.

Conclusion

This current report replicates and extends earlier findings by showing that women indicate their clitoral region to be most important for sexual sensation when assessed with the SAGAS-F self-report measure as well as a gynecological examination. Therefore, some important implications for several populations exist. Great importance has been placed on achieving a normal appearance via surgical means for children born with conditions that affect genital development (disorders of sex development). Genital surgery risks disruption of nerves and blood vessels, which may impair sensation to the genital area and affect future capacity for sexual pleasure. Surgery, including female genital cosmetic surgery in the general female population, should only be undertaken with a clear understanding of the variation in normal appearance and in cases which differ markedly from normal. Data on genital sensation should form part of the long-term follow-up of genitoplasty procedures. The SAGAS-F could be used for this purpose, as it is an easily administered, reliable self-reporting tool. Routine genital

sensitivity assessment is also likely to facilitate psychosexual counseling.

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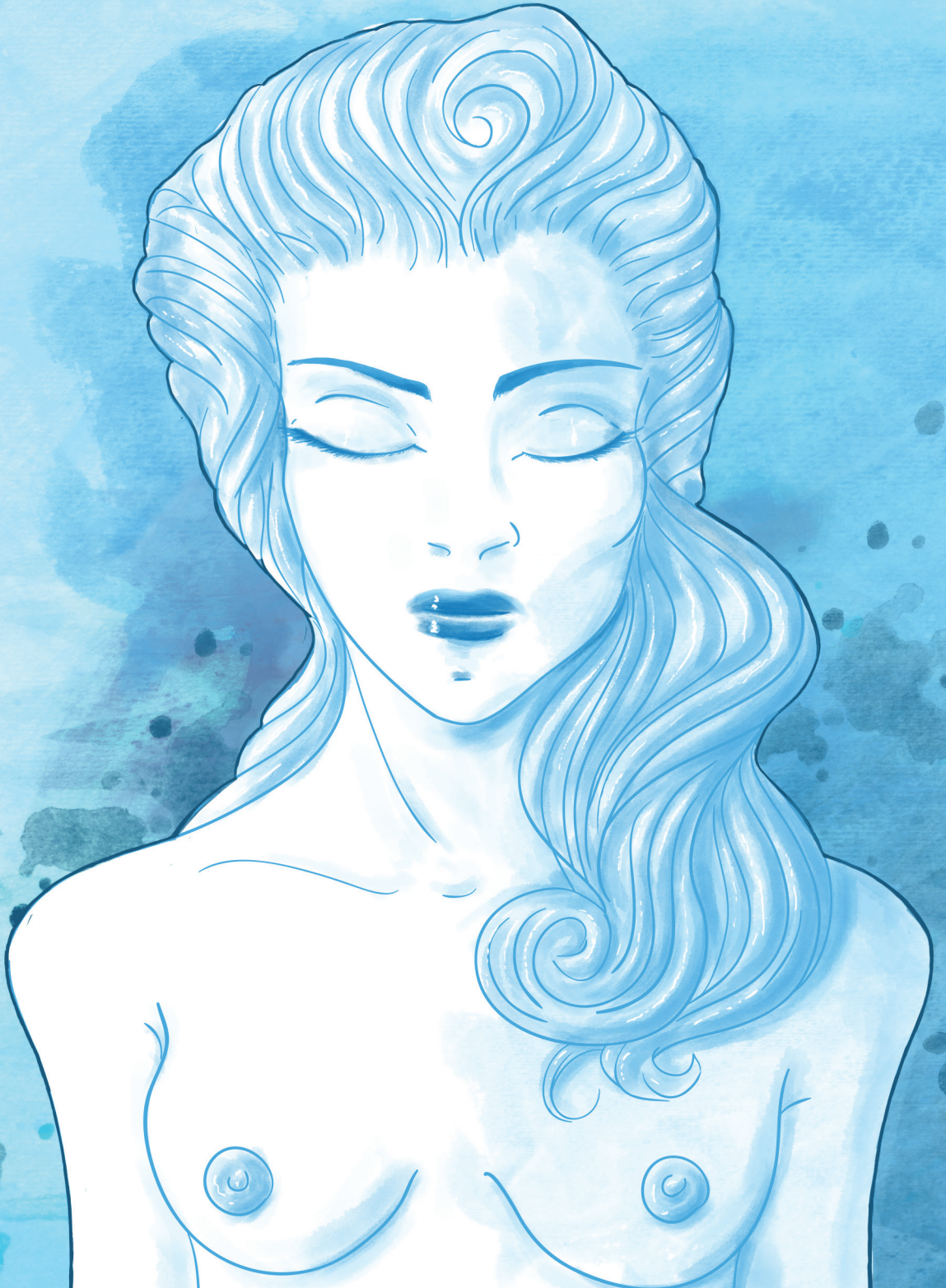
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Under construction: Vaginal creation methods 4.1 for vaginal hypoplasia

ABSTRACT

In women with vaginal hypoplasia, such as in 46, XX Mayer-Rokitansky- Küster-Hauser syndrome (MRKH) and in 46, XY Complete Androgen Insensitivity Syndrome (CAIS), surgical vaginoplasty and non-surgical self-dilation treatments are available to lengthen the vagina and facilitate sexual intercourse, but the best treatment remains controversial. Vaginal dilation has been recommended as a first-line treatment, because of its less invasive character and high success rate. However, it may have a negative emotional impact on the women and the exploration of factors associated with compliance and long-term outcome is incomplete. As with surgical techniques, it is unclear whether maintenance dilation therapy in case of sexual inactivity is crucial to ensure functional success, and whether psychological counseling needs to be embedded in treatment to maximize efficacy. Moreover, diagnosis related success rates (i.e. MRKH vs. CAIS) have not been the focus of papers on vaginal agenesis. In general, the medical literature lacks comparative outcome studies, meaning that the current choice of reconstruction method relies greatly on the practitioner's preference and experience, and prospective, longitudinal studies are scarce. We present the available literature on the various approaches to vaginal reconstruction, focusing on the history of the specified technique, inherent advantages and disadvantages, complications and long-term durability in terms of sexual function. We reviewed known relevant factors which may impact on final clinical decision making, as to inform individual management of vaginal hypoplasia. Finally, we present a treatment algorithm for women with vaginal hypoplasia distilled from the available literature and propose a set of clinical care recommendations.

Key Words. vaginal hypoplasia, vaginal reconstruction, vaginal dilation, vaginoplasty, sexual function, Mayer-Rokitansky-Küster- Hauser syndrome, Complete Androgen Insensitivity Syndrome, long term outcome, Disorders of Sex Development

Introduction

It is apparent that the clinical management of congenital disorders of sex development (DSD) - in which anatomical, gonadal or chromosomal sex is atypical - has been in a state of great flux, debate and controversy the last decade [1,2]. Advances

in medical knowledge and understanding of psychosexual development, as well as an increased emphasis on the rights and autonomy of the individual, have all contributed to discussion about the role and efficacy of medical intervention [3-7]. Clinical practices developed to promote psychosexual wellbeing remain the subject of

critical review [8]. Patients with DSD requiring vaginal reconstruction, because of vaginal hypoplasia or aplasia, typically present with primary amenorrhea in adolescence with an otherwise normal growth and development [9]. The most commonly involved condition is Müllerian agenesis or Mayer-Rokitansky-Küster-Hauser syndrome (MRKH), occurring 1 in 4000 to 5000 females [9,10]. Women with MRKH have a XX karyotype and normal functioning ovaries, but an absent or rudimentary uterus and a short vagina resulting from failed embryonic development of the Müllerian duct [9]. The syndrome (i.e. vaginal hypoplasia) may be isolated (type I) but it is more frequently associated with renal, vertebral, and, to a lesser extent, auditory and cardiac defects (MRKH type II or MURCS association) [11]. In familial cases, the syndrome appears to be transmitted as an autosomal dominant trait with incomplete penetrance and variable expressivity, which suggests the involvement of either mutations in a major developmental gene or a limited chromosomal imbalance. However, the etiology of MRKH still remains unclear [12]. The differential diagnosis of MRKH mainly includes 46,XY DSD, specifically androgen insensitivity syndrome. In the latter, the lack of a functional androgen receptor results in phenotypically normal female external genitalia [13]. These women have testes, absent Müllerian structures and a blind short vaginal pouch due to the action of antimüllerian hormone [14,15]. Estimated incidences vary according to the population studied, ranging from 1 in 41 000 to 120 000 [13,16]. In addition, vaginal hypoplasia can be associated with disorders of testosterone biosynthesis or other rare complex conditions affecting the urinary and gastrointestinal tracts, such as cloacal and anorectal anomalies [17]. In pubertal females, differential diagnosis can be made assessing serum testosterone levels and karyotype analysis. Conventional

transabdominal, translabial, or transrectal ultrasonography; three-dimensional ultrasonography and magnetic resonance imaging can be used to evaluate the absence of the uterus and vagina and can in individual cases be helpful in definitively characterizing anatomy [18]. Besides correct diagnosis of the underlying condition and evaluation for associated congenital anomalies, an important step in the effective medical management is psychosocial counseling before any treatment or intervention [18]. These women may experience variable levels of distress, connected to the perception of having a compromised womanhood and characterized by the fear of being devalued by others [19,20]. Sensitive pacing of information is recommended in order to allow young women and their family to make informed decisions about different treatment modes and a realistic adaptation to living with this condition [18].

Plethora of Vaginal Reconstruction Methods

Sexually experienced patients may present with natural dilation of the vaginal dimple and occasionally require no additional treatment. Enlargement procedures for vaginal hypoplasia in non-sexually experienced women include surgical vaginoplasty and non-surgical dilation therapy [21]. [Table 1 and 2](#), and [Figure 1](#) provide an overview of the variety of techniques and their main advantages and disadvantages (Based on [17,21-26]).

Vaginoplasty techniques

Dupuytren, in 1817 and later, Amussat, in 1835 [27], are frequently mentioned as being the first proponents of surgical correction, which involved creating a perineal pouch between

TABLE 1 Vaginal reconstruction methods.

Non-surgical	
1.	Simple pressure [85]
2.	Pressure from a bicycle stool [93]
3.	Regular coitus [83]
Surgical	
1. Surgical creation of a neovaginal space between bladder and rectum	
1.1 Simple reconstruction with insertion of form, without grafting [29,30]	
1.2 Simple reconstruction with insertion of inlay graft over form	
a) Split-thickness skin graft [31,32]	
b) Full-thickness skin graft & Flap vaginoplasty	
Simple labia minora and thigh flaps [40]	
Tubed pedicle flap from thigh [38]	
Pedicled bladder flap [59]	
Gracilis myocutaneous flaps [45] and transpelvic rectus abdominis myocutaneous flaps [46]:	
Perineal artery axial flap of Hagerty [303]	
Pudendal thigh flap vaginoplasty (Singapore flap) [47,304]	
Free flap graft from scapula [48]	
Vulvoperineal fasciocutaneous flap (the Malaga flap) [50]	
c) Allogenic tissue: Amnion [53], epidermal sheets [305]	
d) Peritoneum [60,61]	
e) Artificial grafts: Interceed adhesion barriers [160], silicone membrane with incorporation of recombinant fibroblast growth factor [56]	
f) Tissue expanders [306]	
g) Autologous in vitro cultured vaginal tissue [58], autologous buccal mucosa [307]	
2. Bowel vaginoplasty	
1.1 Ileum [67], sigmoid colon [308], or cecum and ascending colon [69]	
1.2 Rectum [68]	
1.3 Free jejunal autograft [70]	
3. Vulvovaginoplasty [51]	
4. Surgical traction	
4.1 Vecchietti procedure [75]	
4.2 Balloon vaginoplasty [78,79]	

bladder and rectum with strong digital pressure and then packing the cavity with linen [28]. Wharton (1938) and Counsellor (1948) subsequently refined this technique by using a mold covered with a rubber sheath to hold the perineal pouch open, which allowed spontaneous epithelization to take place [29,30]. It became quickly clear that the mold had to be used for several hours every day to reduce vaginal strictures due to scar formation. Permanent dilation to prevent stenosis of the neovagina (3- 6 months or longer) was further insisted upon by McIndoe & Banister [31]. They popularized a technique, first pioneered by Abbe (1889), in which split-thickness skin grafts, taken from the anterior surface of the thigh or buttock were

inserted over the mold, after dissection of a space between rectum and bladder [32,33]. There were problems with fistula formation secondary to the use of the mold and the need for lubrication as the skin graft tended to be rather dry [34]. Numerous modifications of the mold material (soft, semi-rigid or rigid) or shape, and improvements in postoperative care have been suggested to reduce the incidence of complications [35-37]. However, marked scarring at the donor site and vaginal stenosis or contracture, particularly at its distal end, remains a problem.

The problem of contraction of the vagina postoperatively was thought to be avoided with skin flap vaginoplasty and the use of

TABLE 2 Advantages and disadvantages of different vaginal reconstruction methods.

Technique	Advantages	Disadvantages
1. Dilatation method (Frank/ Ingram)	<ul style="list-style-type: none"> - Non-invasive - No hospitalization - Psychological advantage of the subject being in control - Preserves vaginal tissue - Cost-effective, inexpensive - Minimal morbidity and complications - After failed treatment, the option still exists to proceed to surgical neovaginal creation 	<ul style="list-style-type: none"> - Motivated and mature patients required (low compliance) - Time-consuming (?) - Discomfort and constant reminder of difference - Awkward sitting on Ingram stool - Manual fatigue, boring, and inability to create enough perineal pressure (Frank) - Limited success in younger patients (<18yrs) (?) - Long-term dilatation needed (?) - Poor results with skin dimple (?) - Increased risk of vaginal prolapse (?)
2. Vecchietti procedure	<ul style="list-style-type: none"> - Preserves vaginal tissue - Laparoscopic approach minimally invasive - No excessive mucus production or vaginal stenosis 	<ul style="list-style-type: none"> - Pain and need for strong analgesia during daily tightening - Postoperative self-dilatation required - Significant potential complications because of the limited retrovesicorectal space into which the traction threads need to be placed - Pliable tissue required (not recommended in the presence of scars from previous reconstructive surgeries) - Increased risk of vaginal prolapse (?)
3. Intestinal vaginoplasty (sigmoid colon, ileum, jejunum)	<ul style="list-style-type: none"> - Lubricated segment with reliable blood supply - Grows with the patient (advantageous for younger children) - No scarring - No dilatation needed (?) - Low rate of stricture - Can be performed with previous extensive surgery 	<ul style="list-style-type: none"> - Requires laparotomy and bowel anastomosis - Prolapse 3 to 8% - Excessive discharge - Complication rate between 16-26% (postoperative ileus, bowel obstruction, diversion, ulcerative colitis, adenocarcinoma)
4. Davydov procedure (peritoneum)	<ul style="list-style-type: none"> - Suitable for women who had previous pelvic surgery - Lack of granulation tissue - No scar formation 	<ul style="list-style-type: none"> - Decreased lubrication - Potential for bladder and rectum injury - Potential infections and prolapse - Postoperative dilatation needed
5. McIndoe procedure (split-thickness skin grafts)	<ul style="list-style-type: none"> - Vaginal approach avoids laparotomy - No bowel anastomosis - High rate of graft take - Low rate of prolapse 	<ul style="list-style-type: none"> - Postoperative dilatation needed - High rate of graft contracture and neovaginal stenosis - Disfiguring scar at the donor site - Potential of graft infection - Lack of lubrication - Risk for squamous cell carcinoma - Complication rate up to 14%
6. Full thickness skin grafts Myocutaneous / fasciocutaneous flaps Pudendal thigh flap Labia minora flaps Malaga flap Singapore flap Scapula flap	<ul style="list-style-type: none"> - Good pelvic support following exenteration - Can be done at time of exenteration - Good blood supply, low infection rate - Flap incision incorporated into laparotomy site - Pedicled tissue form better than free-tissue, because no dilatation required - No skin graft with pudendal thigh flaps 	<ul style="list-style-type: none"> - High rate of prolapse and flap loss (gracilis) - Skin appendages - Deficient lubrication - Disfiguring scar at the donor site - Wound site infection - Hair regrowth in the neovagina
7. Williams Vulvovaginoplasty (flaps from labia majora)	<ul style="list-style-type: none"> - Simple surgery - Non-invasive 	<ul style="list-style-type: none"> - Hair bearing skin - Sexual contact is difficult due to angle of the external vagina - Insufficient vaginal depth, no feeling of penetration - Wound opening, haematoma, trauma infection

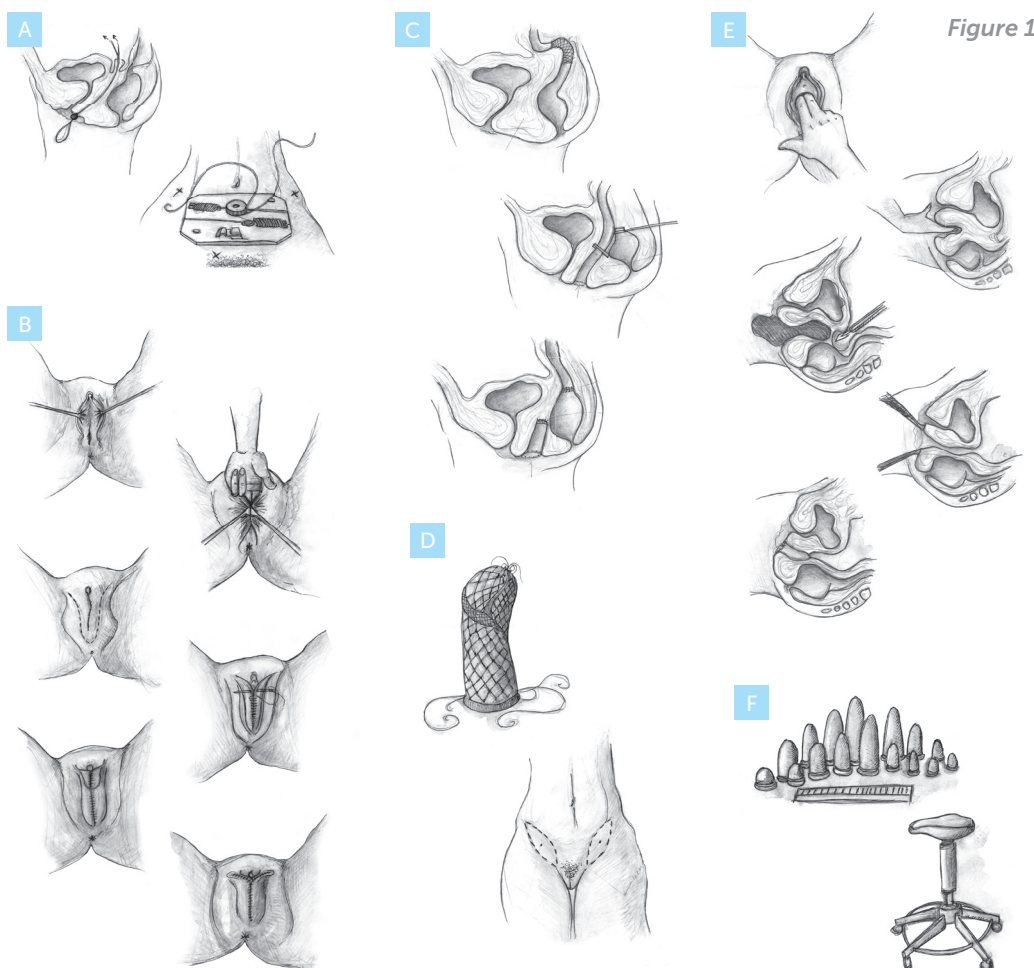


Figure 1

Figure 1. Different vaginal reconstruction techniques. A) Vecchietti technique: pressure is applied on the vaginal dimple by an acrylic olive connected by threads that pass through the potential neovaginal space, are guided preperitoneally along the abdominal wall and exit via the anterior abdominal wall where they are connected to a traction device. The threads are tightened daily [28]. B) Williams' procedure: the labia majora are used to line an external pouch formed by a U-shaped perineal incision [34] C) Bowel vaginoplasty: a short segment of bowel (ileum or sigmoid colon) is isolated. The mesentery of the bowel segment is extensively dissected upwards in order to connect this neovagina with minimal tension [34]. D) McIndoe procedure: split-thickness skin grafts are obtained from the thighs or buttocks and adapted around a mold to line the dissected space between rectum and bladder [28,99] E) Davydov procedure: A transverse incision is made below the urethra; peritoneum is dissected off the rectum, bladder and side wall of the pelvis using fingers, and developing a space; the canal is tightly packed and an incision is made in the peritoneum over the pack; stay sutures in the peritoneum are used to pull a tube of peritoneum towards the perineum; the edges of the peritoneal tube are sutured to the skin of the introitus and the abdominal end of the tube is closed [62,63]. F) Vaginal dilation techniques: Frank vaginal dilators of different sizes increasing in length and width, and the Ingram stool method whereby patients are instructed to sit on bicycle seat-shaped stool for short periods with a vaginal dilator held in position in or at the vaginal opening to stretch the vaginal tissue [257].

full-thickness skin grafts from labia minora or thighs, first described by Graves in 1921, with disappointing results [34,38-40]. The technique was modified by Bhonsale and Sheares who lined the posterior wall of the rectovesical cavity with a single skin flap dissected from the vaginal dimple, retaining its attachment at the perineum [41]. Fortunoff utilized a U-shaped skin flap [42]. Other skin flaps used included rotated buttock flaps [43], and myocutaneous flaps, involving the gracilis muscle, a vulvobulbocavernosus myocutaneous graft [44] and rectus abdominis muscle, which also have been used with success in vaginal deficiencies following neoplasms or trauma's [45,46]. Pudendal thigh flaps [47], free flap graft from the scapula [48,49], and vulvoperineal fasciocutaneous flaps [50] have been used as well. Williams preferred vulvovaginoplasty, where an external pouch is created by suturing the labia majora to form a short vertical 'vagina' [51]. Most of these techniques can suffer from visible scars and keloid formation, and lack of vaginal lubrication and hair regrowth in the neovagina, which can become stenosed [52]. In addition, a risk of squamous cell carcinoma has been reported [6].

In an attempt to overcome some of the disadvantages of the skin graft techniques, a variety of other tissues have been used to line new vaginas. In 1934, Brindeau described a novel approach using chemically processed and sterilized freeze-dried human amniotic membranes that are considered immunologically inert and thus have low risk of graft rejection [53]. It has the advantage that no graft site is required, thereby leaving no external scars for the patient to have to tolerate. However, it is important that the use of this material is properly governed and that donors are suitably screened for transmittable diseases [54]. Various other authors have reported on the use of artificial or biological

materials including buccal mucosa [55], artificial dermis (atelocollagen sponge) and with use of basic fibroblast growth factor to accelerate epithelization [56], oxidized cellulose [57], and autologous in vitro-cultured vaginal tissue [58]. Pedunculated bladder wall flap [59] and peritoneum from the Douglas pouch (i.e. Davydov procedure) have been used in a combined abdominoperineal approach [60,61]. Davydov developed a three-stage operation involving dissection of the rectovesical space with abdominal mobilization of the peritoneum, attachment of the peritoneum to the created introitus, and finally closure of the neovaginal vault with purse-string suture [60,62,63]. The claimed advantages of this technique by the authors are the lack of granulation and scar formation. The procedure was modified to a laparoscopic approach, having the advantages of less bleeding, and postoperative pain in addition to shorter hospital stay, faster recovery, and better cosmetic outcome [64]. These merits are specifically important in adolescent patients in whom cosmesis may be very important and a faster recovery would allow for earlier return to school [65].

The use of bowel segments, reported as early as 1892 by Sneguireff [66], has gained enormous popularity for vaginal reconstruction in DSD and is also widely used following pelvic exenteration for cancer [28]. Because of the high morbidity and mortality rates when ileum segments were first used by Baldwin in 1904, the technique was largely abandoned until 1961, when the use of a sigmoid loop was described [67,68] and later the use of cecum and jejunum [69,70]. A laparoscopic approach is carried out since 1996 [71], but the procedure is still most frequently done through a laparotomy. Overall, the main advantages of this operation are said to be the lack of shrinkage

– with no long-term vaginal dilation needed
 - and the natural lubrication provided by the mucous production which obviates the need for artificial lubricants and decreases the risk of dyspareunia [72]. Greatest concerns surrounding this operation are bleeding or copious and smelly vaginal discharge, which also may mask adenocarcinoma [6,73]. Diversion colitis may also occur, possibly due to a lack of short-chain fatty acids normally present in colonic contents and required for mucosal integrity, but is less of a problem with ileum than with colon segments [28].

Finally, other surgical techniques are based on passive traction rather than dilation. In 1965, Vecchiatti proposed a device permitting an upwards traction on the retrohymenal fovea by an acrylic olive and the creation of a neovaginal space in 1 week, without the use of extraneous tissue [74,75]. The laparoscopic adaptation proposed in 1992 offers enhanced speed and ease [76]. The complication rate including bladder and rectal wall injury is reported to be low [77]. However, a more common drawback for this procedure is the pain resulting from the sustained traction which necessitates a hospital stay throughout the whole traction process [21]. Balloon vaginoplasty is based on the same principle, however, traction and dilation of the vaginal dimple is exerted by a Foley catheter with an inflated balloon [78,79]. Authors claim that the main advantage of this technique is the neovaginal width, which can be manipulated according to balloon distension.

Vaginal dilation techniques

Because there is pliable perineal skin between the urethra and anus in women with vaginal hypoplasia, coitus has been shown to lead to an increase in vaginal depth and width [80-83]. In young women with an understanding and cooperative partner, excellent results can be

obtained with little intervention from medical professionals [84]. When women do not have a partner or vaginal depth does not increase by coital dilation, supportive treatment with dilators has been proposed.

Frank described in 1938 the use of Pyrex tubes of gradually increasing sizes (0.8 cm, 1.5 cm and 2.0 cm in diameter) to force the mucous membrane inward into the introital region [85,86]. Interestingly, for almost 40 years this technique was only infrequently used, although his series and the majority of case reports suggested that this approach was one of promise [87-92]. In 1981, Ingram modified the technique based on presumed inconveniences of Frank's method, such as sheer fatigue of the hands and fingers, the need to squat, and the inability to perform other productive activities during the procedure. He inserted dilators into the saddle of a bicycle stool and had the patients sit astride this to gently create perineal pressure [93]. The seat was later modified by Lee [86] and Lankford [94].

To dilate or not to dilate?

Non-surgical vaginal dilation has been put forward by the American College of Obstetricians and Gynecologists (ACOG) in 2002 as a first choice treatment, because it is a patient-driven technique that is easy to perform, cost-effective and safe [18,23,95]. Meanwhile, the concept of surgery for DSD conditions became increasingly controversial and led to a call in some quarters for a moratorium on genital surgery as long as long-term data are unavailable [6,96]. Successful neovaginal creation by dilation obviates the need for major surgery in most patients, while those not achieving adequate vaginal length with dilation can still undergo vaginoplasty as a second-line intervention. It is expected that only 85%

of women will achieve a functional vagina without a surgical approach [97]. Reasons for failure, however, need further clarification. Moreover, it is not known if failed vaginal dilation therapy jeopardizes further surgical success outcomes, especially because in a number of these procedures ongoing vaginal dilation is required. In addition, if surgery is needed, there is a lack of evidence to inform physicians regarding the optimum surgical technique to use. Also, the extent

to which psychological interventions are needed to maximize treatment success needs to be further elucidated. In view of this ongoing debate and in order to provide a comprehensive, nonbiased reference tool, the available literature on the various approaches to vaginal reconstruction is reviewed below. The anatomical outcomes, referring to vaginal capacity, and functional outcomes, referring to sexual activity levels and successful coital or non-coital sexual

TABLE 3 Summary of surgical studies.

	Traction vaginoplasty: Vecchiatti or balloon traction [74,77-79,105, 113,118, 232-243]	Intestinal vaginoplasty: Sigmoid colon, cecum or ileum [103,107,112,114,115, 164,191-226], jejunum [227,228], rectosigmoid [229-231]	Peritoneal vaginoplasty: laparotomically [60,62,180-182] or laparoscopically [64,114,118,183-190]	Vulvovaginoplasty: [99,103,108,176-179]
N patients	817	912	393	286
Diagnosis	98% MRKH 2% CAIS	85% MRKH 8.3% AIS 6.7% other (e.g. CAH, mixed GD) Note: Excluding [103,112]*	98.5%MRKH 1.5% MRKH or AIS	100 % MRKH
Anatomical success	99%	95%	92%	97%
Definition	≥6cm, except ≥10cm in [239]	Adequate or good anatomical result with no contracture or shrinkage: 94% (103,107,112,115,191,193-95, 198, 201,203,206,207,210,216,226,227) Cosmetically pleasing: 96% [208,221] >7cm: 100% [209] >10cm: 100% [224] >12 cm 100% [114,196,199, 215,225,231] > 15cm: 100% [164,220,228] Note: NR in [192,204,205,211-214,218,219,222,223,229,230]	≥ 6cm: 82% [114,181,183,187,184,190] ≥8cm : 100% [60,180,182,185,189] Complete epithelization of the neovagina: 100% [118] No shrinkage: 100% [188] (100%) Not further specified: 97.5% [62,64]	Vagina of normal length and caliber, mean vaginal length of 12 cm [179] or between 7.5-9.5 cm [178]

activities of the current techniques reported hitherto are discussed.

Outcome studies under scrutiny

For the purpose of this review, a total of 189 studies were analyzed. Single case reports and manuscripts solely on patients born with ambiguous genitalia and associated vaginal hypoplasia (e.g. congenital adrenal

hyperplasia) were excluded. When different vaginal reconstruction regimens were separately discussed, the results were separately handled [74,98-118]. For analysis purposes, the surgical options were divided into seven major types: 1) Vaginoplasty without grafting (i.e. Wharton procedure) [29,98,103,112,119-125] 2) McIndoe procedures [33,36,99-104,108,109,112,115-117,120,126-153] and modified procedures (amnion, [54,116,117,154-159], absorbable adhesion barrier [57,160-162],

Skin flap vaginoplasty: [41,50,165-175,173]	Modified McIndoe: Amnion [54,116,117,154-159], Interceed oxidized cellulose [57,160-162], Buccal mucosa [55,163,164]	McIndoe procedure: [33,36,99-104,108, 109,112,115-117,120, 126-153]	Vaginoplasty without grafts: [29,98,103,112,119-125]
171	154	1720	209
83% MRKH 8% vaginal agenesis and small uterus 4,5% trauma (e.g. oncological resection) 1% AIS 3,5% intersex (mixed GD or CAH)	96% MRKH 2.6% AIS 1.4% cervicovaginal agenesis	92% MRKH 4.3% AIS 2.1% male or female pseudohermaphroditism ¹ 0.7% vaginal atresia with functional uterus 0.9% uterovaginal atresia Note: Excluding [103,112,120,129,131,136,143]*	88% MRKH 1.5% AIS 8% vaginal agenesis with functioning uterus 2.5% other (chromosomal anomalies, male pseudohermaphroditism) ¹
91%	96%	83%	93%
≥ 7cm: 100% [41,168,169,171,175] sufficiently spacious : 70-95% [167,170] fine cosmetic result with natural angle: 100% [50,166,173] no scar and polypoid formation or contracture [165,172,174]: 63-92%	Normal epithelization of the vagina and ≥7cm for amnion procedures: 97% ≥6cm for interceed procedures: 94% ≥8cm for buccal mucosa procedures: 100%	≥ 7cm: 89% [33,36,104,116,126,133,141] ≥8cm : 92% [109,143,153] ≥ 10cm: 83% [131,132,145,147] Max 25% contracture: 82% [101,112,115,120,129,144] 'Normal' vagina: 33% -100% [99,128] 'Good' or 'adequate' result: 89% [103,108,136,140,142,148] Successful take of the graft: 96% [134,149,152,309]	No contractures: 91% [29,119,124], Max 25% contracture of vaginal space: 50% [103] 'Normal' vaginal depth' (≥ 7cm) [98,121-123,125]: 96% 'Good/adequate': 71.5% [112,120].

*Excluding some studies with mixed treatment regimens, because the specific diagnosis was not known according to the specific treatment regimen, although the majority had MRKH. ¹ Not further specified. Abbreviations: MRKH= Mayer-Rokitansky-Küster Hauser syndrome; (C)AIS= (Complete) Androgen Insensitivity Syndrome; GD= Gonadal Dysgenesis; CAH= Congenital Adrenal Hyperplasia

TABLE 3 Summary of surgical studies.

	Traction vaginoplasty	Intestinal vaginoplasty	Peritoneal vaginoplasty	Vulvovaginoplasty
Proportion of patients with complications and main complications	<p>7,7%</p> <p>Bladder trauma (perforation or hematoma): 1.8%</p> <p>Urinary tract infections or cystitis: <1%</p> <p>Vaginal vault bleeding: < 1%</p> <p>Note: Bladder perforation was more common in studies in which women had previous failed surgery (9% vs 1.6%), but not other complications</p>	<p>24,6%</p> <p>Introital stenosis: 9%</p> <p>Vaginal prolapse: 3.3%</p> <p>Vaginal discharge: 2.6%</p> <p>Bowel obstruction: 1.4%</p> <p>Note: Mortality due to bowel obstruction or heart failure occurred in n=5, in two older studies (115,192). Intestinal obstruction only occurred in women who had had previous surgery. In studies in which women had previous surgery, higher stenosis and discharge complications (9% and 3%) were reported, compared to studies without previous surgery (4% and 1%). Prolapse complications were the same (3%)</p>	<p>14,2%</p> <p>Vault granulations at the neovagina: 9%</p> <p>Strictures, stenosis or contracture: 5%</p> <p>Rectal, urethral or bladder injuries: 4%</p> <p>Persistent discharge: 2%</p> <p>Rectovaginal or vesicovaginal fistulae: 1%</p> <p>Note: In those studies in which previous surgery had failed, complications of stenosis, discharge and fistulae were higher (respectively 9% vs 1%, 3% vs < 1% and 4% vs < 1%)</p>	<p>6%</p> <p>Stitching and wound opening: 3%</p> <p>Protruding hairs: 1%</p> <p>Note: No complications were reported in studies in which women had previous failed dilation therapy</p>
Proportion of patients with repeat vaginoplasty	<p>0,4%</p> <p>[113,238,243]</p>	<p>3%</p> <p>[115,200-202,207,213,214,218,225,230,231]</p>	<p>1,5%</p> <p>Dilation under anesthesia for not complying with dilators [62,184]</p>	<p>0%</p>
Sexual activity	96%	70%	88%	93%

Skin flap vaginoplasty	Modified McIndoe procedures	McIndoe procedure	Vaginoplasty without grafts
<p>22,4%</p> <p>Vaginal narrowing and scar formation: 6.4%</p> <p>Hair growth: 6%</p> <p>(Partial) necrosis of the graft: 3.5%</p> <p>Fistulae: 2%</p> <p>Note: No difference in complications rates was observed between the different skin flap techniques (labia minora flaps, gracilis musculocutaneous flaps, fasciocutaneous flaps, pudendal thigh flaps, and full-thickness skin grafts)</p> <p>Fistulae were only reported in studies with previous failed surgery, complications of necrosis and vaginal narrowing were also higher (respectively 9% vs 1.6% and 4.5% vs 2.4%).</p>	<p>16,4%</p> <p>Strictures: 4.5%</p> <p>Urinary tract infections: 4.5%</p> <p>Only in amnion group:</p> <p>Rectal injury: 2%</p> <p>Labial inflammation: 3%</p> <p>Only in buccal mucosa group:</p> <p>Vaginal bleeding: 9.5%</p> <p>Note: Urinary tract infections were higher in studies with previous treatment (after failed surgery 12.5%, after dilation 8% vs 3% after no previous treatment), but no differences were found regarding strictures (respectively 6.3% and 5.4%, vs 6.6%)</p>	<p>22,8%</p> <p>Vaginal, urinary tract and graft infections : 7%</p> <p>Strictures and contractures :5%</p> <p>Fistulae : 3%</p> <p>Hemorraghe and vaginal vault bleeding: 1%</p> <p>Total or partial graft loss < 1%</p> <p>Expulsion of the vaginal stent< 1%</p> <p>Rectal perforation < 1%</p> <p>Note: Studies in which women had failed surgery reported an equal amount of strictures (5.4%) and fistula (2-3%), but more urinary tract and vaginal infections (11% vs 3.6%) compared to studies in which women did not have surgery before.</p> <p>In studies with failed vaginal dilation before surgery, 3% of strictures were reported, and urinary tract infections and fistulae were present in respectively 2% and 3.5%.</p>	<p>19,3%</p> <p>Vaginal contractures: 7%</p> <p>Vaginal strictures: 4%</p> <p>Rectovaginal or vesicovaginal fistulae: 3%</p> <p>Note: complications were only reported in studies in which a previous procedure (vaginoplasty or dilation) had failed, after both short-term (< 6m) and long-term follow-up</p>
<p>1%</p> <p>[165]</p>	<p>0,6%</p> <p>[159]</p>	<p>3,7%</p> <p>[100,104,108,112,115,116,120,128,129,131,135,137,140,145]</p>	<p>11%</p> <p>Note: the majority (77%) already had previous surgery</p>
<p>82%</p> <p>Note: with wide range: 0% -33% in [50,171,174] to > 30% [41,168,169,172,173]</p>	<p>81%</p> <p>Amnion: 78%,</p> <p>Interceed:97%</p> <p>Buccal mucosa: 62%</p>	<p>83%</p> <p>Note: >75% sexually active in all studies, except in [104,127-129,135,153,309]</p>	<p>100%</p>

TABLE 3 Summary of surgical studies.

	Traction vaginoplasty	Intestinal vaginoplasty	Peritoneal vaginoplasty	Vulvovaginoplasty
Functional success	96%	90%	93%	95%
Definition	<p>Satisfactory intercourse without dyspareunia: 96%</p> <p>Satisfaction with non-coital activities and pleasure: 100% [232,238]</p> <p>Satisfying marriage or 'very good quality of sexual relations' [74,239]: 55-100%</p> <p>Significant increase of penetration and satisfaction scores for both partners [79,241]: 100%</p>	<p>Satisfactory intercourse without difficulties: 90%, [103,107,112,114,164,195,199,201,202,204-207,209,214,216-218,220,222,224,227-229]</p> <p>Married sex life: 100% [191]</p> <p>Satisfactory sexual activity: 85% [193,194,196,197,208,211,212,215,221,225,226,230,231]</p>	<p>Satisfactory coitus: 89.7% [62,64,114,118,181,182,185,187-189]</p> <p>Normal heterosexual relationships: 98% [60,180]</p> <p>Same FSFI scores as controls: 90% [118,183,184,190]</p> <p>Note: Only in one study results were 0% over the whole line [186]</p>	<p>Satisfactory intercourse: 95% [103,108,178]</p> <p>Intercourse without dyspareunia or vaginal dryness: 94%</p> <p>Satisfactory intercourse without partner complaints: 86% [99]</p> <p>Normal libido and orgasm: 100% [176,177]</p>
Postoperative dilation management	<p>A tendency of strictures could be overcome in patients who dilated [77,113,232,233], but occasional problems with disgust to dilator [232] and vaginal bleeding were reported [235]</p> <p>Anatomical success: 97%</p> <p>Sexual activity: 82%</p> <p>Functional success: 95%</p>	<p>Advised postoperative dilation in [107,112,114,164,191,195,196,199,207,208,214,215,220,222,224,225,230,231]:</p> <p>Anatomical success: 97%</p> <p>Sexual activity:70%</p> <p>Functional success:93%</p> <p>No recommended dilation: [193,197,201,206,209,213,217,221,226-228]:</p> <p>Anatomical success: 91%</p> <p>Sexual activity: 73%</p> <p>Functional success:90%</p>	<p>In [64,114,118,181,186,187,190], 50-100% of patients dilated for 2-12 months or were currently still dilating</p> <p>Anatomical success:87%</p> <p>Sexual activity:92%</p> <p>Functional success: 82%</p>	<p>In 8% [103,178] postoperative dilation:</p> <p>Anatomical success : 96-100%</p> <p>Sexual activity: 33-67% [103,178] to 100%</p> <p>Functional success: 95-100%</p>
Previous failed vaginal reconstruction	<p>Surgery: 0.4% [105,234]</p> <p>Anatomical succes:100%</p> <p>Sexual activity:83-100%</p> <p>Functional success:100%</p> <p>Dilation: 0.1% [242]</p> <p>The woman had neither sexual intercourse nor regular use of vaginal dilators as advised</p>	<p>Surgery (peritoneal or McIndoe): 10.5% [103,107,164,191,194,196,199,202,206,207,209,210,213,214,216,220,224-226,228,229]</p> <p>Anatomical success: 92%</p> <p>Sexual activity: 75%</p> <p>Functional success:90%</p>	<p>Surgery: 2.8% [62,64,183,186,184]</p> <p>Anatomical success:95%</p> <p>Sexual activity: 89%</p> <p>Functional success:92%</p> <p>Dilation: 1.5% [186]</p> <p>Anatomical success:NR</p> <p>Sexual activity: 0%</p> <p>Functional success: 0%</p>	<p>Dilation: 5% (99)</p> <p>Anatomical success: 100%</p> <p>Sexual activity: 100%</p> <p>Functional success: 86%</p>

Skin flap vaginoplasty	Modified McIndoe procedures	McIndoe procedure	Vaginoplasty without grafts
<p>93%</p> <p>Satisfactory coitus: 91% [41,50,165,166,175]</p> <p>Adequate erotic sensation: 100% [165,174]</p> <p>Satisfactory sex life (for both partners): 71-100% [166,168,169,172]</p> <p>Married women: 100% [173]</p>	<p>97%</p> <p>Pleasurable sexual intercourse, without dyspareunia and lubrications problems, and validated questionnaire scores comparable to controls [159,162]</p>	<p>89,5%</p> <p>(Amnion: 98%, Interceed: 93% Buccal mucosa: 88%)</p> <p>Satisfactory sexual intercourse (no dyspareunia), without partner complaints [99,153] nor differences with a control group [138]</p> <p>'Normal or successful sex life': 100% [134,136,147,149,309]</p> <p>'Satisfaction with sexual function: 67% -100 [100,109,146]</p>	<p>96%</p> <p>Satisfactory intercourse Satisfactory' [69]</p>
<p>Only in two studies reported [171,173], in which effect on anatomical and functional outcome is NR in [144]. In [135], vaginal length increased from 7cm to 9cm in those who dilated, with none of the women being sexually active</p> <p>Vaginal narrowing only in studies in which patients did not seem to dilate [165,167,172,174]</p>	<p>100% used dilators when not sexually active, but those who had poor compliance had strictures [155,158]</p>	<p>Failure to dilate: unsatisfactory (anatomical and functional) results in most [103,108,126,145,150,153], except [144]</p> <p>Most evident in young patients [137] and due to psychological reasons [150]</p> <p>40 % reported it was daily nuisance [151]</p> <p>Postoperative dilation (min 6 months): good results [140,142,143,151]</p> <p>Long-term use: permanence of satisfactory results in > 90% of cases [36,136,149]</p> <p>Contracture yrs after operation if no dilator was used in non-sexually active women [34]</p>	<p>Advised in [29,98,112,123], but 25% did not dilate properly</p> <p>Anatomical success: 58%</p> <p>Sexual activity: 73%</p> <p>Functional success: 92%</p>
<p>Surgery: 2% [167,171]</p> <p>Anatomical success: 95%</p> <p>Sexual activity: NR</p> <p>Functional success: NR</p>	<p>Surgery: 3% [54,155,160,164]</p> <p>Anatomical success: 100%</p> <p>Sexual activity: 56%</p> <p>Functional success: 93%</p> <p>Dilation: 16% [54,155,164]</p> <p>Anatomical success: 100%</p> <p>Sexual activity: 49%</p> <p>Functional success: 93%</p>	<p>Surgery: 3.4% [115,120,127,129,130,137,139,140,151]</p> <p>Anatomical success: 76%</p> <p>Sexual activity: 86%</p> <p>Functional success: 88%</p> <p>Follow-up: 6.5± 8.5 years</p> <p>Dilation: 4.6% [101,102,126,140,151]</p> <p>Anatomical success:92%</p> <p>Sexual activity:96%</p> <p>Functional success:78%</p> <p>Follow-up: 12.6 ± 9 years</p>	<p>Surgery: 7.7% [29,120,122,123]</p> <p>Anatomical success: 85%</p> <p>Sexual activity:80%</p> <p>Functional success: 71%</p> <p>Dilation: 8% [98]</p> <p>Anatomical success: 78%</p> <p>Sexual activity:72%</p> <p>Functional success: 100%</p>

TABLE 3 Summary of surgical studies.

	Traction vaginoplasty	Intestinal vaginoplasty	Peritoneal vaginoplasty	Vulvovaginoplasty
Mean Follow-up (years)	1.9±1.5 years (6 months-13 years)	4.3 ± 2.5years (1 month-24 years)	3.6 ±4.5 years (1 month- 18 years)	NR (6weeks – 25 years)
	Follow up < 1y [113,234,235] vs ≥ 1 y:	Follow up < 1y [193,194,210,212] vs ≥ 1 y:	Follow-up < 1y [60,64,185,189] vs ≥1 y:	Follow-up < 1y (6weeks-1 year) [108,178], vs ≥ 1y (2y- 25 years) [99,311]:
	Anatomical success: 100% vs 98%	Anatomical success: 100% vs 89%	Anatomical success: 100% vs 89%	Anatomical success: 100 vs 98%
	Sexual activity: 87% vs 95%	Sexual activity: 48% vs 67%	Sexual activity: 81% vs 93%	Sexual activity: 33-55% vs 100%
	Functional success: 100% (but with vaginal dryness) vs 89%	Functional success: 92% vs 87%	Functional success: 96% vs 90%	Functional success: 96% vs 90%

and buccal mucosa [55,163,164] 3) Skin flap procedures, including myocutaneous / fasciocutaneous flaps [50], pudendal thigh flaps [165,166], full thickness skin grafts from groins/buttock [167-169], labia minora flaps [41,170-174] or a mix of skin flap techniques [175] 4) Vulvovaginoplasty (i.e. Williams procedure) [99,103,108,176-179] 5) Peritoneal vaginoplasty (i.e. Davydov procedure) carried out laparotomically [60,62,180-182] or laparoscopically [64,114,118,183-190] 6) Bowel vaginoplasty with use of sigmoid colon, cecum or ileum [103,107,112,114,115,164,191-226], jejunum [227,228] or rectosigmoid [229-231] and 7) Traction vaginoplasty, consisting of the Vecchiotti technique or balloon traction [74,77-79,105,113,118,232-243]. Four studies [106,110,111,244] reported the outcomes of different vaginoplasty procedures combined. Seventeen studies also specifically mentioned the sexual long term outcomes in women without treatment (with or without coitus) [81-84,100,110,111,219] or after mixed treatment regimens (dilation, surgery, coitus or no treatment) [20,84,245-250]. Lastly, vaginal dilation studies are reviewed [23,74,84,85,93,98,99,101-104,106,107,109-

111,251-263].

To assess diagnosis related success rates (MRKH vs CAIS), we included in a separate analysis only studies in which the diagnosis of the participants was specified as either 46,XX MRKH (n=150 studies) or 46,XY disorders of testosterone biosynthesis or action (mainly CAIS) (n=22 studies) [54,79,82,100,104,110,135,141,153,155,197,199,203,219,233,241,244,247,249,254,260,261], including nine studies in which there was a mix of 46,XX and 46, XY, but differences between the two groups of women were separately discussed [54,82,135,153,155,197,199,233,260].

Tables 3-6 summarize the outcomes of the various surgical and non-surgical procedures and influencing factors regarding anatomical and functional success, clarified for each of the studies.

Skin flap vaginoplasty	Modified McIndoe procedures	McIndoe procedure	Vaginoplasty without grafts
1.6 ± 1.6 years (2 weeks- 7.8 years)	2.3 ± 3.7 years (1 month – 11 years)	4.0 ± 3.4 years (1 month-50 years)	1.2 ± 1.0 years (2months- 37 years)
Follow-up < 1y [41,50,174,173] vs ≥ 1y:	Follow-up < 1y vs ≥ 1y [116,159,162,164]	Follow-up < 1 y [36,104,120,150] vs ≥ 1y	Follow-up < 1 y [112,119,122] vs ≥1 y:
Anatomical success: 97% vs 93%	Anatomical success: 97% vs 76%	Anatomical success: 83% vs 86%	Anatomical success: 83% vs 95%
Sexual activity: 55% vs 88%	Sexual activity: 73% vs 93%	Sexual activity: 89% vs 90%	Sexual activity: 91% vs 81%
Functional success: 94% vs 93%	Functional success: 94% vs 84%	Functional success: 75% vs 88%	Functional success: 92% vs 88%

TABLE 4

Other influencing factors on anatomical and functional success rates in surgical studies.

Hymen	Psychological counseling	Timing of treatment	Diagnosis
<p>No studies specifically reporting the relevance of hymen in outcomes</p> <p>Presence hymen in [74,77,99,105 ,114,179,238,242]: highly variable results:</p> <p>Anatomical success: 81-100%</p> <p>Functional success: 55-100%</p>	<p>In ≥ 50% of studies: psychological interventions recommended, but no suggestions as to what type or when to deliver</p> <p>Psychological counseling (support group or individual counseling) [20,100,102,139, 151,178,206,217,232,235,239,24 5,246,248] vs no psychological counseling:</p> <p>Anatomical success: both 91%</p> <p>Functional success: 89% vs 82 %</p>	<p>Prepuberty vs puberty in same study (all bowel vaginoplasty):</p> <p>Anatomical success: both 100% [198], NR in [211,213]</p> <p>Complications: more common in puberty group [198,211,213]</p> <p>Functional success: unknown vs 0% [213] -100% [211], NR in [198]</p> <p>13-18 years vs >19 years (145) (McIndoe procedure)</p> <p>Anatomical success: 66.7 % vs 86.5%</p> <p>Complications (graft infections): 53% vs 15%</p> <p>Functional success: 60% (33% for 13-15 years, 85% for 16-18 years) vs 71%</p> <p>Older patients (>30 years): more disappointing, possibly because of an alteration of tissue elasticity [238] (Vecchietti procedure)</p>	<p>46,XX MRKH vs 46, XY CAIS</p> <p>Vaginal length before surgery: 1.4±1.1 cm vs 3.3 ±2.6cm (p= 0.03)</p> <p>Vaginal length after surgery: 9.0 ±1.9 cm vs 8.3 ± 2.9 cm</p> <p>Anatomical success: 92% vs 95%</p> <p>Sexual activity: 81% vs 73%</p> <p>Functional success: 90% vs 85%</p>

TABLE 5

Summary of vaginal dilation studies
[23,74,84,85,93,98,99,101-104,106,107,109-111,251-263].

N patients	888	Sexual activity	86%
	93% MRKH 7% CAIS or disorders of androgen or synthesis	Functional success	96%
Anatomical success	78% Note: No difference between MRKH & CAIS MRKH:78% CAIS:77.5%	Definition functional success	Successful sexual function or satisfaction with sex life not further specified: 96% [109,254,259,262] Comfortable coital and orgasmic function: 74% (range 0-100%) [23,84,85,93,99,101-103,106,251-253,255,256,260] with worst results (<50%) in [23,101,106] Based on standardized questionnaires (FSFI): sexual dysfunction in 100% [110] to no differences compared to controls in 25% [107,258]
Definition of anatomical success	>6cm: 78% [85,93,98,104,106,110,251,254,255,257,262] >7cm: 69% [23,260,263] >8cm: 33% [84,99,261] Max 25% contracture of the vaginal space: 43% [101] Not further specified: >90% [74,103,256,258]		11% [74,98,99,101,255,263] Reasons: Motivational problems [23,84,93,98,101,260] Poor compliance [23,85,252,262] Discomfort, pain (because of lichen sclerosis), vaginal prolapse or prior attempt at hymenectomy with secondary scar formation [23,74,101,256] Anatomical reasons: Absence of an appreciable dimple to begin with [103,256] or sturdy perineum [84,99] and multiple congenital abnormalities [262] Practical reasons such as lack of privacy [23,260] or travel distance to the clinic [106] Psychosocial reasons such as no or an unstable relationship at the time of treatment [84,255,260], cultural or religious beliefs [255,262], young age [101], learning difficulties [262], interpersonal conflict related to the treatment [262] and significant mental health problems [255,262] Not successful despite compliance with treatment recommendations [260,263]. Cause unclear (Note:Majority had MRKH, and thus likely a shorter vaginal start length)
Proportion of patients with complications and main complications	2% [23,74,253,263] Urinary complaints: 1% Pain and bleeding: 0.5% and Vaginal prolapse: 0.3% Note: No differences in frequency or type of complications between CAIS and MRKH	Failed dilation	
Mean follow-up (years)	4.2 ±3.4 years (0.3 months- 27 years) Follow-up < 1 year [25, 259] vs ≥ 1 year: Anatomical success: 88% vs 85 % Sexual activity: 91% vs 81% Functional success: 91% vs 85%		

TABLE 6 Influencing factors on anatomical and functional success rates in vaginal dilation studies.

Total duration of dilation treatment	Frequency of dilation	Age at start treatment	Vaginal length at start treatment	Hymen
<p>7.6 (± 4.8 months) (range 2days- 60 months)</p> <p>No association with anatomical success (R= -0.2, p>0.05)</p> <p>Dilation $\leq 6m$ [99,106, 258-260,263] vs $> 6 m$ [23,98,101,256,257]</p> <p>Anatomical success: 73% vs 63%</p> <p>Sexual activity: 86% vs 73%</p> <p>Functional success: 70% vs 57%</p> <p>Note: dilator treatment was stopped after maximum 6 months of compliance, irrespective of results, or because no further elongation of the vaginal length was observed in [98,99,263]</p>	<p>Frequency of dilation periods, not the total amount of minutes dilating per day (e.g. one time for 30 minutes vs 3 times for 10 minutes) positively associated with anatomical success (R= 0.514, p<0.05).</p> <p>Dilation 2-4x day [23,85,93,99,101,106, 252,259,262] vs 1x/d [84, 109,251, 260, 261,263]:</p> <p>Anatomical success: 76% vs 49% (p=0.06)</p> <p>Sexual activity: 80% vs 91%</p> <p>Functional success: 78% vs 84%</p> <p>Total duration of treatment: 7.6 \pm 5.4 months vs 5.1 \pm 0.1 months</p>	<p>Positive association with anatomical success (R= 0.6, p< 0.05)</p> <p>< 18 years [23,99,101,109,255,261] vs $\geq 18 years$ [85,98,106,251,252,254, 257-260,262,263]:</p> <p>Anatomical success: 47% vs 78% (p<0.05)</p> <p>Sexual activity: 77% vs 88%</p> <p>Functional success: 78% vs 76%</p>	<p>Positive association between start vaginal length and end vaginal length (R=0.69, p< 0.05)</p> <p>Start vaginal length not significantly correlated with anatomical success (R=0.61, p> 0.05)</p> <p>Larger vaginal start length associated with shorter duration of dilator therapy (R= -0.9, p< 0.05)</p> <p>Note: unclear how previous attempts at sexual intercourse might have influenced the start vaginal length, as this information was not reported in most studies [94]</p>	<p>Absence (252):</p> <p>Anatomical success: NR</p> <p>Sexual activity:NR</p> <p>Functional success:92%</p> <p>Hymen, hymenal remnants or pseudo-hymen in (74,85,99,251,256) vs studies in which parameter was unknown:</p> <p>Anatomical success: 68% vs 71%</p> <p>Sexual activity: 89% vs 71%</p> <p>Functional success: 92% vs 67%</p>

Psychological counseling	Diagnosis	Maintenance dilation
<p>In 63% of studies</p> <p>Definition:</p> <p>Emotional support from sensitive physician, not necessarily psychiatric care: [103]</p> <p>Meeting with successfully treated former patient: [93,253]</p> <p>Patient and family counseling: [101]</p> <p>Input from nurse specialist and/or psychologist: [23,110,253,257-260,262,263]</p> <p>Psychodramatic therapy: [254]</p> <p>Support group meetings: [255]</p> <p>Not further specified: [106,251,256,261]</p> <p>Psychological counseling vs no psychological counseling:</p> <p>Minimal amount of months dilating: 3.8 \pm 3.2 months vs 1.4 \pm 0.4 months, p<0.05</p> <p>Anatomical success: 74 % vs 63% p>0.05</p> <p>Functional success: 70 % vs 77% p>0.05</p> <p>Successful completion of treatment not dependent on psychological counseling [106] and not different between inpatients or outpatients [106]</p> <p>The quality of life was high in groups who attended counseling and those who did not [270]; however, mental health was poor compared to physical health [111] and scores for sexual depression, sexual anxiety and fear of sexual relations remained high compared to groups of non-affected women [111]</p>	<p>46,XX MRKH vs 46,XY CAIS</p> <p>Start vaginal length: 3.1 \pm 0.5 cm vs 4.5 \pm 2.1 cm</p> <p>End vaginal length: 6.8 \pm 1.8 cm vs 8.2 \pm 0.8 cm</p> <p>Anatomical success: 70% vs 79%</p> <p>Sexual activity: 76% vs 42%</p> <p>Functional success: 73% vs 44%</p>	<p>No studies compared women who did and did not maintain dilation when not being sexually active regarding functional or anatomical outcomes.</p> <p>Only in two studies [85,260] women without coitus were still dilating at the time of follow-up:vaginal length: 6.5-8.5cm</p> <p>Note: unclear whether women who used dilators had smaller vaginal lengths vs those who were sexually active</p> <p>Possibly, sexual activity further lengthens the vagina [111], and a combination of dilators and intercourse improves both anatomical and functional success rates [84,106,255]</p> <p>Maintenance dilation recommended: 2-3 times/week when no regular coitus [23,98,101,109,251,254,256,260]</p> <p>Motive: to avoid shrinkage of vagina</p> <p>No further dilation recommended [253,262]</p> <p>Motive: when embarking in a relationship after a substantial absence of dilators or intercourse, women very quickly regain their original length, eventually after dilating for a short time [262]</p> <p>Anatomical success: NR</p> <p>Functional success: only assessed in small subgroup of women, reported in [258], with sexual problems (difficulties with maintaining lubrication, pain during intercourse)</p>

Practice informing Theory

Establishing the risk/efficacy profile of the different surgical and non-surgical techniques, we evaluate if vaginal dilation, proposed as first line technique is justified on an evidenced base.

Comprehensive synopsis of main outcomes

Anatomical success and complications

Anatomical success, referring to an adequately sized vagina, seems to be in most studies defined on the basis of two (related) parameters. The first is vaginal length, agreed upon to be at least 6 cm. The second is an absence of complications (and in particular contractures affecting vaginal length, or scar formation), considered to be associated with a cosmetically pleasing result (in the rule according to the clinician's perspective).

Reference values for normal vaginal length were previously described to be 7 to 13 cm (mean 9.25 ± 1.56 cm) [264]. Non-surgical vaginal dilation treatment has been shown to normalize vaginal length in at least 75% of women, irrespective of karyotype or underlying diagnosis. However, when anatomical success was defined as a length of ≥ 7 cm, vaginoplasty techniques alike yielded significantly higher anatomical success rates ($> 90\%$ vs. 78% after vaginal dilation).

In contrast, complication rates were significantly lower within the vaginal dilation series as compared to the published surgical series (2% vs. $6-25\%$). Main complications in the vaginal dilation group were urinary complaints and infrequent pain and bleeding ($\leq 1\%$). Similar complications and rates were found with use of traction vaginoplasty techniques, with the exception of bladder trauma (2%) being more surgery-prone.

Complications of the majority of surgical techniques involving a dissection between the rectum and bladder, were vaginal strictures, contractures or stenosis ($4-9\%$), urinary tract infections ($4-7\%$), vesicovaginal or rectovaginal fistulae ($1-3\%$), and rectal or bladder perforation ($1-4\%$). In the case of skin grafting, extra complications included (partial) necrosis of the graft ($1-3.5\%$) and hair growth in the neovagina ($1-6\%$). Persistent discharge ($2-3\%$) was only apparent after peritoneal and bowel vaginoplasty; in the latter only vaginal prolapse was also common (3%). In general, reported complications rates were higher in studies where previous treatment (surgery or dilation) had failed, and even higher after surgery as a first line treatment compared to after dilation for most main complications associated with the respective techniques.

Functional success

There is more variability regarding the definitions of functional success, although most seem to include the notion of 'full genital performance during heterosexual intercourse as the essence of sexual functioning' [265]. When referring to satisfactory coital function, functional success for vaginal dilation techniques is at least 74% . This is significantly lower as compared to vaginoplasty studies, reporting success rates between $90-96\%$. When functional success is defined as 'satisfaction with sex', including non-genital sex, differences disappear (93% vs. 96%). Overall, in both vaginoplasty and vaginal dilation studies, the terms "active sex life" or "satisfied" were often not operationally defined, so it is left unclear as to what was precisely meant by these terms [266]. In early reports, as well as reports from developmental non-Western countries, it was not uncommon to let functional success depend on the ability of the woman to provide pleasure to the partner. This suggests

that outcomes in the form of 'satisfaction' should not be taken at face value but, rather, interpreted critically in the light of historical and cultural contexts. Recently available standardized questionnaires on sexual function, such as the Female Sexual Function Index (FSFI) [267] can reliably assess female sexual wellbeing and can provide an alternative way to compare the functional outcomes of different vaginal reconstruction options. Table 7 provides an overview of the studies with FSFI results. Mean total FSFI scores (range 0-36) indicate in general, weaker functional scores, after both vaginal dilation (25.2 ± 4.5) and vaginoplasty (28.03 ± 3.0), compared to the standardization population (30.2 ± 6.1). Lower scores are evident in four of the six subscales: arousal, lubrication, orgasm, and pain during intercourse ($p < .01$), with no differences for desire or satisfaction with sex life and/or relationship. As sexual distress is not assessed in most studies - a criterion essential to diagnose a sexual dysfunction according to the Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR), the prevalence of sexual dysfunctions remains unclear. No differences are found between different vaginoplasty methods, but the samples are small. Of interest, women who were medically treated (surgery or vaginal dilation) did not have better indicators of sexual wellness or sexual function than those who were untreated, suggesting an important role of other factors than treatment, affecting sexual well-being in these women. Studies investigating other quality of life parameters suggested that psychological variables such as depression symptoms [231,260,268], doubts about female identity [196,207,244] and body image problems [102] are still prevalent after treatment and that neither surgical or non-surgical options, even if satisfactory, solve all problems [107]. It is interesting in this respect, that women who had undergone treatment

still perceive their vagina as abnormal [247]. The repercussions of a negative genital image on sexual satisfaction have been shown in the general population [269]. Stable relationships and a good communication between partners were further suggested to be crucial contributors to overall sexual satisfaction, independent of neovaginal length or treatment [84,190,270]. As such, the importance of vaginal depth for satisfactory outcomes and the general relationship between anatomical and functional success remains difficult to determine [151,240,260,271]. With regard to the FSFI evidence, sexual problems were not more common in studies in which a mean vaginal length of less than 6.6 cm was reported. However, it is unclear from these studies if individual women with a smaller vaginal length were sexually active and had lower functional outcomes. Methodological problems have been noted with the FSFI when women report not to be sexually active in the last 4 weeks preceding the survey [272]. In addition, standard instruments, such as the FSFI, might not be well-tailored to assess the specific situation of women with vaginal hypoplasia, suggesting that an improved research methodology is needed to fully assess the impact of the involved conditions and its management on sexual experiences and wellbeing.

Quest for the optimal vaginoplasty technique

Based on the currently available evidence, it remains difficult to determine the superiority of one vaginoplasty technique over the other. This is due to problems including the heterogeneous group of patients, and the unavoidable reporting bias of surgeons towards the techniques they are mostly experienced in. Another problem relates to the lack of concordance in recording the long-term outcomes of the different

TABLE 7

Female Sexual Function Index values after alternative vaginoplasty techniques, vaginal dilation and no treatment in women with vaginal agenesis.

Ref	[267]	[110]	[111]	[110]	[111]	[271]	[125]	[114]
N	131	9	10	15	7	18	7	11
Diagnosis	Control	46,XY DSD	MRKH	MRKH & 46,XY DSD	MRKH	MRKH	MRKH	MRKH
Study	Control	No treatment	No treatment	Bowel [n=2], Skin grafts [n=11], Vecchietti [n=2]	Vecchietti [n=4], McIndoe [n=1], bowel [n=1] and skin flap [n=1]	Wharton	Wharton	Bowel
Desire	4.1 (1.1)	3.8 (0.6)	4.9 (1.0)	3.9 (1.2)	3.9 (1.3)	3.6 (1.2-6)	4.3 (1.3)	4.2 (0.2)
Arousal	5.0 (1.0)	4.8 (1.2)	5.2 (1.0)	4.3 (1.3)	4.8 (1.0)	4.5 (2.4-6)	5.4 (0.5)	4.2 (0.1)
Lubrication	5.5 (0.9)	4.8 (0.9)	4.9 (1.3)	3.5 (1.8)	5.3 (0.7)	5.7(1.2-6)	5.1 (1.5)	4.2 (0.1)
Orgasm	5.0 (1.2)	4.9 (1.0)	5.1 (1.1)	4.0 (1.3)	5.0 (0.8)	4.2 (1.2-6)	4.9 (1.0)	4.1 (0.3)
Satisfaction	5.1 (1.2)	4.9 (1.0)	5.6 (0.4)	4.5 (1.2)	5.5 (0.8)	5.6 (2.4-6)	5.1 (1.5)	4.4 (0.3)
Pain	5.5 (1.0)	5.0 (0.7)	NR	4.1 (2.2)	NR	4.8 (0-6)	5.1 (1.1)	4.2 (0.3)
Total FSFI	30.2 (6.1)	27.6 (4.8)	NR	23.9 (5.7)	NR	28.2 (10.8-36)	29.9 (4.3)	24.8 (1.2)
% Sexual distress	NR	55.6	NR	57.1	NR	NR	NR	NR
% FSD	NR	50	NR	62.5	NR	80	NR	NR
Vaginal length (cm)	9.6 (1.5)	8.9 (2.6)	4.8 (2.6)	9.1 (2.7)	7.4 (2.6)	6.3 (4.5-12)	8.3 (7-10)	12.6 (0.4)
Ref	[184]	[118]	[243]	[77]	[110]	[111]	[107]	[258]
N	25	40	23	27	8	20	5	56
Diagnosis	MRKH	MRKH	MRKH	MRKH	46,XY DSD	MRKH	MRKH	MRKH
Study	Davydov	Vecchietti	Vecchietti	Vecchietti	Dilation	Dilation	Dilation	Dilation
Desire	4.4 (0.9)	4.2 (0.9)	4.5 (0.7)	4.4 (0.8)	2.8 (0.8)	3.5 (1.2)	4.7 (1.3)	3.7 (1.0)
Arousal	4.4 (1.1)	4.6 (1)	5.9 (0.8)	4.8 (0.8)	4.3 (1.1)	3.6 (1.7)	5.1 (1.0)	4.0 (1.4)
Lubrication	4.5 (1.4)	4.5 (1.0)	4.3 (0.8)	5.0 (0.8)	4.8 (1.3)	4.2 (1.7)	5.1 (1.1)	4.2 (1.4)
Orgasm	4.1 (1.3)	4.4 (0.9)	4.6 (0.9)	4.6 (1.0)	4.3 (1.6)	3.32 (2.0)	4.8 (0.9)	3.9 (1.5)
Satisfaction	4.6 (1.1)	5.2 (1.2)	5.2 (0.6)	5.4 (0.6)	4.4 (1.0)	4.0 (2.0)	5.4 (1.2)	4.3 (1.2)
Pain	4.4 (1.4)	5.2 (1.0)	4.7 (0.7)	5.0 (0.9)	2.4 (2.5)	NR	5.2 (1.1)	3.6 (1.7)
Total FSFI	26.5 (5.6)	30.2 (1.0)	30.1 (3.8)	29.0 (3.2)	21.6 (2.5)	NR	30.3(6.2)	23.7 (4.3)
% Sexual distress	NR	NR	NR	NR	43	NR	60	NR
% FSD	72	NR	NR	55	100	NR	25	NR
Vaginal length (cm)	7.2 (1.5)	7.5 (1.1)	8.8 (1.1)	6	7.3 (1.3)	5.1 (2.6)	NR	NR

Data presented as mean (SD). Used abbreviations: MRKH: Mayer-Rokitansky-Küster-Hauser syndrome, CAIS: Complete Androgen Insensitivity Syndrome; DSD: Disorders of Sex Development, FSFI: Female Sexual Function Index (range 0-36, domain scores 0-6), FSD= Female Sexual Dysfunction, Ref= Reference, NR= Not Reported

[107]	[231]	[207]	[162]	[159]	[114]	[118]	[186]	[190]
35	45	8	7	5	21	40	6	31
MRKH	MRKH	MRKH	MRKH	MRKH	MRKH	MRKH	MRKH &CAIS	MRKH
Bowel	Bowel	Bowel	Oxidized cellulose	Amnion	Davydov	Davydov	Davydov	Davydov
4.4 (0.9)	NR	5.0 (0.5)	NR	4.9 (1.2)	4.3 (0.1)	4.3 (0.7)	3.9 (1.2)	3.8 (0.9)
4.7 (0.7)	NR	4.9 (0.3)	NR	5.0 (0.8)	4.2 (0.1)	4.7 (0.8)	4.0 (1.1)	4.2 (0.8)
5.2 (0.9)	NR	5.0 (0.9)	NR	4.0 (0.7)	4.0 (0.2)	5.1 (0.6)	4.4 (1.0)	5.1 (0.6)
4.4 (1.1)	NR	4.7 (0.9)	NR	5.5 (1.0)	4.0 (0.3)	5.0 (0.6)	3.3 (1.6)	3.8 (1.2)
5.4 (0.6)	NR	5.6 (0.3)	NR	5.3 (1.4)	4.5 (0.2)	4.8 (1.5)	4.0 (1.8)	4.5 (1.1)
3.9 (1.2)	NR	4.8 (1.0)	NR	5.3 (1.8)	4.4 (0.3)	4.7 (1.0)	1.9 (1.9)	4.7 (1.2)
28.0 (3.1)	28.9 (11.5-35.7)	30.0 (3.0)	32.5 (1.1)	30.0 (6.9)	25.3 (0.5)	31.8 (0.8)	21.4 (5.3)	26.1 (4.8)
85	NR	NR	NR	NR	NR	NR	NR	NR
30	14,8	12,5	NR	NR	NR	NR	75	71
NR	13	NR	9.6 (2.1)	9.8 (1.7)	11.9 (1.2)	8.5 (1.6)	NR	6.3 (1.3)

approaches. A follow-up of less than 1 year seemed to be associated with less sexual activity and functional success, but the effect on anatomical success is unclear. It is possible that the severity of dyspareunia or adequate lubrication are inversely proportional to the time since operation, resulting from the progressive epithelization of the neovagina, a process that is almost complete after one year. Despite significant advances over the past decades in surgical techniques and improved knowledge of the anatomy and innervation of the female genitalia, there is at present no evidence that newer techniques improve long-term outcomes.

In addition, anatomical (based on vaginal length) and functional success (based on coital activity) were not significantly lower in studies in which previous surgery or dilation had failed, although there was a

trend towards more complications in these studies. It could also be that patients in whom previous treatment had failed were those with more complex inherent anatomical features to begin with. As such, it remains unclear if previous attempts at vaginal reconstruction jeopardize surgical success.

Moreover, there is a lack of a standardized approach in reporting the results of postoperative dilation management. In those studies that mentioned a proper postoperative dilation regimen, anatomical success rates were in general higher and contractures and strictures (between 5-7%) could be overcome, even in bowel vaginoplasty where postsurgical dilation is generally said not to be necessary. Therefore, maintenance dilation seems to have an additive value, either with regular dilation or coital activity. Nuancing the need for maintenance dilation

however, success rates are in general also high in studies without postoperative dilation. Finally, from the available evidence, it remains unclear if age at surgery is related to the outcomes or if there exists an optimal time window for the most favorable anatomical outcomes. The majority of women felt however that the appropriate time to undergo surgery was in adolescence [206], seeming to underline that interventions can only be undertaken when the patient is emotionally mature and ready to engage in sexual activity [103,113,121,145,159] or marriage in some cultures [126,158]. It has also been suggested that a vagina is not necessary for a young girl prior to sexual intercourse [6] and that early psychological problems related to regular postoperative dilation can be minimized by delaying surgery [202].

In sum, the quest for the optimal surgical method continues, as no technique is completely without failure risk, and some have (still) high complication rates. In general, however, traction vaginoplasty seems to have the highest anatomical (≥ 6 cm, 99%) and functional success rates (satisfactory coitus, 96%), whereas both split-thickness and full-thickness skin graft procedures and intestinal and peritoneal procedures have the lowest outcomes (83-95% anatomical success and 90-93% functional success). Traction vaginoplasty also has the lowest complication rate, suggesting it to be an appropriate surgical technique either as first line treatment or after failed vaginal dilation.

Effectiveness of vaginal dilation as first-line technique: A time-honored practice?

Combining data from published non-surgical series allows some important insights into relevant factors which may impact on daily

clinical vaginal dilation practices and on decision-making in individual cases.

Anatomical success

Surprisingly, start vaginal length was not significantly associated with anatomical success. This refutes the claims that success can only be achieved in women with an existing vaginal dimple of 2-3 cm [99]. For this reason, women with CAIS and androgen synthesis disorders, who generally have a larger starting vaginal length, do not seem to have an advantage over women with MRKH. Of note, women above 18 years of age at the start of treatment had significantly higher anatomical success rates, which is probably related to motivational reasons. Dilation has to be actively managed by the patient and a sustained effort is required, while progress is slow [273]. Therefore, we suggest dilator treatment only in women in whom motivation is high, for example when being in a current relationship or wanting to engage in sexual activity, which has also been shown to be an important factor in postoperative dilation management. With regard to frequency and duration of dilation treatment, it becomes clear that the best anatomical results were obtained when the frequency of dilation periods was high, suggesting that regular stretching is more beneficent than the actual total time of stretching. Total duration of dilator treatment seems not to be related to anatomical success. Although some, including our own research group [93,251,274], suggested that the highest gain in vaginal depth was reached within 4-6 weeks, and that the gain thereafter is minimal, it is unclear from the available data if there exists an optimal window for gaining length. Unfortunately, despite compliance, which can be increased with psychological support [257,262], conservative therapy can fail [111,263]. No conclusions so far can be

drawn on the presence or absence of the hymen relating to failure of treatment [275], nor whether perineal skin is different from the vagina in its elastic characteristics. However, failed dilation therapy does not preclude anatomical (nor functional) success if vaginoplasty afterwards is necessary. Overall, complication rates were significantly lower within the vaginal dilation groups as compared to the different vaginoplasty techniques (2% vs. 6-25%), being its major advantage, but should be followed-up in the long term as well. Displacement of the bladder neck might occur during vaginal lengthening, which may affect bladder function and cause urinary symptoms [263]. Also, the creation of a vagina in this fashion does not preclude vaginal disease, and cases of vaginal intra-epithelial neoplasia and vaginal carcinoma have been described [276]. To date fifteen (case) reports of vaginal prolapse have been reported [74,140,177,277-283] which is still considerably less frequent than reported prolapse after vaginoplasty (e.g. bowel vaginoplasty: 3%). Finally, although no randomized control data exist regarding maintenance dilation, the available evidence suggests that continued dilation is needed to maintain patency in periods of coital inactivity.

Functional success

From the available evidence, total duration of vaginal dilator treatment might have a detrimental effect on sexual activity levels and functional success rates, suggesting that dilation therapy should perhaps be stopped after 6 months of compliance, moreover because anatomical success seems thereafter not affected. While the reasons for decreased functional success are not entirely clear, it is possible that the emotionally charged nature of the dilation process may make it difficult for women to keep separating on the long term medical dilation treatment from 'real

sex' - with a possible disgust or withdrawal from sexual activities. Especially younger women (< 18 years) might be more vulnerable to such difficulties, as motivational issues are already more prevalent in this age group. This does, however, question the possible impact of the recommended maintenance dilation on psychological grounds. Furthermore, as in surgical series, the importance of assessing functional success on the long-term is confirmed, as there seems to be a decrease with a longer follow-up period. Although some researchers have suggested that psychosexual functioning levels and coping abilities improve with time [20,220], others – including our research group- have indicated that women continued to feel far from normal in the areas of sexual potency and reproduction (i.e. perceived loss of social role as potential mother, loss of sense of equality with peers), contributing to high emotional distress, in different ways and at different times [111,274,284]. Continued long term follow-up acknowledges the importance of developmental-temporal factors to the distress.

Given the physical and psychological challenges then of this lifelong condition, it is unlikely that these women will achieve complete normal sexual function [111]- whatever enlargement technique is used. Interestingly, however, women simultaneously reported relatively high levels of sexual difficulties and sexual 'satisfaction'. Problems related to the definition of 'satisfaction' with sex – for whom and with what (i.e. intercourse) - were already mentioned. In addition, women with MRKH or CAIS might have learnt to be 'satisfied' with barely satisfactory sexual experiences – that is, the women might have felt that sexual difficulties were to be expected and thus that they should not be dissatisfied [247]. Although this raises concerns about the powerful

influence of the current cultural context in which (sexual) difference is still taboo, it also questions how treatment success should be further approached [285]. Moreover, as it was shown in therapeutic work that few women with vaginal hypoplasia allude to pleasure as a reason for wishing to engage in sex but rather reasons related to 'feeling' and 'acting' normal through intercourse [286], assuming intercourse will be a central therapeutic goal for these women is likely to give misleading impressions of what constitutes a successful treatment outcome [287]. A key message here is that - where earlier approaches may have considered 'normative' functions of the genitalia and relative absence of patient complaints as indicators of good outcomes-, future approaches need to reformulate outcome evaluation and specifically raise a wider range of psychosexually oriented questions [286,287]. A simple questioning on sexual 'satisfaction' is not a useful measure in these diagnostic groups.

Pitfalls in treatment success

Psychological profile and the effect of counseling

In general, an inaccurate evaluation of the emotional status before any treatment is suggested to lead to a poor result [103,142], as it was made clear that most women were struggling with body image [102,107], or felt anxious, socially unattractive, depressed or lacked self-control [115,232,245,246]. Psychological interventions, such as cognitive behavioral group therapy in these women have been shown to be effective in reducing anxiety and feelings of depression [288-290]. However, despite the expectancy that the probability of further positive, functional or anatomical, outcomes are maximized with psychological counseling, this could not be confirmed with the

current data. The self-esteem, knowledge, or interpersonal skills built up in therapy or by peer support did not seem to be - both immediately and on the long-term - translated in satisfying sexual relationships [273,274,289]. Despite counseling, some still felt depressed and extremely insecure relating to others [20,245], which is possibly also reflected in rather low sexual activity rates in any treatment paradigm (85%). Findings from our group even showed an unexpected increase in emotional difficulties after a standardized dilation program with input from a clinical psychologist [274]. The majority of participants refused psychological counseling after a few sessions because contact with psychologists was said to engender powerful ambivalent emotions of abnormality as well as feelings of failure in not coping with the condition. Contact with peers was said to be motivating during treatment, but was further limited to discussion of subjects related to the shared condition [19,274]. While the move to including psychological input in clinical teams specializing in disorders of sex development (DSD) is significant, it is still open to negotiation how the psychologist's role in certain situations allows for substantive and worthwhile contribution. It is of utmost importance to gain additional experience concerning the format of acceptable and efficient psychological care and how to integrate it in the regular medical follow-up [285].

Diagnosis effects

The present review further underlines the importance of detailed reporting on diagnosis, as there are differential outcomes for women with 46, XY disorders of androgen action or synthesis (mainly CAIS), and 46, XX MRKH.

Although no differences in anatomical outcomes were found, women with a 46,XY karyotype have a significantly larger start vaginal depth compared to 46,XX women (e.g. [260]). The question arises as to whether this is the reason why the majority of women with CAIS do not opt for vaginal reconstruction interventions. The prevalence of vaginal hypoplasia within a CAIS population has not extensively been studied. Due to the action of fetal testicular antimüllerian hormone on the developing müllerian ducts, it is hypothesized that CAIS might be associated with 25% to 33% loss of vaginal length [247]. In this review, however, despite a wide range, an average loss of 66% was shown in women with CAIS who had no treatment or sexual activity yet (3.8cm \pm 2.2 vs. 9.6 \pm 1.5 cm in non-affected women[264], contradicting previous studies [100,219,247,249], and perhaps indicating that only those CAIS women with the shortest start vaginal length and/or who have not been sexually active yet seek medical advice. After treatment, length of the neovagina is not necessarily proportional to satisfactory outcomes and this topic should deserve more detailed investigation.

In contrast, functional success rates, with all reconstruction techniques, were in general significantly lower in women with a 46, XY karyotype compared to women with 46, XX. A high rate of impairment of desire and arousal and dyspareunia in women with CAIS has been shown before[291], which could be due to the complete lack of androgens affecting libido and orgasm [100,247] and/or lack of androgen imprinting on the brain [291]. Also, gonadectomy and the subsequent estrogen substitution therapy is sometimes said to lead to insufficient vaginal lubrication [263]. However, this information is not recorded in most studies and it is difficult to surmise how it might have impacted upon the results.

Theory informing Practice

What emerges from this overview of selected publications is that evidence for both physical and psychosocial outcomes in women with vaginal hypoplasia remains incomplete and uncertain. Some fundamental questions about whether for instance treatment harms genital sensitivity or produces acceptable cosmetic results according to the affected women themselves are still disputed [292]. How these issues interplay in individual situations may perhaps never be resolved definitively because the answer will always depend on too many variables: the woman's individual anatomy and physiology, the clinician's skills and judgment, the quality of post-operative care, the psychosocial resources available and their perceived usefulness, relationships within the family and the deeply subjective nature of satisfaction with sexual sensation and function as well as cosmetic outcomes [293]. Women must have access to this balanced information, in order to fully weigh the potential risks and benefits of treatment. Furthermore, as the medical literature lacks high quality comparative outcome studies, no evidence-based treatment guidelines can be provided. Despite limitations, with the obtained evidence concerning the results of current techniques, we are in a position to advance thinking and practice in this field in various ways.

Recommended treatment algorithm in women with vaginal hypoplasia

Figure 2 summarizes the treatment decision tree in women with vaginal hypoplasia. Because of the physically low complication rate and an overall success chance of 75%, vaginal dilation treatment (either with or without intercourse) as a first line choice seems to be justified if women had no prior treatment (i.e. reconstructive surgery).

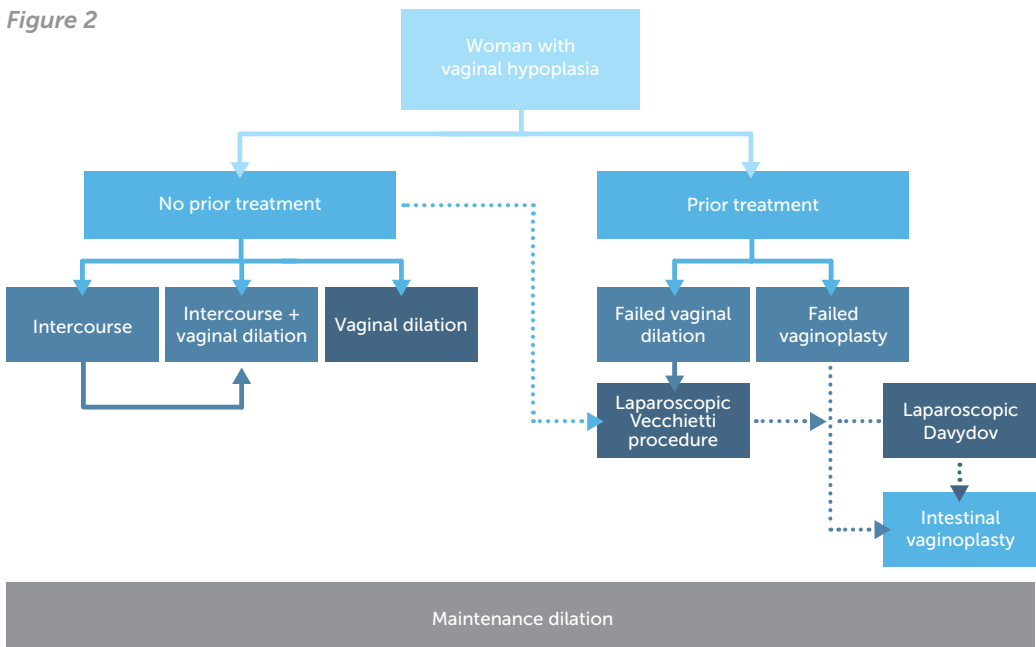
Dilator treatment has not only benefits (e.g. preservation of vaginal tissue), but also barriers, which should not be minimized [273]. Vaginal dilation is time consuming and some patients find it distressing. Overall, the laparoscopic Vecchietti procedure, becoming more and more available in specialized centers, is considered an appropriate surgical option for the creation of a neovagina in patients who are poorly compliant and failed dilation therapy, or for those who do not want to start with vaginal dilation therapy. It is difficult to justify proceeding directly to some of the more complex techniques such as intestinal vaginoplasty with its associated high morbidity and long term side effects. These techniques can have a role in complex patients with previous extensive abdominal surgery, particularly those cases where there is significant scarring from previous surgery. Choosing the right operation in patients who require surgical reconstruction is integral to success. Moreover, it should be noted that the first attempt at any neovaginal

reconstruction has the best chance for success and every failed attempt leaves its traces and should be avoided. Therefore, it is crucial to resolve whether the patient has the mental resources, including perhaps certain personality traits, necessary to cope with the management of her condition in an effort to optimize therapeutic success [246]. Regardless of the vaginal reconstruction technique used, patients should be managed in specialized centers by a multidisciplinary team, where there is adequate emotional and psychological support available. Specialist units should be able to offer all treatment options and also have a duty to provide detailed long-term outcome data [17,21].

*New ideas from old concepts:
Vaginal dilation treatment
in clinical practice*

A practical protocol, informed by the literature and our own experience, for the management of women with vaginal hypoplasia is provided

Figure 2



in *Figure 3* (adapted from [274]). A further individual-based approach with skillful evaluation and negotiation with the patient can help to prevent vaginal dilation treatment failure and limited compliance. *Figure 4* illustrates how a vaginal dilation user model-based on a health belief model of behavior change [294], and on therapeutic interventions within a framework of cognitive-behavioral psychology and motivational interviewing [260,295,296] - would incorporate the influencing factors identified in this review. It provides useful pointers for understanding compliance difficulties with vaginal dilation and suggests that vaginal dilator use can be increased by:

A accounting for modifying factors

before and during the course of treatment, such as diagnosis adjustment. Women may experience a range of symptoms consistent with posttraumatic stress disorder. Psychological difficulties may act as a barrier to dilator treatment, or conversely, the dilator treatment may exacerbate pre-existing psychological symptoms [262] and must be delayed in the presence of psychological disorders (e.g. depression) [257]. The further timing of treatment should be planned on an individual basis as there is considerable variation in psychosocial development and maturity. High motivation to start with sexual activity or a current relationship will benefit dilator use. It is suggested not to start dilator treatment before the age of 16 years, due to motivational issues, which are more prone in adolescence [257]. Also, younger women may be less familiar with their genitalia [274] or might have anxious reactions toward the idea of inserting an instrument in the vulvar region [257], the more so when dilators are perceived as highly sexualized objects [297]. For some women, negative genital perceptions may also be exaggerated by an idealization of 'normal', and negative social

comparisons may raise the anxiety further [298]. Ideally, where appropriate, patients should be encouraged to access support from their personal contexts, as it enhances self-management in many chronic diseases [299]. However, because of the intimate nature of the syndromes, many women feel they cannot talk about it with family or friends and wish to hear about other patients' experiences. Support groups can provide a useful resource for sharing concerns or motivation during treatment. Regular appointments with a clinical psychologist, nurse specialist and/or physiotherapist can provide opportunities for addressing other implications of the diagnosis, such as its effect on fertility or body/genital image and for problem-solving practical difficulties

B providing stronger cues to action, such as additional information (e.g. websites, easy-to-follow instructions boosting patient's confidence to correctly use the dilators), and easy dilator provision (e.g. through the hospital pharmacy). Also, regular vaginal examinations by clinicians and personal experience of anatomical and functional success can act as confirmation of the efficacy of dilators. However, as vaginal size in non-sexual situations can be a poor predictor of pleasurable intercourse upon sexual arousal, clinicians should reduce the level of preoccupation with vaginal size solely and also emphasize sexual enjoyment.

C emphasizing the benefits (e.g. sexual function is possible by achieving greater vaginal length) **and overcoming the barriers** (e.g. having a sense that it is not right or natural to touch genitals or treatment triggers flashbacks to previous traumatic experiences such as unsuccessful attempts at intercourse) [296]. The extent of a positive attitude towards treatment (i.e. benefits outweighing the barriers) and the perceived

Figure 3

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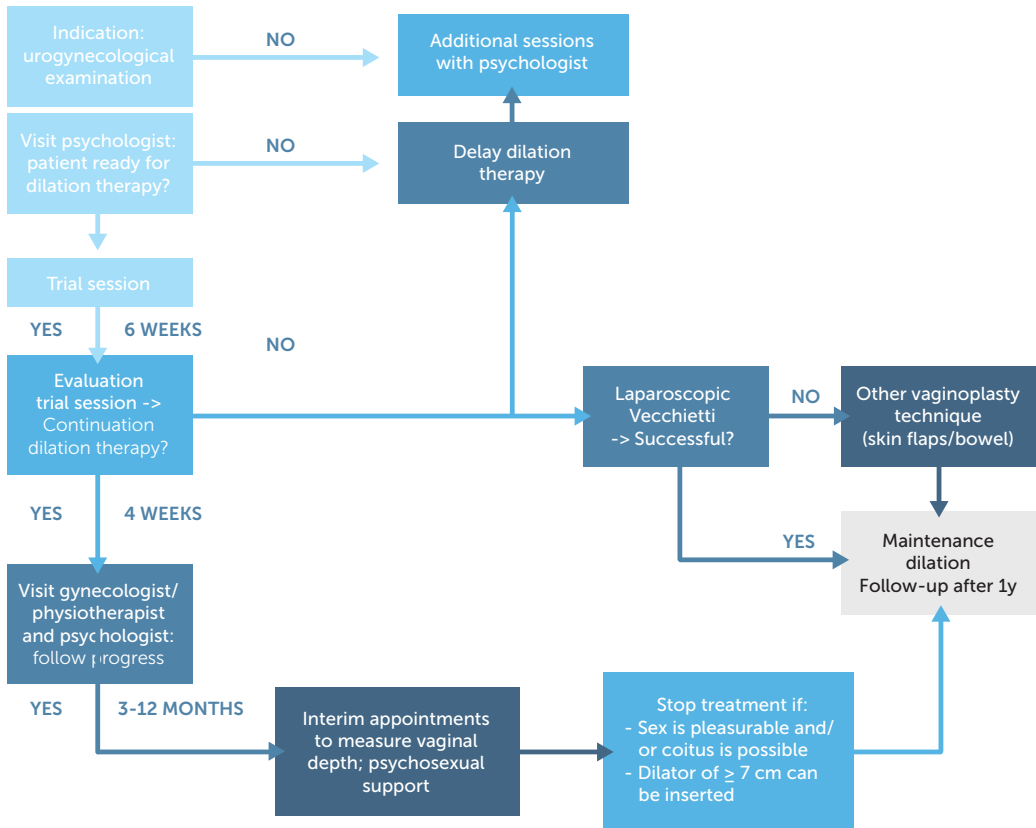


Figure 3. Treatment protocol. Vaginal examination by a gynecologist is followed by at least one therapy session by a clinical psychologist/sexologist to identify any contraindications to using dilators (e.g. depression) and maturity of the patient, optimizing the probability of a positive outcome of treatment. Potential benefits of dilation as perceived by the patient as well as potential obstacles associated with implementing the regime are elicited. The women are encouraged to solve problems around any identified difficulty. Once an initial trial of dilation treatment uptake is agreed upon, standardized spoken and written instructions on vaginal dilation are given and patients are shown by a specialized physiotherapist how to apply gentle pressure to the vaginal dimple using dilators for 20 minutes daily, 7 days a week. The dilators range upward gradually to the size of a man's fully erect penis. The women are asked to self-monitor their practice and associated pain/discomfort ratings in a diary specially designed for this purpose, which includes extra information on pelvic floor muscle relaxation, genital anatomy, dilator use and pain relief. Moreover, they are given the opportunity to meet with patients who are currently dilating or (successfully) completed the program, as was originally proposed by Ingram [93]. After 6 weeks, the initial trial is evaluated with the psychologist and physiotherapist to ensure that the women are still motivated to continue. If not, treatment is suspended and reasons for discontinuation explored and discussed in multidisciplinary team meetings. If the patient decides to discontinue, the laparoscopic Vecchiotti procedure is the method of choice for further neovaginal creation [74]. If dilator treatment is continued, patients attend for up to five follow-up visits at 6–8 weeks apart with the physiotherapist and after 12 weeks with the gynecologist to evaluate the anatomical results. Telephone and email contact is available if required. Emotional and psychological support from the team clinical psychologist is available as needed before, during or after treatment. Treatment is deemed completed when a patient is able to engage in pleasurable sex and/ or coitus with no difficulty or if a vaginal dilator can be easily inserted to ≥ 7 cm. At completion of the treatment, women are encouraged to maintain dilation two times a week for 20 minutes when not sexually active.

efficacy (i.e. personal beliefs of how likely it is that dilation will work) will be central to a woman's motivation to repeat the exercises regularly [257].

D minimizing the perceived threat, such as pain during intercourse. Anxiety can lead to a higher anticipation of pain, thereby exacerbating pain by intensifying muscular spasms. Relaxation training and psychological pain management techniques in the treatment of dyspareunia associated with gynecological conditions such as vulvar vestibulitis, might be useful [300].

Remaining questions and future perspectives

The current review has highlighted the need for further investigations in a number of areas.

First, a fuller awareness of a need to assess treatment outcomes (i) both qualitatively and quantitatively, with an improved research methodology, (ii) including a wider range of psychosexual matters, including the quality of intimate relationships, and partner-independent sexual activities and (iii) at various developmental time points. Longitudinal studies, incorporating a head-to-head prospective evaluation of interventions, should be undertaken. The majority of studies evaluated had a retrospective design, and pre-treatment measures were available for comparison only in a handful of studies [79,114,125,241,260,263]. Comparing pre-and post treatment results, specifically in the long-term, would provide a more precise indication of the effect of any treatment. Second, reports on the associated anomalies have not been the major focus of recent papers on vaginal agenesis. No firm

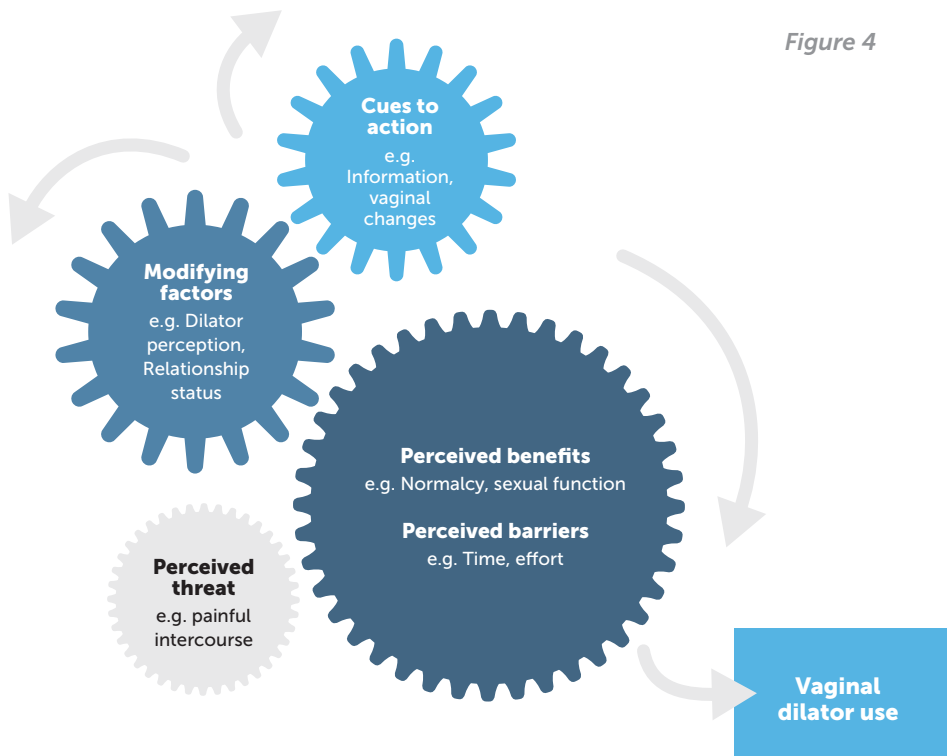


Figure 4. Determinants of vaginal dilator use.

conclusions can be drawn about certain anatomical prerequisites for treatment success (e.g. presence of hymen), and further comparative studies between 46, XX women and 46, XY women with vaginal hypoplasia in different areas are highly valued. For instance, the relative contribution of hormonal factors in sexual dysfunction, in CAIS vs. MRKH, has to be further elucidated.

Third, the possibility of coital dilation should be further taken into consideration and explained to the patients as one of the available therapeutic procedures. The impact of further sexual activity post-treatment on anatomical outcomes needs further investigation, as this could not be confirmed in all studies.

Fourth, additional experience has to be gained on how psychological input may impact on the processes of diagnosis and treatment. Psychotherapy might provide an exploration of alternatives to penetrative intercourse. Of note, the standard sex therapy for couples who experience difficulties with intercourse, is to first of all abstain from it. Masters & Johnson advised couples to 'sensate focus' or (re)-discover a range of pleasurable activities together [301]. However, the typical advice for a woman who has undergone vaginal reconstruction is that she must engage in regular intercourse or dilate indefinitely. This advice may be counter productive for the woman and her partner [298].

Finally, the rarity and (vaginal depth) variability in patients with vaginal hypoplasia precludes the establishment of strict guidelines regarding both non-surgical and surgical management. To our knowledge, this was the first review in which the outcomes of more than thirty vaginal dilation treatment studies were under scrutiny, compared to outcomes of more than 190 surgical studies. The low

rate of physical complications associated with dilator treatment should not lull us into prescribing a treatment that may not be effective and dilation treatment should be further subjected to the same scrutiny as any other intervention [273]. Routine data collection, driven by patients' lived experiences, is the key marker of care quality and should inform service improvement strategies. Meanwhile, with proper care, might we begin to think of the vagina as Oliver Wendell Holmes once viewed the mind: 'Man's mind, once stretched by a new idea, never returns to its original dimensions (p.508) [302].

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Vaginal dilation treatment in women with vaginal hypoplasia: A prospective long term intervention study

4.2

ABSTRACT

Study question: Is non-surgical vaginal dilation treatment, according to a standardized protocol and delivered by a multidisciplinary team, effective in obtaining and maintaining normal vaginal length (≥ 6.5 cm) and psychosexual wellbeing in the long term (>1 year) in women with vaginal hypoplasia?

Summary answer: Vaginal dilation treatment normalizes vaginal length in at least 90% of women, but psychosexual wellbeing remains compromised one year later.

What is known already: Vaginal dilation treatment has been shown to be a (cost) effective first line alternative to vaginal surgery in normalizing vaginal length and improving sexual wellness and function. There remains, however, a need for prospective treatment studies, with a long term assessment of multiple outcomes.

Study design, size, duration: A prospective, single-centre observational study of women with vaginal hypoplasia who were prescribed vaginal dilation treatment, coordinated by a multidisciplinary team, between January 2010 and April 2013, is reported.

Participants/materials, setting, methods: From eighteen women meeting the inclusion criteria, sixteen, of whom twelve with Mayer-Rokitansky-Küster-Hauser syndrome and four with 46, XY Disorders of Sex Development participated. Mean age at start of treatment was $18 (\pm 2.6)$ years. All women underwent an outpatient vaginal dilation program supervised by a clinical psychologist and a physiotherapist. At baseline (T0), at stop of treatment (T1) and at 1 year follow-up (T2), semi-structured interviews and validated standardized questionnaires assessed emotional and sexual wellbeing, including sexual function and distress, self-esteem, vaginal perceptions, health related quality of life and behavioral functioning. Gynecological examinations evaluated vaginal dimensions.

Main results and the role of chance: Ten women completed the program (77%), three are still in the program and three failed dilation and choose for surgical vaginoplasty. Ninety percent of those who finished treatment reached a vaginal length within the normal range (≥ 6.5 cm) in 5.8 ± 3.3 months. Seventy percent was sexually active and had pleasurable experiences at T1, 57% at T2. The significant decrease in sexual distress at T1 ($p < .05$), was followed by an increase at T2 ($p > .05$). Depressive mood symptomatology remained high at T1 and T2, related to the permanent loss of bodily integrity and fertility. The majority refused further psychological counseling after one or two sessions.

Limitations, reasons for caution: Despite the high response rate (89%) and the fact that a series of 16 cases is acceptable for rare conditions, the actual number does not allow for robust analyses to identify key factors in emotional and sexual wellness with confidence. Importantly, a significant proportion was reluctant to fill out the questionnaires, especially at follow-up (50%), which makes the quantitative comparisons difficult and might have biased the results.

Wider implications of the findings: Vaginal dilation with psychophysiological support is

effective in creating a vagina of functional length within an acceptable time period in 90% of the patients, which corroborates previous study findings. However, vaginal creation invariably connects women to the underlying diagnosis, which remains to have a negative impact on emotional wellbeing in the long term. Care providers should investigate multiple clinical needs more thoroughly. In particular, the role of psychological intervention as both a primary and adjuvant treatment needs clear evaluation.

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Key Words: vaginal hypoplasia, vaginal reconstruction, vaginal dilation, vaginoplasty, sexual function, Mayer-Rokitansky-Kuster-Hauser syndrome, Complete Androgen Insensitivity Syndrome, long term outcome, Disorders of Sex Development

Introduction

Congenital vaginal agenesis, as is the case in Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) and Complete Androgen Insensitivity Syndrome (CAIS), is uncommon: 1 in 5000 female births for MRKH [1]; 1 in 13 000 - 40 000 for CAIS [2]. Therefore, a specialized referral center is the optimal environment for diagnosis and management by a multidisciplinary team [3]. The key focus of clinical management is to increase vaginal dimensions to permit penetrative sexual intercourse. Depending on anatomy and operative history, vaginal enlargement may be achieved by nonsurgical vaginal dilation and by surgical reconstructive techniques [4, 5]. Progressive pressure to the vaginal dimple with vaginal molds of gradually increasing length and width, has been used for over 70 years [6]. As it has been shown to be a (cost) effective technique, with few complications and no anesthetic and surgical risks [1,3, 7-9], it is proposed by the American College of Obstetricians and Gynecologists as first line technique [10]. However, it is a time-consuming exercise and anatomical success

seems to be directly related to compliance [1], which is said to be low [11]. Factors associated with non-adherence include embarrassment, anxiety, predicted or actual pain upon dilating, fear of damaging the vagina, or insufficient information about dilator use [12, 13]. The regimen has been described as distasteful in interview studies [13], and because of the intimate and private nature of the treatment, carries emotional implications [12-14]. The usually young, adolescent women have to find a way to accommodate the device [14]. Moreover, upon receiving the diagnosis of MRKH or CAIS, women were introduced to the idea of their body as different, with the physical manifestation being the absence of the womb and vagina. The loss of bodily integrity and fertility can be surmised to have an impact on identity and body image [15, 16]. These factors may also compromise relationship outcomes and sexual function. Therefore vaginal length measurements cannot be used as the single parameter on which to quantify treatment success [15]. Given the emotional sequelae of the diagnosis and the potential drawbacks of vaginal dilation, professional emotional and

psychological support must be planned as integral part of the medical care. With such an approach, barriers to dilation treatment adherence are more likely avoided rendering it viable as first line approach [7]. The effectiveness of dilator treatment, like any other intervention, should be thoroughly evaluated, ideally in a prospective study of multiple outcomes (e.g. sexuality, quality of life and emotional wellbeing), including long-term treatment gains. Our aim was to report prospectively and both quantitatively as well as qualitatively the short and long term results (>1 year) of first line dilation treatment derived from the original Frank technique [6] and delivered by a multidisciplinary team, for

women with vaginal agenesis and without a previous history of vaginal surgery.

Materials and Methods

Study design and population

This was a prospective, longitudinal, single-centre study of all women who were prescribed vaginal dilation treatment for vaginal hypoplasia between January 2010 and April 2013. Participants followed the treatment protocol outlined in *Figure 1*. At baseline (T0), at stop of treatment (T1) and

Figure 1

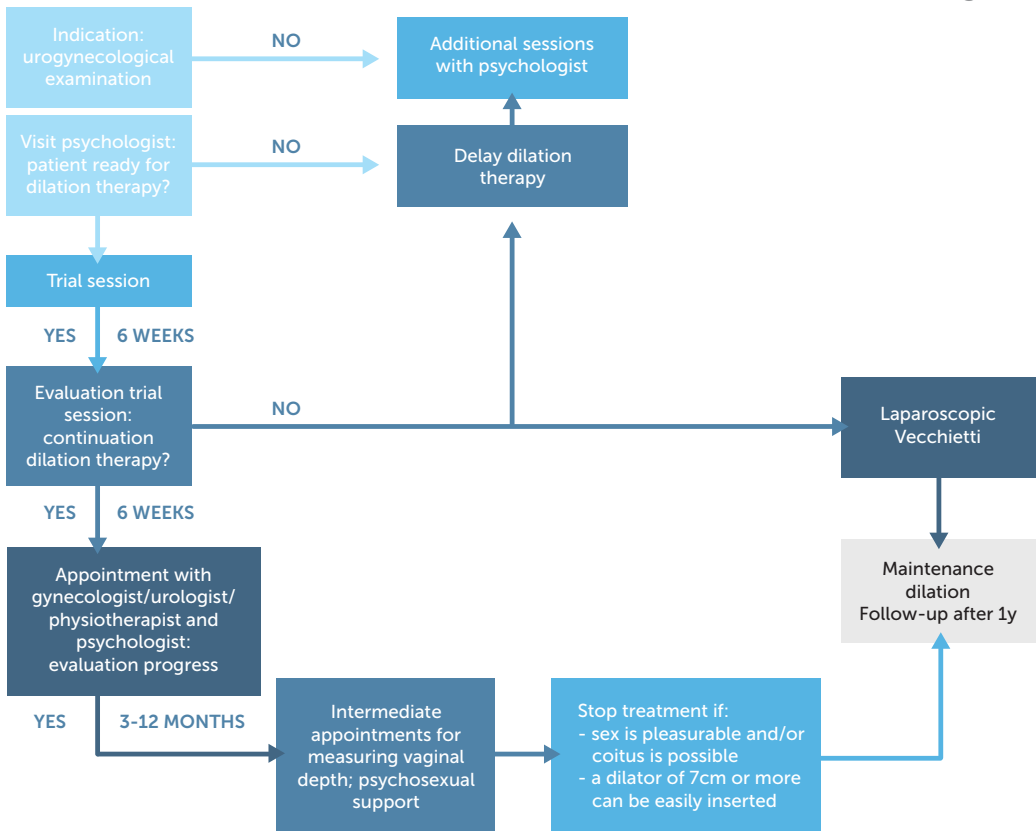


Figure 1. Treatment algorithm for vaginal hypoplasia at Ghent University Hospital

at 1 year follow-up (T2), validated standardized questionnaires on emotional and sexual wellbeing were completed, and gynecological examinations were performed to measure vaginal length. Semi-structured interviews included questions about the participant's reaction towards the diagnosis and experience of dilator treatment, information provision, compliance with dilation treatment and frequency of vaginal dilation.

Ethical approval

The institutional ethics committee of Ghent University Hospital provided ethical approval for this research to proceed (EC 2010/030). A written informed consent had been obtained at T0 from all participants.

Treatment protocol

The out-patient program was designed based on careful exploration of the literature, especially motivational and behavioral psychology [7,12]. A vaginal examination was performed by a single gynecologist and was followed by at least one therapy session by

a clinical psychologist/sexologist to identify any contraindications to using dilators (e.g. depression) and to evaluate the maturity of the patient in order to optimize the probability of a positive treatment outcome. Potential benefits of dilation as perceived by the patient as well as potential obstacles associated with implementing the regime were elicited. The women were encouraged to discuss possible problems around any identified difficulty. Once an initial trial of dilation treatment uptake was agreed upon, standardized spoken and written instructions on vaginal dilation were given and a specialized physiotherapist instructed patients on how to apply gentle pressure to the vaginal dimple using Feminaform (Pelvitec™) dilators for 20 minutes daily, 7 days a week (Figure 2). The size of the dilators was gradually increased up to the size of a man's fully erect penis. If the vagina reached a length of 3 cm, size 2 was used; at 5 cm, size 3 was used. The women were asked to self-monitor their practice and associated pain/discomfort ratings in a diary specially designed for this purpose, which included extra information on pelvic floor muscle relaxation, genital anatomy, dilator use and pain relief. The participants were given the opportunity to

Figure 2

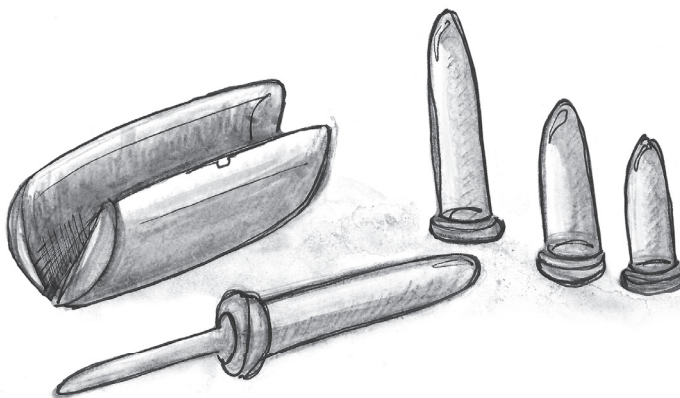


Figure 2. Feminaform (Pelvitec™) dilators. The set is available through the hospital pharmacy and with discrete packaging. The dilators come in four sizes of increasing width and length (Size 1: diameter 22mm, length 85mm; size 2: diameter 27mm, length 105mm; size 3: diameter 32mm, length 135mm; size 4: diameter 37mm, length 160mm).

meet with patients who were currently dilating or had (successfully) completed the program, as was originally proposed by Ingram [17]. After 6 weeks, the initial trial was evaluated with the psychologist and physiotherapist to ensure that the women were still motivated to continue. If not, treatment was suspended and reasons for discontinuation were explored, and discussed during multidisciplinary team meetings. If the patient decided to discontinue, the laparoscopic Vecchietti procedure was proposed as the method of choice for further neovaginal creation [18]. This technique is based on stretching of the patient's own vaginal skin by use of a traction device – in a way very similar to active vaginal dilation – and has been shown to be a relatively safe procedure for women without previous vaginal surgery [19]. Patients who continued dilator treatment, attended for up to five follow-up visits at 6–8 weeks apart with the physiotherapist and after 12 weeks with the gynecologist to evaluate anatomical results. Telephone and email contact was available if required. Emotional and psychological support from the team clinical psychologist was available as needed, before, during or after treatment. Treatment was deemed completed when a patient had pleasurable sex and/or engaged in coitus with no difficulty or if a vaginal dilator size 3 (width 32 mm; length 135 mm) could be easily inserted to ≥ 7 cm. It was predicted that after 3 months a doubling of the start vaginal length could be obtained, and treatment should not last longer than 12 months. At completion of the treatment, women were encouraged to maintain dilation twice a week for 20 minutes when not sexually active, at least during the first 6 months.

Outcome variables

Vaginal length. Vaginal length was measured by inserting a cotton bud into the vagina; the length in centimeters from the posterior

fourchette to the most proximal part of the blind ending vagina was recorded.

Vaginal perceptions. In order to establish whether the objective anatomical change was associated with changes in self-perceptions, patients were asked to report how they perceived their vagina by choosing from the following six statements: 1) My vagina is more or less normal 2) I do not know or I am not sure. 3) My vagina is tiny or non-existent 4) My vagina is small (short or narrow) 5) A sexual partner would notice it is different from other women 6) I would like a bigger vagina (longer or wider) [7].

Sexual dysfunction and distress. Sexual function was assessed by the Female Sexual Function Index (FSFI) questionnaire [20] (Dutch translation with excellent psychometric properties) [21]. This short 19-item questionnaire assesses adult female sexual quality of life in the 4-week period before completing the survey and its score is unbiased regarding age, education, and economic status. The items are assigned to six separate domains of female sexual function: desire, arousal, orgasm, pain during intercourse, vaginal lubrication, and global sexual and relationship satisfaction. All items in the FSFI have a five-point basic response scale (1 to 5) denoting variations in frequency, intensity or degree of satisfaction. Sexual domain scores have a scale score 0–6. Higher scores indicate more normal sexual function. Sexual distress was assessed by the Female Sexual Distress Scale-Revised (FSDS-R) [22], validated for the Dutch-speaking population [21]. This is a self-administered questionnaire consisting of 13 items that relate to different aspects of sexual distress. Every item requires an answer that is then rated as 0–4 (never [0], rarely [1], occasionally [2], frequently [3], or always [4]). The total score, ranging from 0 to 52, provides a measure of sexual distress,

in which the higher the score, the higher the level of sexual distress.

Health related quality of life. The TNO-AZL Questionnaire for Adult's Health-Related Quality of Life (or TAAQOL) assessed the occurrence of particular functional problems on 10 scales (cognition, sleep, pain, social contacts, daily activities, sex, vitality, happiness, depressive mood and anger mood) and the degree to which the patient was actually emotionally bothered by that problem during the last month (1 very much bothered - 4 not at all bothered). Scores for each scale are between 0-100, with higher scores indicating a higher occurrence of problems [23].

Behavioral functioning. The Youth Self - Report (ages 11-18) and Adult Self-Report

(ages 18–59) present participants with statements that relate to emotional and behavioral problems and competencies, using a 3-point response format to establish the frequency of problem behaviors (0-Not True, 1-Somewhat or Sometimes True, 2-Very True or Often True) [24]. The YSR and ASR produce an internalizing and externalizing behavior problem score and total problem score. Externalizing behavior problems—behaviors characterized by an undercontrol of emotions—include difficulties with interpersonal relationships and rule breaking. Internalizing behavior problems—defined as an overcontrol of emotions—include social withdrawal, feelings of worthlessness or inferiority [24] Raw scores are transformed to T-scores, with a mean of 50 and standard deviation of 10. Problems are clinically relevant with T scores > 65.

TABLE 1 Patient population and sexual activity.

Nr	Diagnosis	Age at start dilation (years)	Partner at start dilation	Status	Total duration of dilation treatment (months)	SEXUAL ACTIVITY	
						Pre treatment (T0)	Post Treatment (T1)
1	MRKH	15	Yes	Finished dilation	12.0	No	No*
2	MRKH	17	Yes	Finished dilation	1.5	No	Yes
3	MRKH	17	Yes	Finished dilation	8.0	Yes	No
4	Denis-Drash syndrome	23	Yes	Finished dilation	5.5	Yes	Yes
5	MRKH	18	Yes	Finished dilation	7.0	No	Yes
6	MRKH	18	No	Finished dilation	9.0	No	No
7	CAIS	22	No	Finished dilation	3.0	No	Yes
8	MRKH	16	Yes	Finished dilation	6.0	Yes	Yes
9	CAIS	18	Yes	Finished dilation	3.0	No	Yes
10	MRKH	23	Yes	Finished dilation	3.0	Yes	Yes*
11	MRKH	18	No	Dilation in progress	TBC	Yes	TBC
12	MRKH	17	Yes	Dilation in progress	TBC	Yes	TBC
13	MRKH	17	No	Dilation in progress	TBC	No	TBC
14	MRKH	15	No	Stopped dilation + Vecchiatti	9.0	Yes	Yes
15	MRKH	15	No	Stopped dilation + Vecchiatti	5.0	No	No
16	5a RD	19	Yes	Stopped dilation + Sigmoid vaginoplasty	3.0	Yes	Yes

Abbreviations: MRKH= Mayer-Rokitansky-Küster-Hauser syndrome, CAIS= Complete Androgen Insensitivity Syndrome, 5aRD= 5a Reductase Deficiency, TBC= To Be Continued, could not be evaluated yet, NR= not reported, * did not fill in (all) questionnaires, † She had already dilated before during 3 months in another hospital, but was unhappy about the lack of psychological counseling during treatment.

Body image. An adapted version of a body image scale [25] was used to assess satisfaction with 32 sex-specific and non sex-specific body characteristics on a five-point basic response scale (1 to 5). We determined satisfaction regarding the genital area (4 aspects: vagina, clitoris, labiae, pubic hair) and total body image (28 aspects e.g. arms, legs, nose). Higher scores denote more dissatisfaction.

Self esteem. The Rosenberg Self-Esteem Scale [26], with a validated Dutch translation [27] is a 10-question scale, designed to represent a continuum of self-worth statements. All items are coded on a four-point scale ranging from 0 (strongly disagree) to 3 (strongly agree). Total scores range from 0 up to 30, with higher scores indicating a higher global self-esteem.

Statistical analysis

The qualitative data were analyzed using thematic analysis, defined as a method for identifying, analyzing and reporting themes within data [28]. Quantitative statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL). Non-parametric Wilcoxon signed-rank tests were conducted with a Bonferroni correction applied, for comparing mean rank scores for emotional and sexual wellbeing at T0, T1 and T2. Non-parametric effect size (ES) estimates and 95% confidence intervals (CI) were calculated [29]. Mann-Whitney U-tests were used to assess differences in anatomical success when controlling for frequency of dilation (≤ 4 or > 4 times a week), sexual activity during dilation program (yes or no) and karyotype (46, XY or 46, XX). Associations between variables were sought using Spearman correlation coefficients. $P < .05$ was considered statistically significant. Two-tailed statistical tests were chosen to reduce the risk of type I errors.

VAGINAL LENGTH (CM)			
Follow-up (T2)	Pre treatment (T0)	Post Treatment (T1)	Follow-up (T2)
No	1.5	7.5	NR
Yes	2.0	7.0	7.0
Yes	2.0	7.5	7.5
Yes	1.5	8.0	6.5
Yes	1.5	7.5	NR
No	3.5	6.5	6.5
No	4.5	7.5	11
TBC	2.5	9.0	TBC
TBC	3.5	7.5	TBC
TBC	4.5	9.0	TBC
TBC	3.5 ¹	TBC	TBC
TBC	2.0	TBC	TBC
TBC	1.0	TBC	TBC
No	3.0	4.0	12.0
Yes	2.5	5.0	8.0
TBC	5.0	5.5	11.0

Results

Of the 18 women approached, 16 agreed to participate. Two women were reluctant to discuss this sensitive issue, but both did start with the dilation program. One woman with CAIS (aged 19 years) stopped after a few sessions already as she reported satisfactory coitus with her partner (start vaginal length 4.5 cm, last measure 6 cm). The other woman with MRKH (aged 17 years) obtained an increase of 4cm (from 2 to 6cm) after 5 months and shows little interest in sexual activity and relationships. The characteristics of the participants are displayed in [Table 1](#).

Ten women completed the program, three women are currently still following the dilation program, and three women stopped dilation treatment and underwent a vaginoplasty procedure.

Attitudes towards vaginal dilator use before and after dilation treatment

TABLE 2 Benefits and disadvantages of dilation treatment endorsed by participants.

	Number of participants
Before treatment	
<i>Benefits of dilation</i>	
Being able to have normal/pain free sex, whenever I want	13/13
You are in control (of the pain)	3/13
Better than surgery (e.g. no scars, no possible loss of sensation)	3/13
<i>Disadvantages of dilation</i>	
Feel abnormal	2/13
Pain/discomfort	2/13
Afraid of association of sex with dilation	1/13
After treatment*	
<i>Benefits of dilation</i>	
Enough vaginal length to have sex	8/13
Being more connected with your own body through dilation	3/10
You achieve something yourself	3/10
Feel better as woman	1/10
<i>Disadvantages of dilation</i>	
Unpleasant reminder of something preferably forgotten: e.g. 'It (dilation) reminds me of being abnormal'	8/10
Chore/boring	4/10
Discomfort/pain	4/10
Fear of pushing too hard or hurting myself	2/10
Too slow progress	2/10
Privacy/discretion needed	2/10
<i>Disadvantages of not dilating</i>	
Lose any progress already made and feeling guilty of not doing it	3/10
Won't be able to have 'normal' sex	1/10
Have to have surgery	1/10

*Not including the three women who are currently still in the program

Table 2 summarizes the benefits and disadvantages of dilation treatment as mentioned by the participants. Before start, they demonstrated good knowledge on the purpose of using vaginal dilators, i.e. to have normal/pain free intercourse, and to possibly avoid surgery and scars (i.e. implying visibility of the condition). After treatment, women included also advantages of connectedness to the body through dilation and feeling better as a woman, but the majority reported that it was an unpleasant reminder of abnormality. Interestingly, only half of the women with partner told them about the treatment.

Vaginal dilation frequency, vaginal size and total duration of therapy

With the given instructions and extra information (i.e. pelvic floor exercises, examine genitals with mirror), all of the women felt confident enough to continue with dilator treatment beyond the trial period. Ten women successfully completed the program, and 90% (n=9) achieved a value within the normal range (6.5-12.5 cm) [30] (Table 3). All women started to dilate as recommended (15 to 20 minutes daily, 7 days a week), but after 1 to 3 months the reported frequency decreased significantly, ranging from 3 to 4 days a week to once a week in 5 out of 10 women. Reported motives were: time and effort constraints (e.g. no dilation during certain time periods such as exams (n=5), privacy reasons (i.e. shared student housing) (n=2) and less perceived vaginal increase (n=1). Those who dilated frequently (> 4 days a week), had a significantly larger end vaginal length (p=.034) and a non significant shorter total duration of dilation therapy (p=.459) (Table 3). There was no significant correlation between start or end vaginal length and duration of treatment (Rs= -.44, p=.204 and Rs=-0.14, p=.69 respectively) nor between start and end

TABLE 3 Vaginal size, frequency of dilation and total duration of dilation treatment.

		Vaginal length before dilation (cm)	Vaginal length after dilation (cm)	Total duration of dilation treatment (months)
Dilation only (n=10)		2.7 ± 1.2	7.7 ± 0.8	5.8 ± 3.3
Frequency of dilation	≤ 4d/w (n=5)	2.7 ± 1.3	7.2 ± 0.4	6.7 ± 4.4
	> 4d/w (n=5)	2.7 ± 1.3	8.2 ± 0.8	4.9 ± 1.8
Intercourse during treatment*	Yes (n=4)	2.1 ± 0.9	7.6 ± 0.3	5.9 ± 2.2
	No (n=5)	2.8 ± 1.2	7.5 ± 0.9	6.3 ± 4.3
Dilation + Surgery (n=3)		3.5 ± 1.3	4.8 ± 0.7	5.7 ± 3.1

Abbreviations: d= days, w= week,*Not reported in n=1

Figure 3

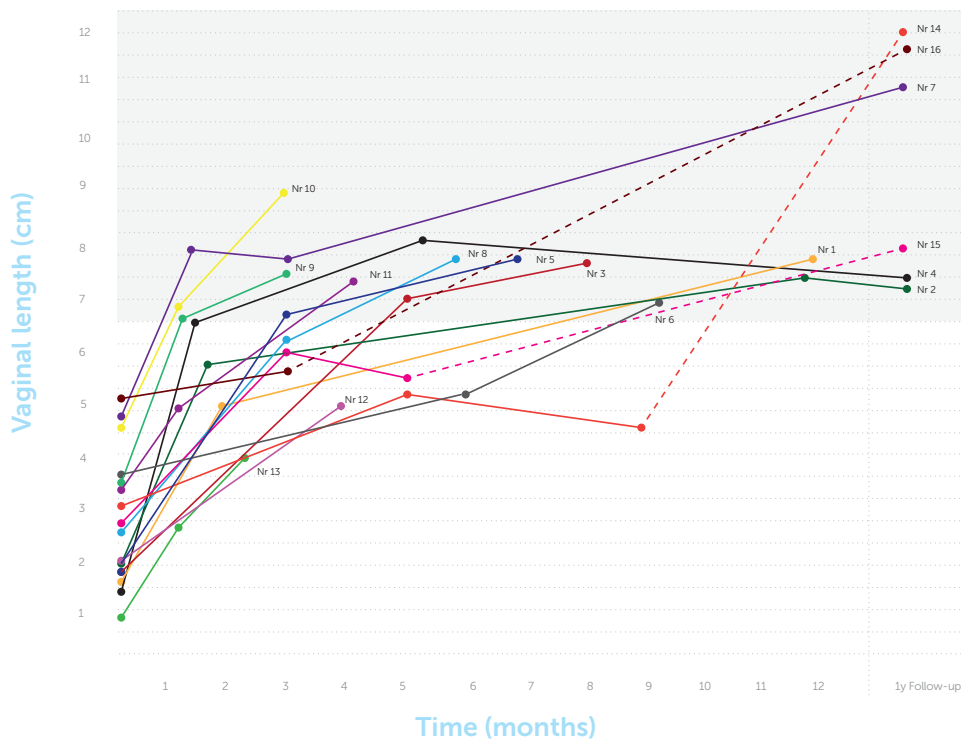


Figure 2. Vaginal length according to duration of treatment. Women who did not complete the treatment program are shown with dotted lines. The normal vaginal length reference range, in grey, is derived from [30]

"We live in the 21st century, everything needs to be quick and deliver quick results. Dilation is a long process, but only on an anatomical level, not psychologically. You, yourself, being things in movement, you learn a lot about yourself"

vaginal length ($R_s=0.06$, $p=.86$). Although not significant, women with 46, XX MRKH ($n=12$) had on average a smaller start vaginal length compared to women with 46, XY DSD ($n=4$) (2.5 ± 1.0 cm vs. 3.6 ± 1.5 cm, $p=.159$). Three participants (nr 14-16) stopped with dilator therapy because of too little perceived progress ($n=3$), pain ($n=2$) and negative confrontation with the condition ($n=3$). At stop they had gained significantly less vaginal length ($p=.009$) (Table 3), although they had a comparable start vaginal length and dilated during a comparable period, but with a lower frequency, especially towards the end (<once a week). A decrease in vaginal length could be observed (Figure 3). These women were on average younger (16.3 ± 2.3 years vs. 18.4 ± 2.6 years), although not significantly ($p=.244$). After surgery, they reached a significant longer end vaginal length (10.3 ± 2.1 cm) compared to the women after dilation therapy only (7.7 ± 0.8 cm, $p=.029$).

Maintenance dilation

In women who completed the program, only two women (nr 1, 7) continued to dilate during the first 6 months after stop (once a week), especially before having sexual intercourse because they were afraid it would not 'work'. Only one woman (nr 7) dilated at the time of

follow-up (approximately 4 times a month for 10 minutes), because she felt that she lost vaginal depth when not being sexually active and because she wanted to gain additional depth. She had a significantly larger vaginal length (and seemed to have gained extra length; Figure 3) at follow-up (11cm vs. 6.5 cm (6.5-7cm, $p<.05$) compared to those who did not dilate at follow-up. Reasons for non-dilation in the other women included regular sexual intercourse (on average 2 times a week, $n=2$), not wanting to do it anymore even when not sexually active ($n=1$), negative confrontation with diagnosis ($n=1$), and no perceived loss of vaginal depth ($n=2$).

Women, who had surgery, wore a vaginal prosthesis day and night during the first 3 months after surgery. For the following 3-6 months, they were advised to wear the prosthesis only at night and at least 4 hours during the day. One woman (nr 14) wore the prosthesis more as she was afraid to lose vaginal length; another (nr 15) did not dilate and lost 2 cm of vaginal length. The third woman (nr 16) dilated as prescribed. After 6 months, 2 out of three were still dilating on average once a week for 20 minutes. None of the two women of whom follow-up was available were dilating after 1 year.

Complications

One participant (nr 12) had started to dilate the urethra, but this was noticed at gynecological checkup after 6 weeks and had no further consequences. No other complications were seen in the women who finished the program. One of the women with the Vecchiotti procedure (nr 15) suffered from continuous cystitis in the first three months after surgery, and was operated for a vesicovaginal fistula a year later. No other complications were reported.

Vaginal perceptions

Improvement was reported for most of the vaginal perception items following treatment, in particular, a significantly higher proportion of women felt that their vagina was no longer tiny or non-existent after dilation therapy ($p=.002$) and at follow-up ($p=.008$). However, more than half of the women considered their vagina still small and would like to have a larger vagina, independent of type of treatment (Figure 4).

Sexual activity

Forty percent of women (4/10) who finished the program successfully had had sexual experiences before treatment, but none of them had had sexual intercourse yet (Table 1). Seventy percent was sexually active after dilation treatment and 80% had had pleasurable intercourse, although not

completely pain free. The women who had intercourse during the dilation program (towards the end) ($n=4$) (nr2, 4, 5, 9) did not have significantly larger end vaginal lengths compared to the women who were not sexually active during the program, nor had a significant shorter duration of dilation therapy ($p>.05$) (Table 3). Fifty-seven percent (4/7 who were eligible for follow-up) were sexually active (including intercourse) at follow-up and vaginal length in all was >6.5 cm. Two women (nr 1, 6) reported no interest in sex nor at stop, nor at follow-up. The first because her partner broke up the relationship during treatment and she still felt afraid to open up to new partners; the second felt she was still too young (20 years).

Two out of three women (67%) who had surgery had intercourse 6 months after surgery and/or at follow-up, which was

Figure 4

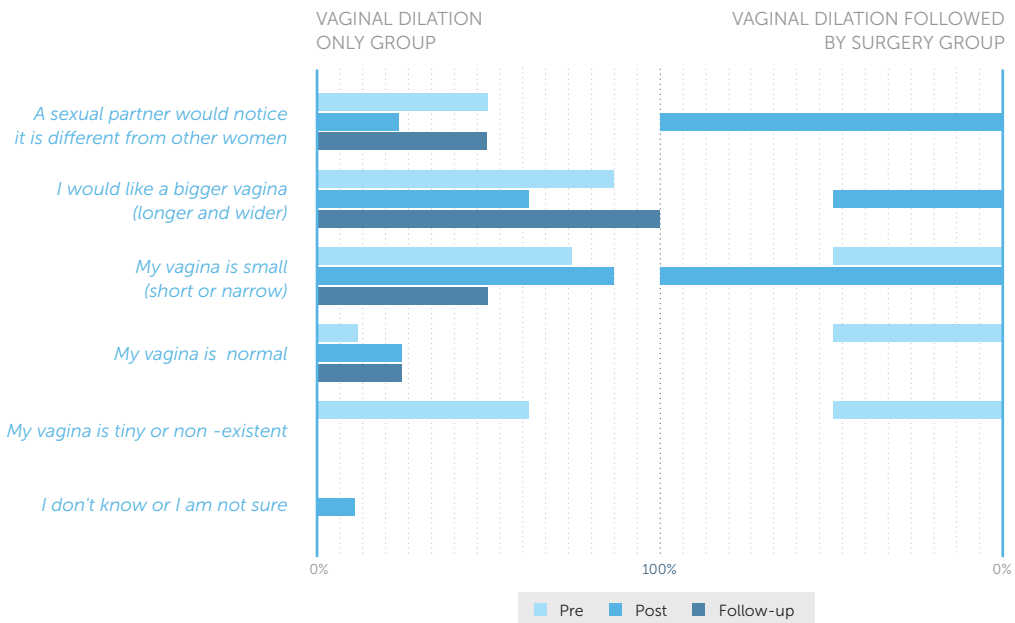


Figure 4. Vaginal perceptions. Responses (i.e. percentage of affirmative answers) in women who finished the dilation program on the left and women who had surgery on the right, before and after the treatment program and at 1year follow-up (only in women who finished the dilation program)

TABLE 4

Median scores and ranges for sexual functioning and distress, behavioral functioning, self-esteem, genital and body image and health related quality of life in women who successfully completed the vaginal dilation program.

	Pre (T0)	Post (T1)	Follow-up (T2)
Sexual functioning			
Sexual distress	22.5 (1- 41), N=8	14 (0- 25), N=8	32 (2-39), N=4
Desire	3.6 (2.4-4.8), N=6	4.2 (3.6- 5.4), N=6	3.6 (3.6-4.2), N=3
Arousal	5.0 (3.3-5.1), N=6	5.1 (4.8-6), N=6	5.1 (4.5- 6.0), N=3
Lubrication	5.4 (3.6-6.0), N=6	5.7 (5.1- 6), N=6	5.1 (4.2- 6.0), N=3
Orgasm	4.8 (1.2- 6.0), N=6	5.4 (2.4-6), N=6	5.6 (5.2- 6.0), N=3
Satisfaction	5.6 (4.8-6.0), N=6	5.6 (4.8-6), N=6	5.6 (2.4- 5.6), N=3
Genital image			
	2.8 (2.3- 3.8), N=8	2.8 (1.8- 4.3), N=8	2.9 (2.3- 3.0), N=4
Body image			
	2.8 (1.9 - 3.6), N=8	2.7 (1.1 - 3.7), N=8	2.9 (2.1-3.6), N=4
Self-esteem			
	19 (12-22), N=8	19 .5 (13-23) ,N=8	18 (14-19), N=4
Behavioral functioning			
Internalizing behavior	57 (36-90), N=8	49.5 (38-71), N=8	55.5 (45-64), N=4
Externalizing behavior	47.3(38- 63), N=8	47 (34-63), N=8	53.5 (41-63), N=4
Total problem behavior	52.5 (30 - 67), N=8	46 (30-66), N=8	56 (44-57), N=4
Health related QoL			
Cognitive functioning	68.8 (43.8 - 100), N=8	81.3 (43.8-100), N=7	93.8 (31.3- 100), N=5
Sleep problems	81.3(50-100), N=8	75 (25-100), N=7	75 (43.8 - 100), N=5
Pain	96.9 (81.3- 100), N=8	87.5 (75-100, N=7	87.5 (75-100), N=5
Social problems	100 (75-100), N=8	100 (81.3 -100), N=7	100 (50-100), N=5
Daily activities	93.8 (31.3 -100), N=8	87.5 (31.3-100), N=7	100 (56.3- 100), N=5
Sexual problems	100 (62.5- 100), N=8	100 (50-100), N=7	81.3 (0-100), N=5
Vitality	54.2 (41.7- 100), N=8	66.7 (58.3-91.7), N=7	66.7 (33.3-100), N=5
Positivity	66.7 (50-100), N=8	66.7 (58.3- 100), N=7	66.7 (25- 83.3), N=5
Depressive moods	70.8 (41.7- 91.7), N=8	75 (66.7-91.7), N=7	66.7 (33.3- 91.7), N=5
Anger moods	83.3(66.7- 100), N=8	88.9 (66.7-100), N=7	77.8 (66.7-100), N=5

Note: The effects of therapy were tested using Wilcoxon Signed Ranks Test), * $p < .05$; ES= Effect size. To calculate the effect size for nonparametric tests, the formula $r = Z/\sqrt{N}$, with Z the value obtained from the Wilcoxon test, and N the sample size. 95% CI (Confidence intervals) = $ES \pm 1.96se$ to $ES + 1.96se$, with asymptotic standard error $se = 1/\sqrt{(n-3)}$ [29]. Below 0.1 is a small effect, between 0.1 and 0.3 a medium effect and above 0.50 a large effect Self-Esteem (Total score: 0-30); Sexual Distress (Total score 0-52); sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, scale 0-6) only in women who were sexually active, Health related Quality of Life domains (0-100); behavioral functioning, T-scores, M= 50, SD= 10); Genital and body image (scale 1-5).

pleasurable only in one woman. The other woman reported subjectively more difficulties reaching orgasm compared to before the operation.

Sexual and emotional wellbeing

Table 4 summarizes the questionnaire results. Only 5 participants of those who finished the vaginal dilation program, wanted to complete (some) questionnaires at 1 year follow-up. Reasons given by the other women included not wanting to be confronted again with the diagnosis and associated infertility issue (n=2), and emotional problems related to the recent passing of the mother (n=1).

There was a significant reduction in reported sexual distress after dilation therapy ($p = .049$, medium ES), but this difference disappeared at follow-up ($p > .05$). There were no statistically significant differences in sexual function domains, self-esteem, genital image, body image or behavioral functioning, before and after dilation therapy, despite some medium effects of dilator treatment on lowering internalizing and total problem behavior (not in clinical range). Regarding quality of life, a significant increase in occurrence of depressive moods after dilation therapy was found ($p = .026$, large ES), decreasing again at follow-up ($p > .05$) (Table 4). Within the surgery group, differences before and after

ES T0-T1	95% CI	P	ES T1-T2	95% CI	P	ES T0-T2	95% CI	P
-0.49	-1.03; 0.05	0.049*	-0.26	-1.14; 0.62	0.47	-0.13	-1.01; 0.75	0.72
-0.41	-0.95; 0.13	0.10	-0.47	-1.35; 0.41	0.18	-0.38	-1.26; 0.50	0.29
0.00	-0.54; 0.54	1.00	0.00	-0.74; 0.74	1.00	-0.34	-1.08; 0.4	0.29
-0.14	-0.68; 0.40	0.59	-0.12	-0.86; 0.62	0.72	-0.36	-1.1; 0.38	0.16
-0.10	-0.64; 0.44	0.69	0.00	-0.74; 0.74	0.00	0.00	-0.74; 0.74	1.00
-0.11	-0.76; 0.54	0.72	-0.26	-1.14; 0.62	0.47	-0.33	-1.43; 0.77	0.41
-0.02	-0.56; 0.52	0.93	-0.26	-1.14; 0.62	0.46	-0.19	-1.07; 0.69	0.59
0.00	-0.54; 0.54	1.00	-0.13	-1.01; 0.75	0.72	-0.26	-1.14; 0.62	0.47
-0.19	-0.73; 0.35	0.45	0.00	-0.88; 0.88	1.00	0.00	-0.88; 0.88	1.00
-0.43	-1.02; 0.16	0.11	0.00	-1.1; 1.1	1.00	-0.22	-1.32; 0.88	0.59
-0.29	-0.88; 0.30	0.27	0.00	-1.1; 1.1	1.00	0.00	-1.1; 1.1	1.00
-0.45	-1.04; 0.14	0.09	0.00	-1.1; 1.1	1.00	0.00	-1.1; 1.1	1.00
-0.34	-0.88; 0.20	0.18	0.00	-0.74; 0.74	1.00	-0.12	-0.86; 0.62	0.72
-0.08	-0.62; 0.46	0.73	-0.26	-1.00; 0.48	0.42	-0.12	-0.86; 0.62	0.71
-0.41	-0.95; 0.13	0.10	-0.12	-0.86; 0.62	0.71	-0.42	-1.16; 0.32	0.18
0.00	-0.54; 0.54	1.00	-0.32	-1.1; 0.42	0.32	-0.14	-0.88; 0.60	0.66
-0.13	-0.67; 0.41	0.60	0.00	-0.74; 0.74	1.00	-0.14	-0.88; 0.60	0.66
-0.11	-0.65; 0.43	0.66	-0.20	-1.08; 0.88	0.58	-0.41	-1.29; 0.47	0.66
-0.23	-0.82; 0.36	0.40	-0.17	-0.91; 0.57	0.58	0.00	-0.74; 0.74	1.00
-0.07	-0.66; 0.52	0.79	-0.52	-1.26; 0.22	0.10	-0.47	-1.21; 0.27	0.14
-0.60	-1.19; -0.01	0.026*	-0.46	-1.2; 0.31	0.14	-0.04	-0.78; 0.70	0.89
-0.14	-0.73; 0.45	0.59	0.00	-0.74; 0.74	1.00	-0.32	-1.1; 0.42	0.32

"Those girls opting for an operation, they give up. They don't deal well with what they have, they just want to get it over with. But with all respect, if they can't do it, they can't."

surgery could not be calculated, because of the small sample sizes and missing data. None of them wanted to complete questionnaires at follow-up, for reasons of severe depression because of familial problems (n=1) and desire of closure (n=2).

Discussion

The present study demonstrates that in the majority of women with vaginal agenesis (77%, 10/13) vaginal dilation therapy, following a strict protocol and with continuous psychophysiological support, can effectively create a vagina within normal ranges (6.5-13cm) [30,31] in a period of approximately 6 months, which corroborates previous study findings [1,3,7,17,32]. If the frequency of dilation was higher, the total duration of therapy was shorter and vaginal end length was higher, irrespective of sexual activity during the program [1]. Successful dilation could also be achieved in patients with a shorter start vaginal length, which refutes the claim by some groups that a vaginal dimple of 3-4 cm is needed [33, 34]. In all but 3 women, of

whom 2 underwent surgery afterwards, at least a doubling of the start vaginal length was reached within the first 2 to 3 months. The increase in vaginal length thereafter was much smaller (mean 1.5 cm, range 0.5- 2.5 cm). This might be due to the decreased dilation frequency and motivational issues after 3 months, but further studies need to elucidate if there exists an optimal window for anatomical success and if women need to generate more pressure thereafter. The three women who did not succeed, had gained significantly less depth at treatment stop, despite the same start vaginal length and although they dilated for a comparable period of time, with the same frequency. These women mentioned pain as an obstacle and it is possible that they had a more sturdy dimple or fibrotic vaginal top [35]. From a psychological viewpoint, maturity and age at treatment might have influenced the results. They were on average younger and it has been shown that patients younger than 18 years had a statistically significant dilation failure rate [32]. In addition, these women mentioned vaginal dilation confronting them negatively with the diagnosis and with being different from peers at an age where they wanted to fit in, although in general the majority of women reported that dilator treatment was a significant reminder of abnormality (80%). It was clear that the women, who successfully finished dilation therapy, accepted the dilator use as part of their normal routine. When motivation decreased, dilator use was prompted both by repeating to themselves the reasons for doing it (e.g. to have normal sex) and by the intermediate gynecological checkups in which they felt sometimes guilty if they had not 'done well' [14], suggesting that these are valuable in adherence with dilator treatment. Although 'normal vagina size' was not an unreasonable goal of treatment, it did not necessarily lead to 'normal perception of

the vagina' and even after treatment, the wish for a larger vagina pertained, even with positive sexual experiences and a marked decrease in sexual distress [7, 12]. The women put a great deal of emphasis on genital underdevelopment as the major barrier to having a sexual relationship. However, post treatment, psychological barriers to engage in sexual activity and sexual enjoyment were at least as great as the (perceived) physical ones. Women described only having sex with partners whom they trusted not to ridicule their genital abnormality, if they would find out.

*"I still have the feeling
that I am not complete,
that I am not normal.
I also do not have a vagina,
it is just a hole that I've created.
Because through a vagina, you
can have children."*

By taking both a quantitative and qualitative long-term approach, it became clear that, despite the appearance of outward 'normality' through treatment, participants continued to feel far from normal in the areas of sexual potency and reproduction [36]. Especially the non-genital aspects of the condition (i.e. perceived loss of social role as potential mother, loss of a sense of normality and equality with peers) contributed to high emotional distress, in different ways and at different times [16]. Continued long term follow-up of these women acknowledges the importance of these developmental-temporal factors to the distress [16].

It seems that the medical and the psychological management of vaginal hypoplasia cannot

be separated. Recognition of emotional problems during dilation treatment has the advantage of signaling to the patient the need to come to terms with the diagnosis [7]. However, only two participants highlighted that the input of a clinical psychologist was of extra value. All other women refused further psychological counseling after two sessions, even when experiencing considerable emotional difficulties, which was also apparent in the unexpected finding of an increase in depressive symptoms and no improvement in self-esteem after treatment [37]. Vagina creation invariably connects them to the diagnosis [15], and previous qualitative studies did identify both positive and negative psychological responses following a diagnosis of vaginal agenesis [38], even several years later [37].

"Psychologists precisely give you the feeling that there is something wrong with you, that you are different. You just want to feel normal and be treated as normal as possible."

Some mentioned that the involvement with a psychologist was likely to generate powerful ambivalent emotional reactions of abnormality as well as feelings of failure in not coping with the condition. Two women who had contact with each other during treatment, suggested that it increased motivation during dilator therapy, but further contact could only be limited to discussion of subjects related to the shared condition, because they had nothing else in common [39]. These disappointing outcomes related

to psychological counseling substantiate the need of re-evaluating the role and/or form of professional psychological support within dilator treatment. Adjusting to a diagnosis of MRKH or CAIS is a traumatic process for these women and may give rise to the development of depressive and negative self-beliefs. Treatment itself may serve to perpetuate or strengthen these feelings and beliefs, which they want to avoid. Paradoxically, the challenge consists in exposing women as much as possible to exposure based- behavior psychological interventions, which involves as such the exposure of the patient to the feared context without any danger, in order to overcome their related anxiety, depression and anger [40]. Letting women engage with the trauma, rather than avoiding it, with interventions centering on maladaptive cognitive and behavioral strategies (e.g. such as avoidance of intimacy) has shown to be effective [41]. The aim of psychological support should be to reduce patients' sense of isolation and alienation, and engender positive feelings, as well as help them to develop skills to negotiate within an environment that is generally ill equipped to deal with taboo, psychological and sexual diversity [36, 42].

An important limitation of this study is its small sample size. Although the response rate was high (89%) and a series of 16 cases is acceptable for rare conditions like MRKH and CAIS, the actual number did not lend itself to robust analyses that would enable us to identify key factors in emotional and sexual wellness with confidence. Many women were reluctant to fill out the questionnaires, especially at follow-up, which makes the quantitative comparisons difficult and might have biased the results. Second, it is not possible from this study to determine whether the efficacy of vaginal dilation treatment or related psychosexual issues

differ between 46, XY and 46, XX women with vaginal hypoplasia. Lastly, relationships between physical and psychological and sexual parameters remain complex and require further exploration. Longer vaginal length at follow-up was rather associated with treatment than with being sexually active, which contradicts previous studies [1,3,15]. Conversely, the vagina was shorter in women who had never been or had not recently been sexually active, which supports the hypothesis that dilation is needed to maintain patency in periods of coital inactivity.

This study also has some strengths. We chose well-validated and widely used outcome measures to allow comparability with previous studies. Perhaps the main strength of this study is that it adds to the limited knowledge of psychological functioning and the associated treatment issues in women with vaginal hypoplasia. To our knowledge this is the first prospective study objectively assessing multiple outcomes after vaginal dilation treatment, also on the long-term. At completion of treatment, anatomical changes are positively associated with (psycho)sexual outcomes; however the long-term outcomes regarding emotional and sexual wellbeing are less optimistic than previously hoped for.

Conclusion

The management of women with vaginal agenesis can be entirely nonsurgical in the majority of cases, without major complications. We have shown that vaginal dilator treatment increases vaginal dimensions within the normal range and that anatomical changes were associated with better psychosexual outcomes, at least immediately after treatment. Therefore,

dilator therapy should remain the cornerstone of neovaginal reconstruction treatment. However, women's compliance with vaginal dilator therapy is influenced by a variety of psychosocial factors, including attitudes towards the dilator, values, beliefs, emotional adjustment to the diagnosis and motivations. The role of psychological interventions as well as peer support as both a primary and adjuvant treatment needs clear evaluation. Above all, the results of this study emphasize a need to look harder at the challenges of living with vaginal hypoplasia syndromes and care providers may need to investigate multiple clinical needs more thoroughly.

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CHAPTER 5

Towards a new treatment strategy in men with DSD and micropenis

As long as men continue to equate penis size with masculinity, they will continue to feel unnecessary sexual anxiety.

Christopher Kilmartin

Based on:

Callens, N., De Cuypere, G., Van Hoecke, E., T'Sjoen, G., Monstrey, S., Cools, M.*, Hoebeke, P.* Sexual Quality of Life after Hormonal and Surgical Treatment, including Phalloplasty, in Men with Micropenis: A Review. J Sex Med, 2013, in press.

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*Joint senior authorship

Sexual Quality of Life after Hormonal and Surgical Treatment, Including Phalloplasty, in Men with Micropenis:

5.1 A Review

ABSTRACT

Introduction. The term micropenis encompasses a range of congenital and acquired conditions that result in an abnormally short penis. Small penis size may persist into adulthood, becoming a major cause of dissatisfaction.

Aim. To review the literature pertaining to the effects of hormonal and surgical treatment on psychosexual functioning and quality of life (QoL) in individuals with micropenis who were raised male.

Main Outcome Measures. Long-term psychosexual and QoL outcomes after hormonal and surgical treatment, including phalloplasty.

Methods. PubMed search for relevant publications (1955–2012) on the role of hormonal and surgical treatment in sexual QoL in adult men with micropenis.

Results. Multiple variations in the etiology of micropenis make it difficult to draw firm conclusions that fit all of the patients within this disparate population. However, the literature review supports the conclusions that (i) male gender assignment is preferable for most 46,XY infants with congenital micropenis because of the likelihood of male gender development and genitosexual function; (ii) small penis size persisting into adulthood and dissatisfaction with genital appearance jeopardize sexual QoL; (iii) there is no known intervention, apart from phalloplasty, to guarantee that the penis will become normal in size; (iv) early data suggest that the phalloplasty technique considered the gold standard for gender reassignment in the transgender population can also be transferred to 46,XY patients with micropenis; (v) psychological support should be an integral part of management in order to alleviate the distress and impairment of QoL experienced by these individuals.

Conclusions. Further publication of series with large numbers and longer follow-up is needed. Specific outcome kits should be designed to measure more precisely patients' degrees of satisfaction with cosmetic, anatomical, and functional variables. Only if health-care professionals fully appreciate the impact of this condition can optimal care be provided.

Key Words. Disorder of Sex Development; Micropenis; Male Genitoplasty; Phalloplasty; Reconstructive Penile Surgery; Hormonal Treatment; Sexuality; Quality of Life; Review

Introduction

The term micropenis encompasses a range of congenital and acquired conditions that

result in an abnormally short penis with a stretched length of more than 2.5 SD below the mean for age and with a urethral meatus at the tip of the glans penis, i.e., no hypospadias

[1–3]. Stretched penile length varies from a mean of 3.5 ± 0.4 cm at birth [4,5] to 12.4 ± 2.7 cm in adults (range 7–18 cm) [6,7] (Table 1). A penis with a stretched length of <2.5 cm in term infants and <7 cm in (Caucasian) adults is by definition a micropenis. Hormonal abnormalities after 12 weeks of gestation can lead to micropenis, either isolated or together with other members of the broad diagnostic category of disorders of sex development (DSD) [2]. DSD refers to all conditions in which the development of the chromosomal, anatomical, or gonadal sex is atypical [8].

TABLE 1 Stretched penile length (in centimeters) by age.

Age	Mean \pm SD
Newborn (30 weeks)*	2.5 ± 0.4
Newborn (term)*	3.5 ± 0.4
0 to 5 months [†]	3.9 ± 0.8
6 to 12 months [†]	4.3 ± 0.8
1 to 2 years [†]	4.7 ± 0.8
2 to 3 years [†]	5.1 ± 0.9
3 to 4 years [†]	5.5 ± 0.9
5 to 6 years [†]	6.0 ± 0.9
10 to 11 years [†]	6.4 ± 1.1
Adult [‡]	12.4 ± 2.7

*Source: Feldman and Smith [4], †Source: Schonfeld and Beebe [5], ‡Source: Wessells et al. [6], SD = standard deviation

The causes of congenital micropenis (also called true micropenis) can be divided into three broad groups: hypogonadotropic hypogonadism (pituitary/hypothalamic failure), hypergonadotropic hypogonadism (primary testicular failure), and idiopathic (associated with a functional hypothalamus–pituitary–testicular axis). (For a full overview, see [3] and [9].) An isolated micropenis seems to occur more commonly with gonadotropin deficiency, whereas micropenis associated with a lack of testosterone (first group) is often accompanied by hypospadias and/or undescended testes, suggesting normal placental human chorionic gonadotropin (HCG)-induced testosterone levels during

the period of organogenesis [2]. Causes of acquired micropenis include trauma, surgery, infection, and genital cancer.

Controversially, feminization of the small phallus was long considered the ultimate alternative in the penile deficient patient [10–12]. The rationale behind this attitude was that it was considered more feasible to create a penetrative conduit than a penetrating organ and that humans were considered psychosexually neutral at birth [13]. Neurological damage caused by phallic reduction, neovaginal inadequacy, and subsequent (gender) identity crises were reported [8,13]. Moreover, as was shown in a review by Meyer-Bahlburg et al. and a study by Reiner, female gender assignment of 46,XY infants and young children with a medical condition involving severe genital abnormalities of nonhormonal origin (including penile agenesis, cloacal and classical exstrophy of the bladder, and penile ablation) carries a risk of later patient-initiated gender change to male that is considerably higher than the risk of patient-initiated gender change to female in male-raised patients [14,15]. The disastrous physical and psychological effects of this practice led many pediatric urologists to revise their recommendations.

If there is an adequate volume of erectile tissue and normal androgen responsiveness, primary treatment revolves around exogenous testosterone administration or HCG treatment to increase penile length [3]. Although good responses are typically seen in early childhood [16–19], the impact on ultimate penile length remains unknown [3]. There may also be differences in pathophysiological aspects of penile development and response to treatment between patients with micropenis as an isolated condition and patients with defects

in the organogenesis of the male genital system (e.g., hypospadias, cryptorchidism) [19]. Moreover, it is not known whether prepubertal hormonal treatment can influence both somatic growth and pubertal penile growth, including penile shaft and skin enlargement, sufficiently to facilitate better surgical results [20]. No data are available on long-term effects of early testosterone treatment, such as negative impact on final height or inappropriate maturation of germ cells during childhood.

In general, surgical treatment should achieve the major goals of (i) correction of chordee and straightening of the penis such that full painless erection enabling satisfactory penetration can be achieved (with or without prosthesis); (ii) urethroplasty enabling functional micturition (including urination from the standing position); (iii) reconstruction of the tissues forming the ventral surface of the glans (glanuloplasty, repair of division of the corpus spongiosum and skin); and (iv) reconstruction of the scrotum and orchiopexy [21]. Developments in total phalloplasty procedures using pedicled or free tissue flaps (and combined with insertion of an inflatable penile prosthesis) seem promising but can still be associated with repeated surgical interventions and high rates of complications (such as urethral strictures or fistula formation), even in the most experienced of hands [2,3,22–26]. The questions remain as to whether male genitoplasty, with or without hormonal treatment, can replicate the complexity of penile anatomy and function and whether conducting phalloplasty procedures improves physical and sexual outcomes compared with genital surgery without phalloplasty. Because case numbers are in general low and many patients are lost to follow-up, there are extremely few reports of the outcome after surgery.

Aims

This review considers the impact and outcomes of both etiology and treatment of penile insufficiency in individuals raised male. We aimed (i) to summarize the literature on surgical, hormonal, and psychosexual outcomes in males with congenital or acquired micropenis; (ii) to identify existing gaps in our knowledge regarding the psychological impact of this condition on Quality of Life (QoL) outcomes; and (iii) to offer suggestions for future research and clinical practice.

Methods

A systematic search of the databases PubMed and Web of Science was conducted for the period between 1955 (the year that John Money published his now classic work on hermaphroditism, currently referred to as DSD [8]) and 2012. The following keywords were used: micropenis, disorder of sex development, intersex, masculinizing/ male genitoplasty, male pseudohermaphroditism, phalloplasty, ambiguous genitalia, perineo-scrotal hypospadias, psychological outcomes, hormonal treatment, testosterone, genital appearance, sexual functioning, surgical outcome. Only English manuscripts and those translated into English that provided data on various aspects of sexuality in 46,XY patients with congenital or acquired micropenis, either isolated or in the context of a DSD, who were sex-assigned as males were included. Studies solely including patients with hypospadias repair but without genital ambiguity and studies involving solely patients with cloacal exstrophy or aphallia were not the focus of this review (see [14] for an overview). Additionally, this article did not address men complaining of a small penis

despite an actually normal size and opting for penile augmentation procedures, as they are managed differently [7].

Results

The literature search yielded 29 studies from the years 1974–2012 examining aspects of treatment and sexuality in 46,XY individuals with micropenis who were sex-assigned as male [17–20,27–51] (see Table 2A). The majority of patients examined had undergone corrective surgery, although three of the studies gave no information on whether and in what way surgery had been done [32,37,39]. Tables 2B and 2C provide information on the functional outcomes grouped according to etiology in the study population (no DSD, underlying DSD, or

both etiologies), testosterone treatment in infancy and/or childhood (yes, no, or unknown), and type of surgical treatment (no surgery, male genitoplasty procedures excluding phalloplasty, or phalloplasty). Reliable information on childhood hormonal treatment to stimulate penile growth or on hormone substitution therapy in adolescence or adulthood was included in half of the studies. Only a minority of studies included comparison data. The studies differ from each other substantially in both number and type of investigated variables. Standardized or partly standardized instruments for data assessment were only used in nine studies [31,33,34,38–40,43,49,50]. Therefore, a meta-analysis calculating the effect sizes of previous results was not possible. In the following sections, the findings are summarized according to the investigated variables.

TABLE 2A

Overview of diagnostic and treatment details in postpubertal individuals with congenital micropenis or acquired penile insufficiency.

Study	Nr	Age	Diagnosis (n)
Money & Ogunro, 1974 [27]	8	Mean 25 years (range 14–39)	PAIS (8)
Money et al., 1984 & 1985 [28,51]	9	22–31 years	Hypogonadotropic hypogonadism (3), adiposogenital dystrophy (2), primary hypogonadism (1), idiopathic (1), Robinow's syndrome (1), atrophic testes (1)
Van Seters & Slob, 1988 [29]	3	31–48 years	CAH (2), anorchia (1)
Reilly & Woodhouse, 1989 [18]	12	17–43 years	Hypogonadotropic hypogonadism (4), idiopathic (3), mixed GD (3), MPH (2)
Farkas & Rosler, 1993 [20]	5	3 adolescents, 2 adults	17βHSD3 deficiency
Gilbert et al., 1993 [30]	16	7 children, 4 adolescents, 5 adults (range 18–24 years)	Posttraumatic amputation, developmental anomalies, micropenis or circumcision accident (NR)
Miller & Grant, 1997 [31]	19	17.7–36.6 years	Perineoscrotal hypospadias with undescended testes and micropenis: 46,XY (12), 45,X/ 46,XY (6), 46,XX (1)

Anatomical Outcomes

Penile Length After Hormonal Treatment in Childhood and Adulthood

In 11 studies, males with micropenis, either true [17,18,28,33,36,38,51] or in association with a DSD [18–20,29,36,40,49], were or had been treated with HCG, testosterone cream applied to the genitalia, and/or intramuscular injections of testosterone enanthate in infancy and/or childhood.

Within the true micropenis group, the reported immediate effect on penile size in infancy and/or childhood was significant in all but one study [36], but only in half of the studies did stretched penile length (SPL) also fall within the normal range in adulthood, following hormone replacement therapy (HRT) beginning at the age of puberty

[17,33,38]. In one study [33], the adult penile lengths of three men treated in childhood showed a trend toward longer final length compared with those men whose treatment was initiated later in development, suggesting the value of early diagnosis and treatment, at least in this group. The prognosis for adult SPL seemed to be better in Kallmann's syndrome compared with the other etiologies of true micropenis.

Within the DSD group, results were more varied. Despite a significant increase of penile length in childhood in two studies [18,19] (but not in two others [36,40]), the penile length remained significantly shorter than the reference values for young adults after HRT and surgical correction. It seems that testosterone treatment in childhood accelerates penile growth but does not increase the size of the penis beyond its

Other genital features of defective virilization (n)	Phalloplasty (n)	Other masculinizing genitoplasty (n)	Complications (n)
Hypospadias (8), cryptorchidism (2), clitoris-sized phallus (4)	Abdominal skin graft (1)	Hypospadias repair (5)	Not erectile and insensitive after phalloplasty, hypospadias repair failed (2)
Inadequate testis function (6)	Skin graft, not specified (1)	Z-plasty (9)*	Not erectile after phalloplasty (1)
Hypospadias (3)	NR (1)	Prosthetic testis (1)	Phalloplasty failed (1)
Hypospadias (5), underdeveloped scrotum (3), small (3) or absent testes (1)	No	Hypospadias repair (5)	NR
Chordee (5), cryptorchidism (4)	No	Chordee release, penile lengthening, [†] and dorsal skin mobilisation to penile ventrum as preparation for second-stage hypospadias repair (Duplay or modified Denis Browne-type) (5)	NR [†]
NR	Forearm fasciocutaneous free flap (16)	NR	Total flap failure (1), urethral fistula (5), urethral strictures (3), meatal stenosis (1); redo surgery because of complications in 7 and esthetic reasons in 4
Hypospadias (19)	No	Staged hypospadias repair (19)	Persistent abnormalities of micturition and spraying (13)

TABLE 2A

Overview of diagnostic and treatment details in postpubertal individuals with congenital micropenis or acquired penile insufficiency.

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Study	Nr	Age	Diagnosis (n)
Bin-Abbas et al., 1999 [17]	8	18–27 years	Fetal and postnatal gonadotropin deficiency (5), hypogonadotropic hypogonadism (3)
Schober, 2001 [32]	4	Mean 34 years (range 22–47)	Hypogonadotropic hypogonadism (1), PAIS (1), CAH (1), MPH (1)
Wisniewski et al., 2001 [33]	13	Mean 38 years (range 21–54)	Hypogonadotropic hypogonadism (6), panhypopituitarism (2), hypergonadotropic hypogonadism (2), idiopathic (1)
Wisniewski et al., 2001 [33]	13	Mean 38 years (range 21–54)	Hypogonadotropic hypogonadism (6), panhypopituitarism (2), hypergonadotropic hypogonadism (2), idiopathic (1)
Migeon et al., 2002 [34]	21	Mean 34 years (range 20–54)	PAIS (5), partial GD, (7), unspecified intersex (9)
Sengezer et al., 2004 [35]	18	Mean 22.2 years (range 20–26)	Penile amputation (8), congenital micropenis (4), penile gunshot wounds (4), traffic accident (2)
Husmann, 2004 [36]	20	Mean 23 years (range 18–30)	PAIS (5), multiple hormonal effects (4), hypogonadotropic hypogonadism (2), idiopathic micropenis (9)
Meyer-Bahlburg et al., 2004 [37]	32	Mean 35 years (range 22–52)	Unspecified with ambiguous genitalia (21), micropenis (11)
Lee & Houk, 2004 [38]	22	Mean 22 years (range 18–32)	Hypogonadotropic hypogonadism (11), primary testicular failure (3), idiopathic (8)
Warne et al., 2005 [39]	17	Mean 25 years (range 18–32)	Mixed GD (1), CAH (1), PAIS (2), severe hypospadias (11), 5 α RD deficiency (1), bifid urethra and ectopic urethra (1)
Bouvattier et al., 2006 [40]	15	Mean 24 years (range 16–43)	PAIS
Djordjevic et al., 2006 [41]	8	Mean 12 years (range 10–15)	Failed epispadias repair (4), micropenis (3), intersexuality (1)
Nihoul-Fékété et al., 2006 [42]	25	Mean 20.7 years (range 14–38)	Testicular dysgenesis (2), true hermaphroditism (6), 5 α RD2 deficiency (1), PAIS (7), MPH (9)
Szarras-Czapnik et al., 2007 [43]	10	Mean 21.4 years (range 19–26)	Partial GD (6), mixed GD (4)
Lumen et al., 2008 [44]	7	15–42 years	Bladder exstrophy (3), crippled penis (1), shriveled penis (1), penile amputation (2)
Schwentner et al., 2008 [45]	8	Mean \geq 15.3 years after surgery in childhood or infancy	46,XY DSD (AR pathway problem) (8)
Kojima et al., 2009 [46]	12	Mean 21.0 \pm 3.6 years	Ovotesticular DSD (3), 45,XO/ 46,XY mixed GD (4), 46,XX testicular DSD (4), AIS (1)
Perovic et al., 2009 [47]	43	Mean 28 years (range 5–52)	Iatrogenic trauma (20), traffic accidents (11), burns (3), self-amputation (2), ritual circumcision (2), penile fracture (2), gunshot trauma (2), electrocution (1)

Other genital features of defective virilization (n)	Phalloplasty (n)	Other masculinizing genitoplasty (n)	Complications (n)
Small testes (8)	No	No	NA
NR	No	NR, but most had "surgical alteration"	NR
Small testes and poor quality of corpora (6); mean pubic hair Tanner stage 3.6 (range 1–5)	No	Prosthetic testis (3)	NA
Small testes and poor quality of corpora (6); mean pubic hair Tanner stage 3.6 (range 1–5)	No	Prosthetic testis (3)	NA
Hypospadias (21); mean pubic hair Tanner stage 4.1 (range 3–5)	No	Chordee release, staged hypospadias repair, prosthetic testes, removal of müllerian remnants, orchiopexy (17)	Fistulae, strictures, urinary tract infections, urethral dilations, testicular pain, hair growth in urethra (NR)
NR	Free sensate osteocutaneous fibula flaps (18)	NR	Flap failure (1), persistent urethral stricture (1)
Undervirilization based on genital and pubertal hair development (Tanner stage 1 (15) and 2 (5))	No	Release of suspensory ligament and injection of autologous fat (5)	Dissatisfied with "lumpiness" of penile shaft (5)
Hypospadias (21)	NR	NR (at least 16, not specified)	NR
NR	No	None	NA
Hypospadias (at least 11)	NR	NR	NR
Cryptorchidism (bilateral 6, unilateral 5), hypospadias (15), severe undervirilization (EMS < 5, 15)	No	Hypospadias repair (15)	NR
NR	Musculocutaneous latissimus dorsi free flap (8)	Inflatable penile prosthesis (2)	Urethral fistula with redo operation (3)
Hypospadias and chordee (25), undervirilization (PAIS, 5; true hermaphroditism, 1; testicular dysgenesis, 1)	No	Correction of penile curvature, hypospadias repair (25)	Perineal or penile fistula (4), penile deformity (1)
Hypospadias (7), an abnormal testis on one side and a streak gonad on the other side (4), or bilateral dysgenetic testes (6)	No	Hypospadias repair, removal of müllerian remnants, penile reconstruction (not specified) (10)	NR
NR	Radial forearm free flap (6), anterolateral thigh flap (1), inflatable penile prosthesis (4)	NR	Urinary stricture and/or fistula (2), removal of penile prosthesis (2)
Hypospadias (8), cryptorchidism (8)	No	Hypospadias repair (8)	NR
Hypospadias (12), cryptorchidism (5)	No	Hypospadias repair (12)	NR
NR	Redistribution of remaining penile skin and scrotal flaps (35), variety of surgical techniques (8) [§]	NR	Infection after implantation of penile prosthesis (1), protrusion of a semirigid prosthesis (1), urethral stenosis (1), urethral fistulae (2), partial skin flap necrosis (2); redo surgery (5)

TABLE 2A

Overview of diagnostic and treatment details in postpubertal individuals with congenital micropenis or acquired penile insufficiency.

Study	Nr	Age	Diagnosis (n)
Gupta et al., 2010 [48]	60	Mean 19.3 years (range 15–25)	MPH (43), mixed GD (3), true hermaphrodite (7), CAH (7)
Sircili et al., 2010 [49]	59	Mean 22 years (>18 years, n = 38)	46,XY/45,X mosaicism (8), partial GD (4), Frasier syndrome (1), 17βHSD3 deficiency (3), 3βHSD2 deficiency (1), 5αRD2 deficiency (10), PAIS (6), undetermined 46,XY DSD (19), ovotesticular dysgenesis (4), CAH (3)
Blanc et al., 2011 [19]	19	Mean 17.6 years (range 14.5–20.8)	Partial GD (7), 5αRD2 deficiency (2), PAIS (1), undefined 46,XY DSD (9)
Kohler et al., 2012 [50]	10	Mean 19.5 years (range 18–50)	Mixed or partial GD (3), penoscrotal hypospadias (3), penile hypospadias and micropenis (1), epispadias (1), 46,XY hermaphroditism (1), unclassified (1)

*Z-plasty to release the body of the micropenis from being entrapped behind adhesions and phimosis of an excessively redundant preputial formation, †Dissection of fibrous tissue from the ventrum of the phallus extending down in between the crura of the corpora cavernosa and dissection of the suspensory ligament on the dorsal aspect of the penis ‡In total population of 16 patients, including 11 children: distal meatal stenosis (n = 2), breakdown of neourethra (n = 1), fistulae (n = 3), §Treatment according to the involved penile entity, type and extent of injury. For a full overview, see Perovic et al. [47]. SPL = stretched penile length; DSD = disorders of sex development; HRT = hormone replacement therapy (testosterone); PAIS = partial androgen insensitivity syndrome; CAH = congenital adrenal hyperplasia; GD = gonadal dysgenesis; 5αRD2 = 5-alpha reductase 2; 17βHSD3 = 17-beta hydroxysteroid dehydrogenase 3; 3-βHSD2 = 3-βhydroxysteroid dehydrogenase 2; MPH = male pseudohermaphroditism; NR = not recorded

“predetermined” length [20,46,49]. Persistent microphallus was most often diagnosed in patients with partial androgen insensitivity syndrome (PAIS), where little or no SPL gain was noticed, irrespective of HRT [27,40,42,49].

Surgical Outcomes and Genital Appearance After Phalloplasty or Masculinizing Genitoplasty

The use of male genitoplasty techniques in combination with one another and the differences between cases (e.g., degree of hypospadias, amount of erectile tissue present) make direct comparison of surgical results difficult (Table 2A). The first phalloplasty procedures (with a nonspecified skin graft) performed in patients with congenital micropenis yielded no anatomical

success [27–29]. Later studies in patients with both congenital and acquired micropenis showed more encouraging results, although complications were reported in 28% of cases (26/92), ranging from flap failure (n = 4) and problems with the penile prosthesis (n = 4) to urethral fistulae, stricture, or stenosis (n = 18). A redo operation was necessary in 27% of the cases (25/92) [30,35,41,44,47]. Complication and resurgery rates were relatively higher after use of forearm free flaps and latissimus dorsi flaps (29–44%) compared with use of fibula flaps (11%) (Table 2A), although it is difficult to compare the main phalloplasty techniques used, as patient samples were diagnostically diverse and treatment was adjusted according to the involved penile pathology and the type and extent of injury. Almost 100% of men reported the ability to void in a standing

Other genital features of defective virilization (n)	Phalloplasty (n)	Other masculinizing genitoplasty (n)	Complications (n)
Hypospadias (at least 6)	No	Not specified (60)	Scrotum diverticulum (1), proximal penile diverticulum (1), urethral stricture (2), hair in the urethra causing obstruction and infection (3), residual chordee correction (3), distal urethroplasty (4), urethral fistula (21)
Microphallus (44), bifid scrotum (43), penoscrotal transposition (23)	No	Hypospadias repair (modified Denis-Browne) (59)	Urethral fistula (30), urethral stenosis (13)
Hypospadias (19), cryptorchidism (5), bifid scrotum (10), impaired testicular function (14)	No	Hypospadias repair (19)	Urethral fistula (9), urethral stenosis (3); additional procedures for penoscrotal transposition (3), buried penis (1), and recurrent ventral curvature (1)
Hypospadias (10), severe underandrogenization (7)	No	Hypospadias repair (10)	Complications (5), resurgery (3)

position with a sufficient urine caliber [30,35,44,47]. Cosmetic appearance was judged to be satisfying in more than 85% of cases (63/74) [30,41,44,47]. Reasons for dissatisfaction included scarring [41,44] and color mismatch problems with scrotal skin and the skin of the penile stump [35], making redo surgery for esthetic reasons necessary in some cases [30].

Male genitoplasty procedures other than phalloplasty mainly involved (staged) hypospadias repair, chordee correction, and/or penile lengthening (i.e., excision of the pubic fat pad and division of the suspensory ligament) [18–20,31,34,36,40,43,45,46,48–50]. Table 2A summarizes the specific techniques used, but only a minority of studies included further details of the performed procedures. Frequently reported complications (in 55%) were urethral fistulae and/or stenosis, micturition problems, and hair growth in the urethra causing obstruction and infection [19,31,42,48–50]. The majority of men reported urinating from a standing position [20,49], but

11% to 47% complained of spraying during micturition [19,31], postvoid dribbling, or a need to “milk” the urethra after voiding [49]. Dissatisfaction with genital appearance and penile size was found in 45% of patients who underwent these procedures and was thus markedly higher compared with the dissatisfaction rate of 15% after phalloplasty ($P < .01$) [19,20,31,34,36,37,42,43,45,48–50]. Interestingly, dissatisfaction was significantly higher (81%, 39/48) in men who did not undergo any masculinizing genitoplasty procedure [28,33,36,38] ($P < .01$ by Fisher’s exact test). In three studies, a third to half of the patients were teased by peers or received comments on the appearance of their genitals, irrespective of surgery or type of surgery [18,28,48].

TABLE 2B

Hormonal, anatomical, and psychosexual outcomes in men with micropenis who received androgen treatment in infancy and/or childhood.

Surgical treatment and etiology	Number of cases	Normal SPL, n (%) [*]	Dissatisfaction with genital appearance, n (%)	Sexuality, n (%)	HRT, n (%) [†]
No surgery					
Non-DSD etiology					
Wisniewski et al., 2001 [33] [‡]	3	3 (100)	1 (33)	Erection and ejaculation, 3 (100)	3 (100)
Bin-Abbas et al., 1999 [17]	8	8 (100)	NR	Intercourse, 6 (75)	8 (100)
Lee & Houk, 2004 [38] [§]	20	14 (70)	9/12 who completed questionnaires reported (75) [*]	Intercourse, 8/12 who completed questionnaires(67); masturbation, 20 (100)	14 (70)
Money et al., 1984 & 1985 [28,51]	4	0 (0)	3 (75) Intercourse,	0 (0); masturbation,2 (50)	2 (50)
DSD etiology,					
Van Seters & Slob 1988 [29]	2	0 (0)	0 (0)	Orgasm and satisfaction with sex life, 2 (100)	2 (100)
Both DSD and non-DSD etiologies					
Husmann, 2004 [36]	15	2/20 (10) ^{††}	15 (100)	Sexually active, 12/20 (60); Intercourse, 8/20 (40) ^{††}	NR
Reilly & Woodhouse, 1989 [18]	7	0 (0)	6/12 (50) ^{††}	Intercourse, 9/12 (75); erection and orgasm, 12/12 (100) ^{††}	7 (100)
Surgery (without phalloplasty)					
Non-DSD etiology					
Money et al., 1984 & 1985 [28,51]	1	1 (100)	1 (100)	Masturbation, 1 (100)	Not needed
DSD etiology					
Blanc et al., 2011 [19]	19	1 (5)	2 (11)	NR	8 (42)
Farkas & Rosler, 1993 [20]	5	5 (100)	3 (60)	Intercourse, 1 (20); erection and ejaculation, 2 (40)	Not needed
Sircili et al., 2010 [49] [¶]	38	36 (95)	3 (8)	Sexually active, 33 (87); sexual intercourse, 21 (55)	NR
Bouvattier et al., 2006 [40] ^{**}	15	0 (0)	NR	Intercourse, 0 (0); masturbation,5 (33); avoidance and non-communication, 15 (100); dissatisfaction with sexual acts, 13 (87)	4 (27)
Both DSD and non-DSD etiologies					
Husmann, 2004 [36]	5	2/20 (10) ^{††}	5 (100)	Sexually active, 12/20 (60); intercourse, 8/20 (40) ^{††}	NR
Reilly & Woodhouse, 1989 [18]	5	0 (0)	6/12 (50) [*]	Intercourse, 9/12 (75); erection and orgasm, 12/12 (100) ^{††}	5 (100)

Androgen treatment consisted of treatment with human chorionic gonadotropin, testosterone cream applied to the genitalia, and/or intramuscular injections of testosterone enanthate. ^{*}SPL within 2 SD of mean for age in adulthood, [‡]Only HRT-compliant patients were included [§]Used the Sexual Behavior Assessment Schedule-Adult to obtain information on sexual orientation, [¶]Used the Social Adjustment Self-Report Questionnaire and Hopkins Symptoms Checklist, ^{¶¶}Used the International Index of Erectile Function, ^{**}Used the Simplified International Index of Erectile Dysfunction and Golombok-Rust Inventory of Sexual Satisfaction, ^{††}Results reported for total patient population, as results were not separately discussed for men who underwent surgery and those who did not, SPL = stretched penile length; HRT = hormone replacement therapy; NR = not recorded

Psychological Outcomes

Sexual Experiences and Sexual Activity

The majority of studies did not use validated instruments. Likewise, it remained unclear in some studies whether only coital sexual activity was included in the assessment or whether noncoital activities (e.g., masturbation) were included as well. Overall, literature data suggest that at least three-quarters of 46,XY males with DSD including micropenis were sexually active or had at one time engaged

in sexual activity. At least 50% (up to 100%) were satisfied with their sex life at the time of investigation, including both men with a history of genital surgery and those without [29,32,34,37,45].

Firm conclusions on the effect of surgery cannot be drawn, as in almost all studies, either patients had already undergone surgical alteration or it was not specified to what extent surgery affected eventual functional outcomes [18,27,36]. The first phalloplasty

TABLE 2C

Hormonal, anatomical and psychosexual outcomes in men with micropenis not known to have received androgen treatment in infancy and/or childhood.

	Number of cases	Normal SPL, n (%) [*]	Dissatisfaction with genital appearance, n (%)	Sexuality, n (%)	HRT, n (%) [†]
No surgery					
Non-DSD etiology					
Wisniewski et al., 2001 [33] [‡]	10	5 (50) ^{§§}	2 (50), all with micropenis	Good to fair erection and ejaculation, 10 (100)	7 (70)
Lee & Houk, 2004 [38] [§]	2	0 (0)	NR	No intercourse but other sexual activities, 2 (100) ^{¶¶}	NR
Money et al., 1984 & 1985 [28,51]	3	3 (100)	2 (67)	Masturbation, 1 (33)	0 (0); not needed int ^{††}
DSD etiology					
Migeon et al., 2002 [34] [¶]	4	2/3 who participated in urological exam (67)	NR	Somewhat to totally inadequate sexual function, 3 (75); erection 4 (100)	5 (24) ^{¶¶}
Money & Ogunro, 1974 [27]	2	0 (0)	NR	Sexually active with genital contact, 5 (71) ^{¶¶}	3 (38) ^{¶¶}
Surgery (without phalloplasty)					
DSD etiology					
Migeon et al., 2002 [34] [¶]	17	8/15 who participated in urological exam (53)	NR	Somewhat to totally inadequate sexual function, 12 (71); erection, 17 (100)	5 (24%) ^{¶¶}
Money & Ogunro, 1974 [27]	5	0 (0)	NR	Sexually active with genital contact, 5 (71) ^{¶¶}	3 (38) ^{¶¶}
Kojima et al., 2009 [46]	12	0 (0)	NR	Intercourse, 4 (40); masturbation, 9 (90); ejaculation problems, 5/7 (71) ^{†††}	3 (25)
Miller & Grant, 1997 [31] ^{**}	19	NR	6 (32)	Intercourse, 12 (63); erection and orgasm, 15 (79); ejaculation, 7 (37)	NR
Nihoul-Fékété et al., 2006 [42]	25	18 (72), all except PAIS	13 (52)	NR	NR
Szaras-Czapnik et al., 2007 [43] ^{††}	10	NR	3 (30)	Intercourse, 7 (70); erection and ejaculation, 10 (100)	7 (70)
Schwentner et al., 2008 [45]	8	NR	0 (0)	Satisfactory sexual function, 8 (100)	NR
Gupta et al., 2010 [48]	60	NR	44 (73)	Erection, 53 (88); ejaculation, 44 (73)	37 (62)
Kohler et al., 2012 [50] ^{††}	10	NR	5 (50)	Erection, 9 (90); ejaculation, 5 (50), genital arousal, 7 (70); fear of sexual contact and initiating sexual contact, 4 (40)	3 (30)
Phalloplasty					
Non-DSD etiology					
Money et al., 1984 & 1985 [28,51]	1	1 (100)	1 (100)	Hypoactive masturbation, 0 (0)	0 (0)
Perovic et al., 2009 [47]	43	43 (100)	2 (5)	Intercourse, 35 (81)	NR
DSD etiology					
Van Seters & Slob, 1988 [29]	1	0 (0) ^{***}	0 (0)	Satisfied with sex life, no intercourse, premature ejaculation and fear regarding sexual performance, 1 (100)	1 (100)
Money & Ogunro, 1974 [27]	1	1 (100)	NR	Intercourse, 0 (0)	NR
Both DSD and non-DSD etiologies					
Gilbert et al., 1993 [30]	16	16 (100)	NR	Erogenous sensibility and masturbation, 5/5 adults (100)	NR
Sengezer et al., 2004 [35]	18	18 (100)	NR	Intercourse, 18 (100)	NR
Djordjevic et al., 2006 [41]	8	8 (100)	4 (50)	NA (still in adolescence)	NR
Lumen et al., 2008 [44]	7	7 (100)	1 (14)	Neophallus sensitivity, 5/6 (83) ^{§§§} ; sexually active with orgasm, 2/4 with erection prosthesis (50)	NR

^{*}SPL within 2 SD of mean for age in adulthood, [†]Only HRT-compliant patients were included, [‡]Used the Sexual Behavior Assessment Schedule-Adult to obtain information on sexual orientation, [§]Used the Social Adjustment Self-Report Questionnaire and Hopkins Symptoms Checklist, [¶]Used the Kinsey Scale to obtain information on sexual orientation, ^{**}Used the Case Western Reserve University Sexual Function Questionnaire, Spielberger Anxiety Questionnaire, Goldberg General Health Questionnaire, and Beck Depression Inventory, ^{††}Used the Gender Identity Index analyzed according to Bem's gender schema theory, together with three projective tests: the Human Figure Drawing test, Three Wishes Test, and Rorschach test, ^{†††}Used the ZUF-8 questionnaire measuring patient satisfaction, ^{§§}Three men not compliant with HRT had micropenis, ^{¶¶}Results reported for total patient population, as results were not separately discussed for men who underwent surgery and those who did not, ^{***}Phalloplasty failed, ^{†††}One man with Robinow syndrome and one with adiposogenital dystrophy (familial agonadism) had adequate male hormonal function of their own testes, ^{§§§}Sexual activity was only assessed in n = 10; 7 (70%) had experienced ejaculation, and 5 of these 7 patients had ejaculation problems, including dribbling, retained, or delayed ejaculation, ^{§§§}Genital sensitivity was only assessed in n = 6, as one man had only recently been operated. The five men who underwent radial forearm free flap phalloplasty all experienced sensitivity, the one man with anterolateral thigh flap phalloplasty did not, SPL = stretched penile length; HRT = hormone replacement therapy; NR = not recorded; NA = not applicable

procedures performed yielded no functional (or anatomical) success [27–29], but those performed later in patients with penile deficiency (both DSD-related and idiopathic micropenis) showed good results [30,44,47], with erogenous sensitivity present in the neophallus [30,35,44].

Data are inconclusive regarding the age at first dating or sexual contact [18,29,31,32,38], as only one study included control data [38]. Warne et al. reported that men with DSD in general were less sexually active than men with diabetes mellitus or Hirschsprung's disease, although sexual interest was similar in both groups [39]. In men with PAIS, sexual satisfaction and function were seriously impaired, and in comparison with a norm sample, lower sexual interest was found [40]. Despite obvious anatomical limitations, the mechanisms of sexual dysfunction in PAIS remain unclear. It is not known whether the deficient sexual function is the result of an abnormal phallus and androgen resistance or just of an abnormal phallus [40].

Many studies showed that men with micropenis can experience sexual pleasure and orgasm [18,27,29,33,34,43,45,49]. However, problems with erection and/or with precocious or no ejaculation [18,31,46,48–50] and compromised penetrative ability are often reported [18,20,27–29, 36,40,46].

Whether or not a correlation exists between small penile length and dysfunctional penetrative intercourse remains unclear. Penile length was not associated with satisfactory or unsatisfactory sexual activity in the study by Sircili et al. [49]. On the other hand, having a micropenis was associated with absence of sexual intercourse in some studies [27–29,40], but not in others [18,46]. In men with a history of micropenis but with an adult SPL within normal range, only around

three-quarters reported having satisfactory (but not ideal) intercourse [17,38]. In general, having a micropenis has a major negative impact upon sexual self-confidence [40,48,50]. Reasons for compromised penetrative ability other than SPL can include dissatisfaction with genital appearance and/or postoperative complications. Also, perceived penile shortness or inadequacy may lead to social or sexual avoidance in some men with a history of micropenis and normal adult SPL [36,38,49].

Quality of Life Outcomes: Psychopathology and Psychosocial Adjustment

Men with DSD do not have more difficulties regarding psychosocial well-being (depression, anxiety, physical and mental health) as compared with a control group of men with Hirschsprung's disease [39] and have no increased psychiatric morbidity [38]. However, other research shows that these men face more specific QoL concerns, such as poor body image and fear of sexual rejection and sexual inadequacy [31,36,38]. Additional features of concern are dissatisfaction with the amount of facial hair, dissatisfaction with small testes, and the problem of infertility [48]. Hence, social adjustment and adaptation [18,31,48] and interpersonal interactions [34,40,42] are frequently impaired.

The effect of male genitoplasty on psychological well-being could not be estimated, as in the majority of studies it was not mentioned. Two studies report a boost in self-esteem after phalloplasty [41,44], possibly related to the increase in phallic length. On the other hand, psychosocial and psychosexual adjustment, as well as satisfaction with surgical results, may also have been influenced by the long-term psychological support these patients received. Parental counseling in children [18] and an encouraging partner

attitude [29] have been associated with better outcomes. Future studies should further investigate the impact of parents, siblings, partners, and spouses on long-term psychosexual development in this group.

Satisfaction with Gender of Rearing and Male Gender Role

The majority of men with micropenis were satisfied with their male gender of rearing. Among studies covered by this specific overview, there was only one report of a case (with unclear etiological diagnosis) of patient-initiated legal gender change to female [34]. Gender dysphoria and dissatisfaction with gender of rearing were expressed by 7.7% of men in one study [33] and 21% to 24% in two others [34,37]. More specifically, 16% (4/25) talked about having an "intersexual" gender identity, not a male gender identity [32,34], corroborating the findings in Gupta et al.'s study that five out of 60 men (8%) had mixed feelings about their male gender role [48]. Interestingly, these feelings were only expressed by men with an underlying DSD, not in those with a true micropenis condition.

Sexual Orientation

When applied to individuals with a DSD, the concept of sexual orientation means that individuals who identify as heterosexual feel sexually attracted to persons who fulfill the opposite gender role [52]. Most studies suggest that 46,XY persons with DSD and micropenis are primarily or exclusively heterosexually oriented [17,18,27,29,33,34,36,38,40,43,46,48-50]; homo- or bi-sexuality is reported in 5–15% [33,34,36,38]. Only in the studies by Schober and Money et al. was the nonheterosexuality rate significantly higher (around 30%) [28,32]. Most studies with a mixed population did not separate data according to diagnostic groups for evaluation.

Discussion

Individuals with conditions associated with micropenis differ from other groups on important counts. Compared with "healthy normals," they differ in having a chronic medical condition. Compared with other medical populations, they differ in bodily presentation and attendant experiences [53]. It is generally conceivable that psychosocial aspects related to their medical history can have a negative effect on sexual QoL. These can include compromised self-esteem and impaired psychological well-being in addition to social and sexual anxieties, social stigmatization, anxiety about the inability to conceive, and traumatic treatment experiences [52,54]. However, it is difficult to determine how far physical, psychological, and social aspects influence sexual behavior and experience because the various interacting factors cannot be examined separately [52]. *Figure 1* illustrates a dynamic and interactive model of sexual QoL, affected by several factors including desire, situations, and sexual ability [54,55].

Figure 1

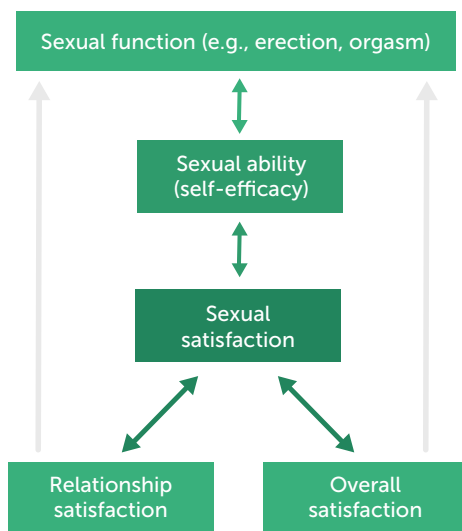


Figure 1. An interactive and dynamic model of sexual quality of life (adapted from [54,55])

In relation to all investigated aspects of sexual QoL, the results of the studies reviewed are inconsistent and show great variability. However, they do suggest that 46,XY persons with DSD and micropenis tend to identify as heterosexual, that they have more sexual dysfunctions, and that they are less satisfied with their sex lives, their sexual function, and the appearance of their genitalia as compared with norm samples. It has been found that men's global satisfaction with their genitals (e.g., size, shape, coloration, testicles) is directly linked to increased body satisfaction [56] and sexual functioning [57]. In 46,XY patients with DSD-related micropenis, it is not only genital appearance but also overall physical development—such as body development and eventual breast growth, as is the case in PAIS—that can lead to a negative body image and impaired social interactions. Their having atypical genitals, frequently not suitable for heterosexual intercourse, can lead to fears of not meeting sexual partners' needs or fears of rejection [52]. The current cultural context (including the studies reviewed) reflects the continued dominance of the so-called "coital imperative" in heterosex, where coitus is seen as "normal" and "natural" and where other forms of sexual activity are not seen as "real sex" [53]. Interestingly, some men reported a mutually sexually satisfying sex life with their partners, although no partner corroboration was sought. These men were reported to be able to de-emphasize the importance of intercourse, to have found alternative ways to reach orgasm, and to be able to meet the sexual needs of their partners [29,53].

Micropenis associated with hypogonadotropic hypogonadism seems to have a better prognosis with regard to hormone treatment response and adult penile size as compared with DSD-related micropenis. This probably reflects a difference in

embryological pathophysiology, with disturbed organogenesis of the penis only in the latter group. To our knowledge, no outcome studies exist comparing individuals affected by these two conditions.

It is a matter of concern that, even after hormonal treatment in childhood and/or during puberty, small penis size persists into adulthood, especially in DSD-related micropenis, becoming a major cause of dissatisfaction [19,34,36,49]. Excessive worries about penis size have been found to contribute to poor self-esteem [57]. A micropenis is defined as a SPL > 2.5 SDs below the mean length for age and ethnic background or, in adulthood, a SPL < 7 cm in Caucasians [58]. However, it remains to be clarified if this also represents a cutoff for psychosexual functioning. Our group found that men who reported not being able to have penetrative intercourse indeed had a mean penile length < 7 cm [59]. It is unclear, however, if other psychosexual or QoL parameters were also negatively affected in this subgroup of men. Therefore, determining the cutoff SPL at which phalloplasty can be proposed as a viable option is highly challenging [46].

It seems that male genitoplasty—with or without hormonal treatment—can improve satisfaction with genital appearance and penile size, although the effect of surgery on length is often minimal, in the range of 1–3 cm [60,61]. Also, the gradual improvement in complex hypospadias repair during the last 30 years does not seem to have been directly translated to better (or worse) psychosexual outcomes. Repeated surgical procedures and complications are of particular concern because of associated scarring and loss of tissue as well as the presumable negative impact on sexual function. Phallus reconstruction by phalloplasty seems to lead to higher satisfaction with the surgical

result (including a larger SPL and fewer problems with voiding in a standing position) compared with genital surgery without phalloplasty. However, further publication of series with large numbers and longer follow-up is needed to evaluate if and to what extent phalloplasty improves physical and sexual outcomes. The early data here suggest that complete phalloplasty, today still mostly used for gender reassignment in the transgender population, opens new horizons for the treatment of 46,XY DSD patients with micropenis.

A high incidence of psychological health and sexual concerns among micropenis patients, combined with the patients' perception that their micropenis has negatively affected their QoL, indicates that psychological counseling should be recommended routinely in the treatment of these patients [9,36] and should aim at minimizing stigmatization and achieving greater self-acceptance as well as social acceptance of their condition. Doing a thorough job of educating and counseling is paramount, and the role of the parents cannot be overemphasized. Clinicians should be encouraged to participate in providing the patient with a progressive, age-appropriate explanation of the diagnosis, pathophysiology, and potential for fertility from childhood through adolescence. It may be that long-term psychological support is of equal or superior importance to the anatomical result [12]. However, in our experience, many patients, especially at adolescent age, refuse further counseling, and research and other initiatives focusing on how to reach this group are highly needed.

Limitations and Future

The generalizability of previous results is compromised by the limited number

of studies, the small and diagnostically heterogeneous samples, and differences in cultural and societal backgrounds. Most studies focus too strongly on heterosexual penetrative function. Qualitative and psychological aspects of sexual experience, including partner perspectives, should be investigated as well. For example, it has been shown that within the general population, the percentage of women who are satisfied with their partner's penis size is much higher than the percentage of men who are satisfied with their own penis size [56,62]. Both the treatment history of the study participants (e.g., hormone treatment, age at time of surgery) and the operationalization of variables were insufficiently documented in most of the studies. Sexuality and adjustment of individuals with DSD have rarely been studied in detail because of the lack of specifically designed instruments accounting for the unique qualities of these people. In the effort to understand and better appreciate the DSD condition, there is need for a DSD-specific outcome-reporting kit that includes standardized questionnaires and discriminating scales to measure more precisely patients' degrees of satisfaction with regard to cosmetic, anatomical, and functional variables [12]. QoL research will provide vital information about the appropriate age for medical/surgical intervention and the utility of various approaches, including psychological counseling, for clinical management.

Conclusion and Recommendations

First, according to the available data, the majority of adult male-raised patients with micropenis are satisfied with their childhood gender assignment and can achieve male sexual function. However, dissatisfaction

with sexual quality of life, dissatisfaction with cosmetic appearance, and stigmatization are reported.

Second, there is a lack of systematic studies of the impact of (different) hormone replacement therapy protocols on adult penile length and psychological outcomes, as well as of their long-term safety.

Third, the effect of male genitoplasty on penile length is often minimal and is, for most patients with micropenis, not enough to improve genital image and sexual quality of life.

Fourth, phalloplasty may improve outcomes, but patient expectations need to be realistic. A balanced discussion, including multidisciplinary and psychological support for patients, is important in order to achieve appropriate treatment decisions.

Fifth, reporting long-term outcomes into adulthood is essential to appreciate the global effect of the decisions made. Methodologies of treatments should be rigorously documented in future research, following the principles of evidence-based medicine. Equally importantly, it should be assessed how important surgical sex adjustment is in comparison with other factors that influence the psychosexual development of men with micropenis.

In conclusion, a structured counseling protocol and guidelines for the indications of phalloplastic surgery in men with micropenis (and 46,XY DSD) should be developed.

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Sexual Quality of Life after Total Phalloplasty in Men with 5.2 Penile Deficiency

ABSTRACT

Background. Total phallic reconstruction, currently the gold standard in female- to- male transgender patients, has a potential indication for men with penile deficiency who are dissatisfied with their genital appearance or have unsatisfactory intercourse.

Objective. To report long-term follow – up of phalloplasty in men with penile deficiency

Design, settings, and participants. Sexual Quality of Life (QoL) was assessed in 10 men (aged 20 - 43 years) at least one year after phalloplasty in a single institution (80% radial forearm free flap, 20% anterolateral thigh flap). In all but one an erectile prosthesis was implanted on average one year after phallic reconstruction.

Outcome measurements and statistical analysis. Neophallus sensation, complications and genital appraisal were recorded. Sexual QoL outcomes were compared to those of men with hypospadias repair (n=73) and control men (n=50).

Results and limitations. After phalloplasty (mean 36.9 months, 14-92 months), all men were sexually active (80% intercourse, 100% masturbation with orgasm and ejaculation). However, 75% indicated to be inhibited in seeking sexual contacts, compared to 40% of hypospadias patients (p<.05) and 11% of controls (p<.01). Although 90% were satisfied with the final surgical result, dissatisfaction with some aspects of genital appearance was present in 50%. Erogenous neophallus sensitivity was said to be less than previously hoped for. Six men developed urinary complications (urethral stricture and/or fistula) and one man underwent revision of the erectile implant because of dysfunction. Nevertheless, all indicated they would choose again for phalloplasty if necessary.

Conclusions. Total phalloplasty opens new horizons for the treatment of men with penile deficiency, but limitations of the technique should be emphasized prior to surgery. Psychological support should be an integral part of the management in alleviating the impairment of sexual QoL. Publication of series with large numbers and longer follow-up is needed.

Key Words. Disorder of sex development; micropenis; penile deficiency; phalloplasty, psychosexual functioning; reconstructive penile surgery

Introduction

Until the late 20th century, surgical construction of a cosmetic and functional penis was not feasible and traditional clinical

management of male neonates with severe phallic inadequacy (i.e. stretched penile length < 2.5 cm) included social and surgical female sex assignment, acknowledging the importance of normal penile cosmesis

and function for male social integration and sexuality [1,2]. (Gender) identity crises and reported neovaginal inadequacy in female-raised 46, XY men [3,4], as well as improvements in the understanding of the phallic nerve supply [5] together with refinements in surgical techniques [6,7] led reconstructive surgeons to revise the indications [8-10].

However, total phallic reconstruction is rarely performed today in males with penile deficiency, despite its widespread and successful use in the transgender population [11,12]. Small series have reported cosmetically acceptable and sensate neophalli with incorporation of a neourethra to allow voiding in a standing position and with enough bulk to allow the insertion of a penile prosthesis for pleasurable sexual intercourse [13-19]. However, the absence of control groups or norms, the use of non-

validated measures, particularly with respect to psychosexual outcome, unclear protocols and indications (e.g. age of patient, penile length, specific diagnosis) and the premature reporting of results limit the conclusions that can be drawn [8]. Our experience with phalloplasty in ten adult men with penile deficiency and their long term sexual quality of life (QoL) (≥ 1 year postsurgery) is reported here.

Patients and Methods

Patients and procedure

This was a retrospective monocentric study of patients aged 18 and older who underwent phalloplasty for penile deficiency between March 2004 and November 2011 (Table 1). Approval was granted by the Medical Ethical

TABLE 1 Age and medical characteristics of non-responders and participants.

Characteristic	Participants (n=10)	Non-responders (n= 8)	P-value
Mean age (range)	28.2 (20-43)	31.9 (20-49)	0.53 [†]
Diagnosis			
46, XY DSD and micropenis	3	1	0.47 [†]
Bladder or cloacal exstrophy	5	3	
Trauma or penile amputation	2	3	
Idiopathic micropenis	0	1	
Type of phalloplasty			
RFA	8	6	0.80 [†]
ALT	2	2	
Complications			
None	30% (n=3)	37.5% (n=3)	0.68 [†]
Urethral stricture and/or fistula	40% (n=4)	37.5% (n=3)	
Urethral stenosis	10% (n=1)	0% (n=0)	
Infection (urinary infection, infected seroma or haematoma)	20% (n=2)	12.5% (n=1)	
Pilonidal sinus	0% (n=0)	12.5% (n=1)	
Erectile implant	9	7	
Removal of erectile implant	10% (n=1)	43% (n=3)	0.15 [†]

Used abbreviations: DSD= Disorders of Sex Development.; RFA= Radial Forearm Free Flap; ALT= Anterolateral Thigh Flap; No statistical differences between the two groups were found. [†]Mann-Whitney U-test for continuous variables; [†] χ^2 -test for categorical variables. In case that >20% of the cells showed an expected frequency <5, Cramer's V was applied $V=\sqrt{\chi^2/(n(k-1))}$, with χ^2 = Pearson Chi square value, n=number of observations, k=the smallest value of the number of columns or rows of table

Commission of the Ghent University Hospital (Trial number EC2011/466) and written informed consent was obtained from all participants. They were offered a urological examination and sexual QoL was assessed by means of a standardized personal interview-conducted by a psychologist previously not involved in the care of these men - and previously used in 73 men with hypospadias repair and 50 controls who were treated for isolated inguinal hernia by the group of Mureau et al [20]. As the same methodology was used and no differences were found in terms of sociodemographic participants' characteristics, this study was used for comparison with our results [20].

Surgical techniques

Our method of choice for penile reconstruction was the modified technique

of Radial Forearm Free Flap (RFA) [7], described in detail before [21,22] (Figure 1). When vascular anatomy was uncertain, like in cloacal exstrophy, a free flap was contraindicated and a pedicled Anterolateral Thigh Flap (ALT) was used [21,22]. Phalloplasty involves the following steps: 1) creation of the phallus with a competent neourethra and microvascular transfer to the recipient site, 2) anastomosis of the native urethra to the phallic urethra when applicable, 3) sculpture of the glans using the Norfolk technique [12] 4) connection of a nerve of the flap to any dorsal penile nerve that can be identified and 5) incorporation of residual genital sensitive tissue at the base of the phallus (e.g. native glans penis). The second procedure consists of insertion of inflatable Ambicor™ or semi rigid Spectra™ penile prostheses with one or two cylinders (American Medical Systems, Minnetonka, Minnesota) on average 1 year after phalloplasty. When possible, the base

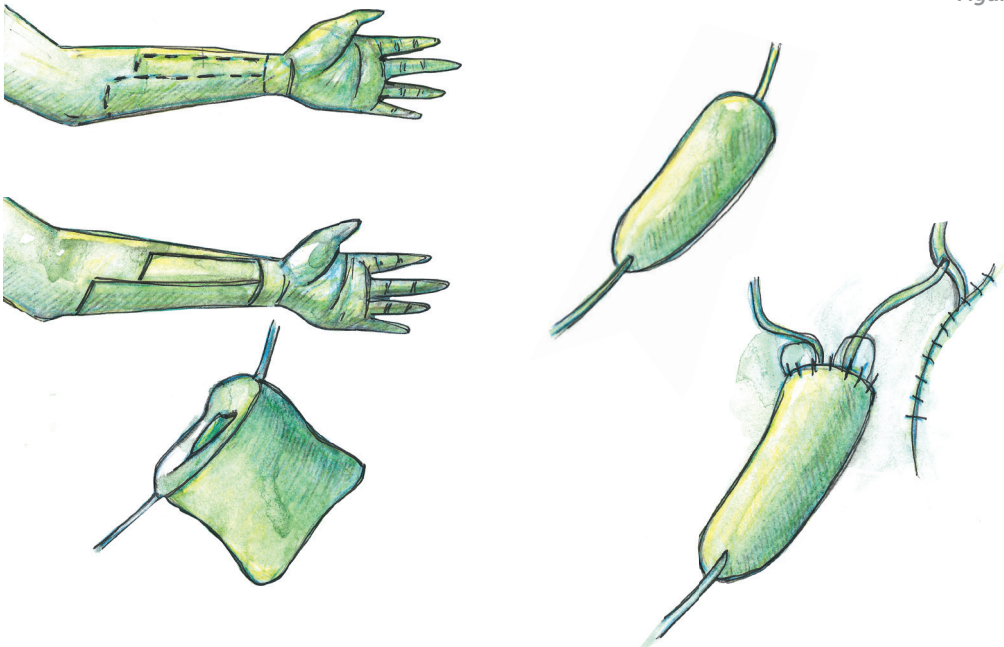


Figure 1

Figure 1. Radial forearm free flap phalloplasty

of the cylinder (Figure 2) was fixed in the remnants of the corpora cavernosa. If not, the cylinder was attached to the ramus inferior ossis pubis with a non-resorbable suture.

Figure 2

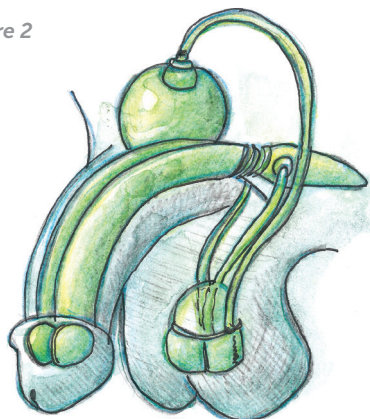


Figure 2. Penile prosthesis

Results

Patient group

Ten of the 18 invited men participated (response rate: 56%). The remaining eight either declined participation, or could not be reached (by phone, e-mail, or post mail). Non-responders and participants did not significantly differ in the medical variables (Table 1). However, in the early postoperative period two major complications were only seen in the non-responders: one patient developed a pulmonary embolism and was treated with a therapeutic dose of low-molecular-weight heparin. Another developed severe hematuria with clotting and obstruction of the urinary catheters which was treated conservatively.

TABLE 2 Participants' characteristics.

Patient	Age at follow-up (yr)	Indications	Follow-up (mo)	Type of phalloplasty	Complications	Erectile prosthesis ^a
1	43	Penile amputation – squamous cell carcinoma in situ	17	RFA	(Transient) urethral fistula	AMS Spectra™, 1 cylinder, 12 cm
2	31	Shriveled penis – bladder exstrophy	92	RFA	None	AMS Ambicor™, 2 cylinders*, 14cm
3	25	Micropenis – 17, 20 lyase deficiency	20	RFA	(Transient) urethral fistula and stricture	No
4	43	Penile necrosis – embolisation for priapism	47	ALT	Urethral fistula and stricture	AMS Ambicor™, 2 cylinders, 18cm
5	20	Shriveled penis – bladder exstrophy	14	RFA	Urinary infection	AMS Ambicor™, 2 cylinders, 14cm
6	22	Shriveled penis – cloacal exstrophy	63	ALT	None	AMS Ambicor™, 1 cylinder, 16cm
7	22	Shriveled penis – bladder exstrophy	35	RFA	Urethral stenosis, fistula, hair incrustation in neo urethra	AMS Ambicor™, 1 cylinder, 14 cm
8	20	Shriveled penis – bladder exstrophy	33	RFA	None	AMS Ambicor™, 1 cylinder, 14cm
9	32	Micropenis – partial androgen insensitivity syndrome	24	RFA	Urethral stricture and fistula	AMS Spectra™, 1 cylinder, 12cm
10	24	Micropenis – partial androgen insensitivity syndrome	24	RFA	Infected haematoma, (transient) fistula	AMS Spectra™, 1 cylinder, 12cm

*Revision prosthesis because of aneurysmal swelling. Abbreviations: RFA= Radial forearm free flap; ALT= Anterolateral Thigh Flap; AMS= American Medical Systems, yr= year; mo= months. ^a The decision on the number of cylinders implanted was made at the beginning of surgery based on the girth of the phallus and the possibility of dilating two pockets without damaging the urethra. With the observation of unesthetic outcomes due to asymmetry in the final position of the cylinders, the two-cylinder option was no longer proposed to the patients.

TABLE 3 Satisfaction with surgical result and possibilities of penile prosthesis during sexual activity.

	Mean \pm SD (N)		
	Phalloplasty (10)	Hypospadias surgery (73) ^a	
		Distal hypospadias (57)	Proximal hypospadias (16)
Satisfaction with surgical result (1 to 7)	6.3 \pm 0.9 (10) ^b	5.3 \pm 1.4 (57)	4.8 \pm 1.6 (16)
Satisfaction with quality of erection during sexual activity (0 to 10)	7.3 \pm 3.4 (9) ^c	-	-

Motives for dissatisfaction with penile prosthesis (total N=6)

- 1) Problems with rigidity: 50% (n=3)
- 2) Having to (de)activate the penile prosthesis interferes with the natural flow of sex: 17% (n=1)
- 3) Occasionally painful pressure of prosthesis in groin area or lower abdomen during intercourse: 83% (n=5)
- 4) No control over activation of penile prosthesis: 17% (n=1)

^aData from [20], ^b significant differences between phalloplasty and hypospadias groups (0.8 [0.4 – 1.1] 95% CI < Cohen d Effect size < 1.1 [0.6 – 1.6] 95% CI), p < .01, ^c Not including the man without penile prosthesis, who was dissatisfied with the quality of erections (score 2/10); Note: more motives per subject are possible, no differences in satisfaction were found between men with one or two cylinders implanted

Surgical procedures and satisfaction with surgical result

Main features of the ten participants (mean age 28.2 years, range 20–43 years) are presented in Table 2. All were older than 16 years at the time of surgery. Mean follow-up after phalloplasty was 36.9 months (range 14–92 months). All but two patients (nr 1, 4) underwent multiple penile and urethral reconstructions in early childhood and had a stretched penile length of < 6 cm. One patient with cloacal exstrophy (nr 6) and one patient who underwent penile amputation because of penile necrosis after persistent priapism treated with an unsuccessful cavernosal-femoral shunt and later with embolization of the pudendal artery (nr 4) were not good candidates for RFA as pelvic anatomy and vasculature were uncertain. In all but three patients (nr 1,3 and 4), there was sufficient penile and/or cavernosal tissue to be incorporated at the base of the newly reconstructed phallus. Flap survival was noticed in all patients, and there were no

complications concerning the donor area. All patients were satisfied to highly satisfied with the global surgical result (Table 3) and none of the patients regretted surgery. Emptying of the bladder was done transurethrally in five patients and by catheterization through continent diversion in five patients with bladder or cloacal exstrophy. Three of these patients requested a urethral reconstruction for ejaculation, the other two preferred to keep their ejaculatory opening at the ventral aspect of the scrotum.

All five patients in whom urethra was constructed, developed a fistula at the anastomosis of the neo-urethra to the native urethra, of whom three also developed a urethral stricture. Only two patients needed a secondary procedure for closure of the persistent fistula; in one of them (a patient with a concomitant urethral stricture) a two-stage urethroplasty was performed. All patients without continent diversion, except two waiting for a revision for the urethral stricture, could void normally in a standing position.

TABLE 4

Mean ages in years of adult phalloplasty patients, hypospadias patients and comparison subjects at which sexual milestones were reached.

	Mean ± SD			Effect size Cohen's d [95% CI] [†]	
	Phalloplasty	Hypospadias surgery ^a	Comparison group ^a	Phalloplasty vs hypospadias	Phalloplasty vs comparison
N	8 ^b	73	50		
Age at interview	24.5 ± 4.7	25.6 ± 5.7	25.3 ± 3.7		
First time in love	11.8 ± 1.8	14.0 ± 3.7	12.6 ± 3.4	-0.6 [-1.6; 0.1]	-0.3 [-1.1; 0.6]
First time masturbation	12.5 ± 2.1	13.9 ± 2.0	13.4 ± 1.7	-0.7 [-1.1; -0.3]	-0.5 [-1.0; -0.1]
First time dating	14.6 ± 1.8	15.3 ± 2.2	15.0 ± 2.6	-0.3 [-0.8; 0.1]	-0.2 [-0.8; 0.5]
First time French kissing	15.1 ± 2.6	14.8 ± 2.7	15.1 ± 2.8	0.1 [-0.5; 0.7]	0.0 [-0.7; 0.7]
First time undressed necking and genital fondling	16.4 ± 5.5 ^c	17.0 ± 2.5	16.8 ± 2.7	-0.2 [-0.9; 0.4]	-0.1 [-0.9; 0.7]
First time sexual intercourse	18.7 ± 2.4 ^c	17.9 ± 2.3	17.3 ± 2.6	0.4 [-0.2; 0.9]	0.6 [-0.1; 1.2]

[†] Effect sizes (ES) of mean differences according to Cohen (1988) were computed, using pooled standard deviations of the two groups (Cohen's $d = M1 - M2 / sd \text{ pooled}$, where $sd \text{ pooled} = \sqrt{(sd1^2 + sd2^2) / 2}$). An ES of 0.2 is considered to be small, an ES of 0.5 to be moderate, and an ES of 0.8 to be large. 95% confidence intervals are reported. A positive ES reflects a higher score in the phalloplasty group, whereas a negative score reflects a higher score in the hypospadias group or comparison group. ^a Data from [20], ^b Not including the two men with acquired penile deficiency as adults, ^c one man (aged 20 years) did not have had sexual experience yet

A penile prosthesis was implanted in nine patients on average 16.8 months (range 10–25 months) after the phalloplasty procedure (Table 2). One man underwent a revision of the prosthesis because of malfunction based on an aneurysmal swelling of one of the cylinders (nr 2) after 5.8 years. The majority of patients were satisfied with the possibilities of the penile prosthesis for sexual activity, although problems with the devices were reported, independent of the number of cylinders implanted (Table 3).

In three men with a 46, XY disorder of sex development condition (DSD), a defeminizing gynecmastia surgery (Mean: 14 years (range 12–16 years) was additionally performed. In four patients a unilateral testis prosthesis was implanted (left side: nr 3, 5; right side: nr 9, 10).

Psychosexual outcomes

Sexual adjustment. There were no differences in mean ages at which sexual milestones were

reached (small to moderate effect sizes, Table 4). 12.5% (1/8) of men with congenital penile deficiency had not yet experienced sexual intercourse after surgery, versus 20.5% of the hypospadias group and 12% of the comparison men ($p > .05$). Four of the seven men who had experience with intercourse, had already (tried) intercourse before phalloplasty, but reported an improvement after surgery. Four men had a satisfactory stable relationship, in which communication about sexuality was present. Although inhibition in sexuality with their present partner had diminished, three out of four indicated that this might return with a possible new future partner. In three out of four men without a partner, even with sexual (coitus) experience, inhibition and fear of sexual rejection were highly present, compared to 40% of hypospadiac patients ($p < .05$) and 11% of controls ($p < .01$). Reported motives were related to the fear of 'technical' failure ($n=2$), reaction of the potential partner on the prosthesis ($n=2$) or not knowing how to use it in a sexual situation ($n=1$). One man is currently following psychotherapy to overcome these barriers, another had

extensive psychological support in the past, more related to problems associated with his specific DSD condition (e.g. young appearance, no masculine hair growth). Although offered, all others were reluctant to seek psychological advice for problems. Both men with acquired penile deficiency in early adulthood suffered from depression and loss of sexual self-esteem after the trauma. One man divorced and did not have coitus experience yet after surgery, causing great distress for which he is treated with antidepressants.

"I was always
this strong man.
Now I feel so
vulnerable."

Sexual behavior and functioning. In general, no significant group differences between the phalloplasty patients and the hypospadias or control groups were found with regard to frequency of sexual activity with a partner,

masturbation frequency or sexual desire (Table 5). Accordingly, effect sizes were small to moderate. 100% of men had experienced orgasm with ejaculation; in 8/10 through intercourse, in 2/10 exclusively through masturbation. None of the men had a penile curvature causing difficulties during intercourse. In two men painful bladder cramps after ejaculation were reported, causing no distress. One man complained of precocious ejaculation, which he thought was of psychological origin and for which he had sought professional advice.

Genital sensitivity. In the seven patients in whom there was sufficient penile and/or cavernosal tissue to be incorporated at the base of the newly reconstructed phallus, sensitivity to sexual touch was reported to be better at the base of the phallus ($M= 7.6$, $sd= 0.5$), compared to the top ($M= 3.7$, $sd= 0.6$) (Wilcoxon $p<.05$). The three other men (nr 1, 3 and 4) indicated to have little penile sensitivity; in one man (nr 3) the skin between scrotum and anus and base of scrotum was however highly orgasm sensitive. No significant correlation was found between follow-up time after phalloplasty and sensitivity scores.

TABLE 5 Sexual behavior and sexual functioning of adult phalloplasty patients, hypospadias patients and comparison subjects.

	Mean \pm SD			Effect size Cohen's d [95% CI] ^c	
	Phalloplasty	Hypospadias surgery ^a	Comparison group ^a	Phalloplasty vs hypospadias	Phalloplasty vs comparison
Sexual activity with a partner/month	8.3 \pm 4.5 (4)	7.6 \pm 7.4 (58)	6.8 \pm 6.3 (44)	0.1 [-1.7; 1.8]	0.3 [-1.5; 1.9]
Masturbation frequency/month	5.7 \pm 8.0 (10)	6.8 \pm 6.9 (66)	5.0 \pm 5.3 (47)	-0.2 [-1.7; 1.4]	0.1 [-1.4; 1.6]
Sexual desire (0 to 100) ^b	79.5 \pm 20.8 (10)	64.9 \pm 20.2 (73)	69.7 \pm 21.7 (47)	0.7 [-3.6; 5.0]	0.5 [-5.0; 6.0]

^a Data from [20]; ^b visual analog scale; ^c In order to be able to compare the results across different studies, effect sizes (ES) for group differences according to Cohen (1988) with 95% confidence intervals were calculated. A positive ES reflects a higher score in the phalloplasty group, whereas a negative score reflects a higher score in the hypospadias group or comparison group.

TABLE 6 Genital appraisal and problems with undressing in public.

	Phalloplasty	Hypospadias surgery ^a	Comparison group ^a	Phalloplasty vs hypospadias	Phalloplasty vs comparison
Genital appraisal (0 to 4)	2.2 ± 1.5 (10)	2.4 ± 1.1 (73)	3.2 ± 0.8 (15)	-0.2 [-0.4, 0.1] ^c	-0.9 [-1.3, -0.5] ^c
1. Penile appearance different as other men	80% (10)	84.7% (73)	40% (50)	-0.2 [-1.1; 0.7] ^d	1.0 [0.1; 1.9] ^d
2. Dissatisfaction with penile appearance	50% (10)	25% (73)	12% (50)	0.6 [-0.1; 1.4] ^d	1.1 [0.3; 1.9] ^d
3. Dissatisfied with penile length in flaccid state	20% (10)	38.4% (73)	20% (50)	-0.4 [-1.3; 0.5] ^d	0.0 [-0.9; 0.9] ^d
4. Dissatisfied with penile length in erect state	22% (9) ^b	13.7% (73)	4% (50)	0.3 [-0.6; 1.3] ^d	1.1 [-0.1, 2.2] ^d
Problems with undressing in public	60% (10)	32.9% (73)	22% (11)	0.6 [-0.1; 1.4] ^d	0.9 [0.1; 1.7]

Note: A genital appraisal score (mean ± sd (N)) was computed by adding the answers to the 4 questions, with a score of 1 attributed to answers marked 'yes'. The genital appraisal score varied from 0 (very negative) to 4 (very positive). Percentages represent the proportion of participants endorsing a positive answer on the specific genital appraisal items or have problems with undressing in public; ES= Effect size [95% confidence intervals]. ^aData from [20]; ^b Not including the man without penile prosthesis as he could not have erections; ^c Effect size calculated according to Cohen (1988); ^d Effect size calculated according to Hasselblad and Hedges (1995) due to dichotomous outcomes. A positive ES reflects a higher score in the phalloplasty group, whereas a negative score reflects a higher score in the hypospadias group or comparison group.

Genital appraisal. Phalloplasty (as well as hypospadias) patients reported on average a more negative genital appraisal than the comparison men (large effect sizes, Table 6). Approximately twice as many of the former groups considered the penile appearance to be different from that of other men and tended to be dissatisfied with the penile appearance. The main spontaneously reported motives for dissatisfaction in the phalloplasty patients were a small penis size (n=2, 20%) and/ or artificial look (e.g. color difference) (n=5, 50%). In both the hypospadias and comparison groups, the main motive for dissatisfaction was penile size, respectively 11.1% and 8%. It appeared that more hypospadias patients than phalloplasty or comparison subjects considered the flaccid penis to be too small. However, these percentages diminished significantly for penile size during erection in the hypospadias and comparison subjects (p<.05 for both), but not in the phalloplasty group. Moreover, twice as many phalloplasty patients reported difficulties with undressing publicly (e.g. after sports, sauna) compared to hypospadias and control men (moderate to

large effect size, Table 6). Self-consciousness about the penis, including potential questions about scars, were the main motive, compared to prudishness reported by most controls. None of the men have received any negative reactions or comments on penile appearance from others, including sexual partners.

Discussion

It is reassuring that the majority of adult men with penile deficiency who underwent phalloplasty experience relatively normal sexual adjustment and lead an adult sex life that does not differ greatly from men with normal genitalia or men who underwent hypospadias repair in childhood [20]. These results corroborate previous findings at long-term follow-up (>1 year post surgery) [15, 16]. However, a higher percentage of these men (50%) were dissatisfied with certain aspects of genital appearance compared to other studies after phalloplasty (5-14%) [14, 16] and hypospadias correction (25%) [20].

Genital appraisal satisfaction did thus not exclusively rely on the surgical outcome, as 90% of men were highly satisfied, but also seemed to be related to psychological factors and expectations, as is illustrated by poor satisfaction scores in the two men who had traumatic penis loss as compared to men with congenital micropenis and which also corroborates findings within the transgender population [11].

"The thing is, when you get out of the hospital, you feel liking having something that is not yours."

The majority of men described how they felt sex to be impossible before treatment i.e. that their genitals were structurally inadequate to sustain the mechanics of penetrative intercourse. However, post-treatment, they were surprised to learn that having the 'right equipment' allowing intercourse was only part of the story. Three quarters of the men still felt inhibited in seeking sexual contacts, even with sexual experience. Psychological barriers to getting involved in sexual activity were experienced to be at least as great as the physical ones and the cost of being found out by potential partners to be less than 'normal' men was imagined to be high [23]. Therefore, we advocate the importance of early and continued counseling as a standard practice, since most seem reluctant to seek psychological support on their own initiative, even when they are experiencing considerable difficulties.

The major drawbacks of phalloplasty are the high urethral complication rate (stricture

and/or fistula) and the problems with the penile stiffeners, comparable to the rate experienced in transsexual phalloplasty [22,24].

"...And even if you want to kiss her, you don't do it, because maybe while she kisses you, she can feel that you don't have a penis. This is so stupid, but it is in your head the whole time."

Obtaining sufficient rigidity to allow penetration is extremely difficult because there is no good substitute for the unique erectile tissue of the penis [24]. The anastomosis between the fixed and phallic part of the urethra is the most important stricture location and prone to fistulation in the early postoperative period. These fistulas often close spontaneously, but sometimes, due to excessive scarring, can lead to stricture formation [31]. A broad variety of techniques – based on the general principles of wound healing and tissue transfer- is needed to handle each type of stricture (for an overview, see [31], but recurrence remains frequent (41%). Moreover, as loss of penile tissue is a dreaded complication of bladder or cloacal exstrophy repair and the majority of the study sample had a multiplicity of previous penile reconstructions in childhood, complications and psychosexual outcomes are possibly worsened. Moreover, genital sensitivity was said to be less than hoped for in all men, especially at the dorsal locations the neophallus, compared to the base where incorporation of penile or cavernosal tissue still provided erogenous sensation in 70% of men.

This cross-sectional study bears an exploratory character and is not without limitations. We compared our data with those from a different historical and cultural study cohort, as control, which is a possible threat to the internal validity. A contemporary and representative control group would be more meaningful, in particular as the sample consisted primarily of white, heterosexual men, which limits the external validity of the findings. The return-rate was rather low, and although the non-responders did not differ regarding additional surgical procedures or complications, nor demographics, the results might be biased. The small size caused low statistical power and restricted statistical analytic options. In addition, an improved research methodology is needed. As standardized psychometric sexual Qol instruments designed for a normative sample are not always able to detect the specific distresses experienced by affected individuals, in the present study a personal interview was deemed more valuable. Likewise, methodological differences might explain the higher genital sensitivity problem rate, as self perceived sensation regarding sexual stimulation (by self or partner) was assessed instead of vibratory or thermal psychophysiological thresholds [14]. Further follow-up of genital sensitivity outcomes is essential as sensation at the top of the phallus might improve with time. Moreover, long-term function of the erectile devices remains uncertain, as they are designed for men with erectile dysfunction, who are older and less sexually active than men within this specific population [14]. Prospective multicenter studies with larger numbers, recruited from several sources (i.e. clinic and support groups) and control groups are necessary to fully understand the factors that may influence long-term sexual outcome, such as specific coping mechanisms or family background and attitude of patients' parents

or partners towards the penile condition [25]. A structured counseling protocol and guidelines for the indications of phalloplasty in these men, including penile deficiency within the broader diagnostic category of DSD conditions, should be developed. More specifically, a penile length of less than 6 to 7 cm seems to represent a cut-off for satisfactory intercourse [20,26], but suggesting a cut-off for phalloplasty remains highly challenging.

Despite the shortcomings of this study, we are encouraged by our initial experience with RFA in this challenging population, including boys with 46,XY DSD and severe undervirilization. Penile (re)construction may require, however, multiple steps, and satisfaction and resumption of intimacy and sexual identity is more complex than just creating a phallus. As dissatisfaction with genital appearance or size, and fear of sexual rejection leading to great psychosexual distress have been reported before in studies with boys [25] and men with atypical genital development [23,27-30], we recommend that from childhood onwards patients should be given opportunities to develop coping skills and a more positive genital (and self) image. These may ultimately lead to improved sexual quality of life for men recovering from phalloplasty.

Conclusion

Penile reconstruction is a matter of concern as severe penile insufficiency might jeopardize sexual satisfaction. The results of this series concur with others in that the microsurgical radial artery-based forearm free flap phalloplasty technique provides the patient with an excellent result. However, patients must be fully informed about

"I have to
accept my new self,
my limitations
and personality."

possible limitations and complications of the technique, as to have realistic expectations. In order to guarantee a comprehensive treatment concept, continued follow-up and the incorporation of psychological factors may be equally important.

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Children
DISTRESS
CONTROL
SACRIFICE
PERFORMANCE
HUMAN
COOPERATIVE
PSYCHOTHERAPY
ESTEEM
INFERIORITY
ANXIETY
COMMUNICATION
Shame
PLEASURE
INFORMATION
CHANGE
SUPPORT
IMAGE
Adaptation
EMPOWERMENT
EMBODIMENT
Vulnerable
HOLISTICALLY
SENSITIVE
Happiness
REGRET
RESPECT
IGNORANCE
FEMININITY
EQUALITY
VISIBLE
Caring
Unfair

SECRET
EXPECTATIONS
PSYCHOLOGY
COMPENSATORY
ACCEPTANCE
FEELINGS
Reflecting
NORMAL
LOSS
LIFE
HEAVY
PERFECT
HELPLESSNESS
Confidence
Pain
INCOMPLETE
CONFRONTATION
DILEMMA
ENTITLEMENT
ISOLATION
Personality
Belongingness
INVISIBLE
DISCLOSURE
Mask
COMPARISON
INTERCONNECTEDNESS
CHOICE

TABOO
FUTURE
ABNORMAL
INFERTILITY
LIES
ANGER
PRIVATE
SOCIAL
TRUST
RELATIONSHIPS

CHAPTER 6

General discussion

*Even our “parts” are
(much) more than
the sum of their parts.*

Virginia Braun

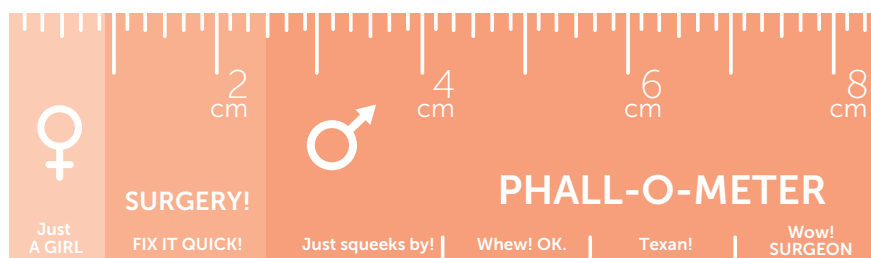
6.1 Genital treatment practices in context

Westerners live in societies premised on two widespread, and linked, assumptions related to gender(ed) identity [1]. The first is that humans are discretely sexed into two categories [2], with fundamental assumptions about gender or sex differences - as can be seen in the current popularity of evolutionary psychology, and in the enormous success of pop-psych books like 'Men are from Mars, Women are from Venus' [3]. The second is that gendered identities map onto biological bodies, such that genitals are a crucial part of difference and identity [1]. Socio-culturally, "everyone knows that women and men are very basically distinguished by their genitals, so that a female is a person with a vagina; a male is a person with a penis"[4] (p. 113). At birth - or before - we are often assigned a sex simply on the basis of a visual inspection of our genitals. Psychosexual (gender) identity is assumed to develop based on this genital difference. Freud for instance, based his theories on the 'absolute salience of the genitalia' with penis presence or absence as key component [1,5,6]. The link between genitals and gendered identity, then, seems to constitute a basic, everyday, taken-for granted commonsense, in society, medical practice, and psychology. These assumptions also come into play for individuals with a DSD, who do not have discretely "sexed" genitals, and for transgender individuals, whose gendered identity does not 'match' their body (e.g.,[7]).

The historical importance attributed to outward and easily checked appearance and the later development of surgical techniques for altering genitals, contributed to a shift from gonads to genitals as *the* signifier of gender, and the modern centrality of genital surgery in the demarcation of the two sexes [4, 8-11]. Within the standard pediatric practice of sex assignment and genital surgery for infants with ambiguous genitalia, considerations for the male or female sex differed. For sex-assigned males, potential of sexual function (erectile and penetrative potential of the phallus) was a major consideration; in the case of chromosomal females, fertility (the presence of womb and ovaries) was deemed most important [10, 12]¹. Joan Hampson wrote in 1955: 'If the external genitalia cannot possibly under any conceivable circumstances be surgically reconstructed for functioning in one sex, then the other sex should be assigned and subsequent medical and surgical efforts should be directed towards securing hormonal as well as morphological congruity with the assigned sex' (p.271) [13]. Although the Money and Hampson protocols ostensibly sought to avoid a change of sex, their emphasis on sculpting genitalia made surgical sex assignment in infancy common [14]. This also meant that where genital ambiguity was pronounced, surgeons traditionally recommended female assignment, because it was easier to create a 'functional' vagina (i.e. capable of receiving a penis) than a 'functional' penis (i.e. capable of erection and penetration) [10]². Following the sex assignment (and surgery), parents were advised to raise the child without ambiguity, which might include having to withhold information from the child (and adult) [15-17].

These practices have been challenged, not least through the 'coming of age' of those who had such interventions as children and, as adults, have spoken negatively on their experiences

[10,12,18-23]. Drawing energy from other social movements, such as women's rights, civil rights and gay liberation, as well as through the rapid expansion of the Internet – with the development of anonymous online discussion forums- the efforts of DSD activists were facilitated in objecting against the timing and necessity of genital surgeries, the presumption of heterosexuality in treatment recommendations and the authority of science and medicine in general [14]. Although there are still disagreements on the desirability of sex assignment at birth, there is general agreement among those seeking changes in practice – translated into consensus statements [24,25] – on the need to involve parents fully in decision making; to foster more open communication among parents, children and professionals; to provide psychosocial care as an integral part of management; to stop viewing the birth of an infant with ambiguous genitalia as an 'emergency' (unless glucocorticoid treatment and surgery is medically necessary to prevent salt-wasting crises or urinary obstruction such as in CAH) and as far as possible delay genital and gonadal surgery until the person can give informed consent [10, 12,26]. In essence, the DSD reform movement is a human rights movement – like the civil rights movement against racism and the women's right movement against sexism – and is founded on the assumption that people with DSD should not be oppressed because their bodies simply do not fit social norms [27].



The aims of this dissertation were to comprehensively review some of the complexities and factors relating to the process and outcome of (mostly) non-consensual genital treatment in women with CAH and men with DSD in childhood (**Chapter 2**) and consensual genital treatment practices for adolescent and adult women with an absent vagina and adult men with micropenis (**Chapter 2,4,5**). The study of adult choices for genital reconstruction, either surgical or non-surgical, is important, because it addresses cultural imperatives also underlying infant

¹ The asymmetric- or should we say sexist- way femininity and masculinity is treated is problematic. For instance, physicians have done far more to preserve the reproductive potential of children born with ovaries than with testes. While genetically male patients often have infertile testes, some men with micropenis may be able to father children if allowed to retain their testes [11].

² What are the limits of acceptability in terms of clitorises and penises? Clitorises are frequently being considered too big in children if they exceed one centimeter in length. Penises are considered too small if the stretched penile length is less than 2.5 centimeters [11]; Most notably, the Intersex Society of North America produced 'phall-o-meters', intended to expose the arbitrary measures used for genital inadequacy

sex assignment, such as the female-male dichotomy and assumptions about what genitals are 'for' [10]. In addition, studies that show outcomes of genital treatment to be problematic, raise questions about the information patients receive, the decision-making process and criteria for 'success' [10,28]. Therefore, we were concerned with the lived experiences of women and men with DSD, focusing on decision-making (e.g. perceived advantages and disadvantages of the procedures, expectations), the experience of both widely adopted as well as newer genital treatment practices and perceived outcomes, particularly in relation to self-perception, forming intimate relationships and sexual activities.

6.2 Exitus acta probat (Ovidius) : the end justifies the means?

6.2.1 What means?

6.2.1.1 Treatment for ambiguous genitalia

Feminizing genitoplasty for ambiguous genitalia usually comprises clitoral surgery, vaginoplasty and labial refashioning, generally performed within the first year of life. Clitoral surgery can also be performed without concomitant vaginal surgery and is purely cosmetic, with the objective of reducing clitoral size. Vaginoplasty as part of the feminizing genitoplasty is most commonly performed for women with congenital adrenal hyperplasia (CAH). In this condition, the internal genital anatomy is normal and a uterus is present with the potential for menstruation. The vagina is fused with the urethra resulting in a single opening on the perineum (i.e. high or low confluence of the vagina). The aim of surgery is to create the lower vagina to avoid urinary infections in severe cases of virilization, to allow menstrual flow, and intercourse [29]. In addition, female assigned patients with XY, DSD and virilized genitalia (such as in partial androgen insensitivity syndrome, PAIS) may also warrant feminizing genitoplasty.

In **Chapter 2**, it was shown that women with CAH were less likely to have experienced sexual intercourse with male partners and were more likely to report pain with intercourse, as well as experience considerable anxiety about sex, which corroborates previous study findings [19,30-36]. Overall sexual function scores were poor when compared to the standard female (control) population. It is clearly possible that the genital abnormalities and their surgical correction may have resulted in physical difficulties during intercourse for women with CAH, problems connected for instance with penetration, insufficiently large vaginal introitus, lubrication, residual pain from tissue repair and reduced clitoral sensitivity [36]. CAH women who had experienced sexual intercourse, attributed problems with penetration to their genital anatomy (i.e. tightness or shortness of the vagina), embarrassment of their body or that they were not ready for it (yet). Failure of penetration, or anxiety about penetration, had resulted in the complete avoidance

in some. Lubrication of the vagina is an essential factor in the ease of penetration and is also believed to be an indicator of arousal. Arousal, and therefore lubrication, can be inhibited by anxiety [37]. Women with CAH did report significantly more problems with lubrication and arousal compared to non-affected women, reinforcing the pain and difficulties they experience and possible reinforcing concerns about normality of the genitalia and confirmation of 'not being like the other women'[36]. It is clear that besides physical, also social and psychological factors may be important (Figure 1). 'Will it work, will it not work?[...] I know I have to relax, but I just tense up, making it even more painful. Moreover, there was a general attitude in the CAH group that nothing could be done and that there was no one to go to for help, consequently removing self decision-making processes and future initiatives for change, including options to improve their sexual situation (e.g. use of lubricants, seeing a sexologist). Similar findings were reported before, in which women with CAH held the view that their sexual problems were entirely a result of CAH and their failure to consider methods of alleviation, some women believing that 'the right man would somehow make everything right' [36,38].

Figure 1

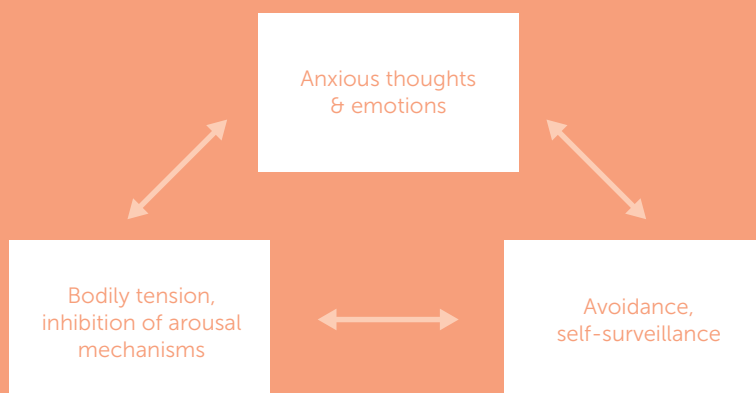


Figure 1. Interaction of psycho-physiological contributory factors to sexual difficulties (adapted from [39])

In considering the relationship between the physical problems or sexual difficulties, surgery and the level of masculinization, a number of factors need to be taken into account. The sample is small and includes a number of women who have not had sexual experience. The fact that some aspects of surgery were similar for women across levels of abnormality makes any relationship between levels of masculinization and sexual problems difficult to examine [36]. In contrast, cosmetic appearance was associated with the degree of virilization at birth, in that women with the more severe forms of CAH had worse cosmetic outcomes. Previous studies showed greater stenosis and a more narrow vagina correlating with more prenatal virilization, with patients in the null genotype group having more surgical complications, fistulae and strictures compared

to the I2splice group [31,40,41]. In **Chapter 2**, it is shown that the impact of the severity of virilization on cosmetic outcome increases with increasing number of surgeries performed and with the age at first surgery. Because most of the participants (80%) had the more severe form, and more extensive surgery at a younger age, it remains difficult to determine if early feminizing surgery had a detrimental effect on cosmetic outcome and if delaying it might have led to better outcomes. Also, cosmetic results were still variably evaluated by these women, who tended to be only somewhat more critical than the physicians (25% vs 21% rated cosmetic outcome as insufficient). To our knowledge, this is the first study reporting the correlation between severity of virilization at birth, the extensiveness of surgery and age at surgery, and cosmetic satisfaction with surgery in CAH, from both a patient and clinician perspective. It is important to try and obtain prospective outcome data. Controlled observational studies are currently not available to document whether genital surgery prevents adverse psychosocial consequences. Parents and patients do need to be informed extensively about the multiple aspects that contribute to outcome after feminizing surgery and of the fair chance that reoperation is necessary in adolescence (54%), despite a planned 'one-stage' procedure. Vaginal strictures were common (22%). Although the percentages were in general lower, it confirms previous study findings of high rates (40–100%) of introital stenosis and frequent requirements for repeat reconstructive surgery in adolescence before tampon use or intercourse [20,42,43]. Adjunctive treatments to prevent stenosis such as vaginal dilators may be helpful, but cannot be used in the young child [44]. The atypical urinary tract formation, possibly modified again by reconstructive procedures [45], was associated with urinary difficulties in 21% of women.

Most of the clitoroplasty procedures performed in the participants comprised a reduction of the clitoris with preservation of the neurovascular bundle and glans. The effect of these nerve-sparing procedures on sexual function and in essence, orgasm, remains however unclear. No significant differences could be found with a control group of non-affected women, although orgasm scores were in general lower. In the two women with clitorectomy, in contrast, sexuality was highly impaired.

Concern about the impact of childhood clitoral surgery on future sexual function is of surprisingly recent origin. Pediatric surgeons in the past have been confident that extensive surgery to the clitoris would not have an impact on sexual sensation [46]³; however adult patient support groups have raised awareness of potential difficulties as a result of clitoral surgery, triggering further neurological research, with varying conclusions [19,50,51]. Recent work on the anatomy of the clitoris has shown it to be more extensive than previously thought, extending behind the pubic bone to reach the anterior vagina [52,53]. Further examination of the innervation of the clitoris has demonstrated nerves surrounding the tunica with multiple perforating branches entering the dorsal aspect of the corporeal body and glans [54,55]. Thus any incision to the clitoral glans, corpora or hood may damage the innervation [44] and repeated clitoral surgery

³ One of the first studies was again conducted by Money and the Hampsons, declaring that : 'clitoral amputation in patients living as girls does not, so far our evidence goes, destroy erotic sensitivity and responsiveness, provided the vagina is well developed' (p.334) [47]. They surveyed a dozen women about their sexual sensation following the surgery and none of them reported a loss of orgasm. In fact all twelve were 'unanimous in expressing intense satisfaction at having a feminine genital morphology after the operation' (p. 295) [48]. Money further declared that 'in the female as well as the male it is remarkable how much erotic tissue can be removed without loss of erotic pleasure and the capacity to reach a sexual climax' (p.93) [49].

may be more damaging to sexual function than a single procedure [20]. Recent studies have been unable to find any significant difference when comparing outcomes of clitorrectomy and clitoral reduction despite the assumption that nerve preservation is essential [19]. However, caution regarding clitoral surgery is advised for preventing possible difficulties, as it was shown (**Chapter 3**) that the clitoris is the most erotically important perceived sensory organ contributing to female orgasm. Moreover, women might accept a larger clitoris than is considered to be 'normal' by clinicians, with perceptions of clinicians and women not always aligning (**Chapter 2, 3**). Definitions of genital 'normality' in practice also appear to vary among clinicians, making decisions on where to put the boundaries on 'acceptable' levels of anatomical variation highly challenging [11].

Lastly, with regard to the purpose of surgery, there is a long-held assumption that early surgical alteration of anomalous genitalia- such as an enlarged clitoris being visible- is first of all necessary for the sake of facilitating parental bonding and coping⁴. However, measures of parent's stress do not necessarily correlate with the degree of the child's genital atypicality [57] and uncertainty about diagnosis and prognosis have been found to elicit greater distress than physical sex ambiguity [58,59]. Second, clinical management assumes that normalizing the genital appearance will also influence psychosexual development of the child, although the extent to which gender development arises out of genital anatomy is far from clear, despite popular psychoanalytic theories [5,29]. There is a dearth of evidence that early 'feminizing' surgery is associated with a 'female' gender identity. The latter is generally preserved among CAH girls, despite the presence of atypical genitalia and anecdotal reports of gender dysphoria [60]. Of course, choosing to defer surgery and leaving the genitalia unaltered, remains a difficult decision, and psychological wellbeing in affected individuals might be at risk. This notion finds also support by some studies indicating a preference for early surgery by patients [34, 40,61]. However, psychological research suggests that children raised with a visible atypicality are not necessarily distressed by that atypicality, but more by the pressure to conform - with interventions to appear more typical being a manifestation of that social pressure [62]. The value of training in coping and stress strategies, as well as negotiation skills (e.g. for not going ahead with surgery) is pointed out here [63], for both patients and parents alike. Finally, in contemplating the avoidance of early genital surgery, one must also consider that no studies have been conducted to demonstrate that potential adverse psychosocial consequences of gender-incongruent genital appearance can be ameliorated by psychological counseling or psychotherapy, making this an important area of future research [64].

⁴ One problem with performing surgery to allay parental anxiety is that the surgery cannot destigmatize the condition; it can only reshape the genitals. Moreover, some parents may regard surgery as a panacea for a variety of concerns - such as fears about homosexuality or a girl's XY chromosomal type - that have very little to do with the child's genital configuration and that often persist despite genital surgery. It is important that clinicians explicitly address misconceptions during decision-making so that parents base their decision on the actual benefit of the proposed intervention to the child [56].

Vaginoplasty or vaginal dilation are very different processes. From a woman's point of view, surgery is swift and carried out by experts, whilst dilation requires her active management – she would need to remain motivated despite sometimes slow progress, pain and in some situations for an imaginary relationship [28]. It is reasonable to expect many more women to opt for surgery. However, this is not the 'quick fix' as they imagined it to be. From our comparative retrospective study in women with vaginal hypoplasia (**Chapter 2**) it became clear that surgery was not viewed as straight forward, especially regarding the complications and resulting scars, reminding them daily of what had happened, and reflected in the lower satisfaction scores regarding genital and total body image. They also struggled with the postoperative dilation regime. As such, for many women, the choice is maybe not so much surgery or dilation, but dilation with surgery or dilation without surgery. Some women mentioned (**Chapter 2,4**) that an operation gave them a 'head start', so that they only needed to maintain the vaginal volume already created. However, many women did not comply with postoperative dilation treatment, which made future treatment options for them narrower [28].

In many situations then, vaginal dilation is a safer first line approach, precisely because it carries fewer risks (including significantly less lubrication problems, **Chapter 2**), is reversible and does not compromise future treatment options (**Chapter 4**). In more than 75% of the women it can normalize vaginal length within normal ranges (6.5-13 cm) and successful sexual function is reported – although most studies solely focused on satisfactory coitus, which is problematic given the preoccupation with intercourse and its connotations in women with vaginal hypoplasia (see *infra*). That said, dilation therapy alone is not particularly rosy as an option, and there are important psychological issues to be addressed, which is also reflected in the high failure rates of women (40%) who tried dilation therapy first before proceeding to vaginoplasty (**Chapter 2**).

Anatomical changes must be accompanied by psychological changes if women with vaginal hypoplasia are to fulfill some of the aspirations underpinning their decision to take up vaginal reconstruction. The motivation for reconstruction is often based on the desire for women to appear and feel 'normal', not only in terms of sexual anatomy, but also in terms of sexual activity and experiences (see *infra*) [28]. The psychological distress associated with vaginal hypoplasia has been shown to be a barrier for positive experiences of sexual intimacy (**Chapter 2,4**). Although there was an absence of psychiatric morbidity, this cannot be equated with positive adjustment. Whilst women were 'functioning' well on the whole (keeping up with day to day activities), and did not present major mental health problems, they were deeply concerned about certain aspects and implications of their condition, especially regarding infertility and how and when to communicate this to others. These results corroborate previous studies making use of qualitative in-depth interviews [10,36,65-67].

What is of major concern, is the perceived usefulness and the avoidance of psychological support. Avoidance effectively removes opportunities for learning skills to negotiate within certain social or sexual situations, such as disclosure of the condition to a potential partner, which

is viewed as the most daunting task for those women not in relationships. It was frequently mentioned as a reason for not seeking relationships. One of the positive outcomes of the consensus meeting in Chicago, was making the full diagnostic and treatment knowledge available to women, making decisions about treatment, but also about disclosure now 'their' responsibility [28]. However, many women still feel that they are not in control of these decisions. There is a dearth of tools to prepare women - with a DSD condition in general - to become fully involved in decision-making processes on (disclosure of) their condition (treatment and non-treatment related) and to reduce the likelihood of future worries and regret. 'Right' decisions in this field are not that obvious and are for every woman different. An outline of possible psychological approaches is provided later in this thesis. Based on experience built up over the years and informed by a review of the literature (**Chapter 4**), a theory-based model of dilator treatment and strategies to facilitate compliance were also developed, in order to inform individualized clinical management and further research (see *infra*).

6.2.1.3 Treatment for micropenis

Many patients with a micropenis (stretched penile length (SPL) <2.5cm at birth) receive androgens in infancy/childhood, as first-line medical treatment. Such treatment has in 65-71% of boys an immediate effect on SPL in childhood (**Chapter 5**). However, only 40% has a normal SPL in adulthood following HRT at puberty, most likely due to the existence of a 'masculinization window' during fetal life or in early infancy. Boys with a true micropenis condition seem to have a better prognosis than boys with a micropenis as part of the broader category of DSD, but in general, a child with a micropenis will become an adult with a micropenis [68]. Attention has, therefore, shifted to the effects of masculinizing surgery, on two levels. A first level relates to the severe hypospadias most men with a DSD condition and micropenis suffer from, further optically shortening the penis as the genital tubercle is bent; a second level relates to penile enlargement techniques, including phalloplasty.

As in feminizing genitoplasty, issues around the ideal timing of hypospadias repair have also been raised, yet not with the same intensity [69]. Based on recent reports, it seems that patients with a specific DSD diagnosis do not have worse outcomes from surgery than their counterparts without a specific diagnosis [70]. Most surgeons still follow the recommendation of the American Academy of Pediatrics, according to which hypospadias repair should take place between 6 and 12 months of age [71]. However, quality of the evidence for such an approach is limited and will likely be challenged until there is additional strict scientific data in support of it (for an overview, see [69,72]).

In a first study (**Chapter 2**), it was shown that men with DSD, all of whom had (recurrent) hypospadias repair in childhood, were significantly less satisfied with their penile appearance than non-affected men. The majority of studies have found that patients with hypospadias repair still report at least some degree of genital dissatisfaction (for a review see [72]). Sixty percent indicated that a negative genital appearance had influenced their sexual development, confirmed by a review of the literature (**Chapter 5**), in which it was clear that a deviant and

small(er) penis can be central to the experience of psychological distress and might jeopardize wellbeing. Retrospective investigations of adults who had suffered from hypospadias in their youth also showed that the men who had ever had to endure hurtful comments about the visual aspect of their penis experienced their genitals less 'positively' than those who had never had any comments [73]. In addition, data in non-clinical populations suggest that men with a more positive genital image have less sexual anxiety, and have greater self-esteem [74,75]. Both excessive worry about penis size and inflated perceived importance of penis size, have been found to contribute to poor self-esteem [76] and negative psychosocial outcomes [77]. Of note, for most of the participating men described, having a smaller than average penis was not the only difference. Studies examining sexual experiences, wellbeing and quality of life suggested that, where puberty is delayed or disturbed as is the case for instance in PAIS, appearance factors such as absent facial hair and gynecomastia were also important factors –perhaps the most important- organizing social interactions in adolescence [78]. Such appearance factors prevented the young men to 'pass' in their social world [78].

Interestingly, a small penile size was mentioned to be sexually disruptive in only 30% of men with DSD (**Chapter 2**) (as in e.g. [79]). They reported on average more sexual difficulties than men without DSD, but only significantly regarding frequency of desire to have sex, problems with firmness of the erection and reduced or weak ejaculation. However, they seemed not to be distressed about these problems. This is in line with other studies, in which most 46,XY DSD males expressed high dissatisfaction with the cosmetic result of genital surgery, but not necessarily with the functional surgical result [23]. This suggests that cosmetic aspects of surgery should not be underestimated. When assessing the relationship between satisfactory intercourse and penile size, men who reported to be able to achieve penetration had a significantly larger size (7.9 cm vs. 4.9 cm) (**Chapter 2**). Thus, a penile length of more than 6 to 7 cm seems to constitute a premise for successful sexual contact [73]. Interestingly, previous authors briefly described a few men with micropenis who reported a mutually satisfying sex life (but with difficult intercourse) with their heterosexual partners [80, 81], albeit the authors had not sought partner corroboration. The men were said to de-emphasize the importance of intercourse and had found alternative ways for themselves and their partners to reach orgasm. Does size really matter? Matter for what or for whom? (see infra)

Traditional penile lengthening procedures, such as penile extenders, can only elongate the penis by an average of 1.5 – 2.5 cm [82]. It would be a sign of hubris to propose phalloplasty – currently the only treatment being able to restore penile length within normal sizes – as a panacea. It is not. Radial forearm phalloplasty, the gold standard in transgender surgery, might be transferred to patients with a micropenis, and the first results seem promising, both regarding sexual function and cosmetic outcome (**Chapter 5**); however, there are complications and without full preoperative workups assessing patients' expectations and reasons for undergoing surgery, patients will still struggle with self-image/penile image and with psychological barriers for engaging in sexual activity.

Again, most patients refused to seek advice. *I didn't want to know a thing, I just wanted to have my penis and leave this hospital.* The difficulty with suggesting a visit to the psychologist is that such a visit is only regarded as an 'examination'; the patient denies any (psychological) concern

or problem, personal or in his relationship, but simply has the problem of having a small penis, which needs to be 'fixed' [83]⁵. Alternatively, patients might experience the visit to a psychologist as an extra threat, if admitting to struggle with emotional difficulties means that the surgery -which they have been waiting for, for a long time- might be possibly delayed or canceled. To operate on such cases nevertheless implies an attempt to solve an emotional problem with a scalpel [83]. A possible approach for the psychosocial management of penile deficiency conditions is formulated later in this thesis. Obviously, honesty and openness, especially about the possible disadvantageous consequences (e.g. urethral complications and fistulae, low genital sensitivity, scars), are essential ingredients in the informed consent process⁶. "We must know when to appropriately perform or withhold surgery. Our ethical duty as surgeons is to do no harm and to serve the best interests of our patient. Sometimes, this means admitting that a 'perfect' solution may not be attainable" [84]. Even improved surgical techniques and technologies cannot eliminate ethical dilemma's surrounding treatment [11].

6.2.2 What end results?

It is important to further appreciate the reasons for the level of preoccupation with certain issues regarding genital treatment and its 'success', among men and women with DSD, reasons that are understandable given our social context.

6.2.2.1 Becoming 'normal' and doing 'normal' through 'sex'

First, women and men who seek or undergo genital reconstruction are, consciously or unconsciously, driven by gendered aspirations [28]. They want to *feel* (more) like a 'normal' female or male by having a vagina or by having a penis [10];

"You just want to hear you are equal. Equal means that you are like the others. Not worse. Also not different. Also not better. Just equal."

⁵ It is not self-evident that a psychological problem should be handled medically or surgically. We do not attempt to solve the problems many dark-skinned children will face by lightening their skin [11]. Similarly, Cheryl Chase suggested: 'when a baby is born with a severely disfigured but largely functional arm, ought we quickly remove the arm and replace it with a possibly functional prosthetic so that the parents and the child experience less psychological trauma?' Genitals are more psychically charged than arms, but also more easily and more often kept privative, whatever their state [11].

⁶ In fact, others authors have shown that disclosure to parents can make a difference, 'as the well-informed and open parents produced more confident and better adjusted boys' [81], although they were not considered 'typical' in their sex lives (i.e. more experimental attitudes to sexual positions and methods) [11].

"I already don't have a uterus, so I would be a total freak show if I wouldn't have a vagina too."

However, such as in the case of many women with MRKH or CAIS, it was also shown that the vagina was just considered 'a hole', and not a 'real' vagina, and by implication, they were still not 'real women', because their fertility issues remained unchanged. The vagina as a symbol of reproduction and core of womanhood –amongst other sociocultural representations - have been reported before in detail [1,85]. In men's culture, the (erect) penis has been the ultimate symbol of masculine qualities, such as strength, endurance, bravery, potency, and power [86]. Precisely because of this symbolism, men are likely to feel insecure and even embarrassed if their penis is below average size.

"[By having intercourse]you want to know how it is to be normal, like someone sitting in a wheelchair wanting to know how it feels to walk. Maybe this is more what counts, rather than it [intercourse] being necessary."

Second, reconstruction is not chosen just to possess a body part. Rather, genital treatment enables them also to act like normal women and men, because they now can have 'normal sex'. The act of penetration was seen by both women and men as essential in allowing them to *be* or *feel* like a real woman or man, suggesting the conflation of (hetero)sex and intercourse [87].

"Penetration is important for my male image, that I can do it as a man."

6.2.2.2 The coital imperative: the vagina as the 'docking station' for the penis.⁷

Ironically, there was an intense preoccupation with 'successful' penetration, which invariably meant that the partner 'couldn't tell the difference' and for many becoming a real obstacle in optimal sexuality outcomes. For men, it was simply the ability of being able to penetrate, for women the ability to accommodate a penis without too much discomfort or pain, which was also apparent in the criteria for success in for instance most vaginal reconstruction outcome

⁷ L-M Liao, Workshop Disorders of Sex Development, 14-15 October 2011, Bologna

studies (**Chapter 4**) (e.g. 'normal' sexual function, satisfactory intercourse). The excessive preoccupation with intercourse has encouraged many to undervalue other forms of sexual expression, in line with many magazines as well as orthodox sex therapy manuals, referring to non-penetrative sexual activities as 'foreplay', never as sex [28].

"You can have oral sex, but that is still something different. Intercourse... well, that gives me the impression that I had real sex."

This raises further interesting questions as to what or whom the reconstruction is for. Although the women and men in this thesis conveyed the impression that although they expected to gain psychologically from genital treatment themselves, these procedures were also undertaken for (imaginary future) partners, who, as it was assumed, would not want a relationship without intercourse [10]. Just as hardly any individual spontaneously allude to pleasure as the reason of sexual expression. As one woman commented *'Penetration is no party. But I guess a lot of women have that feeling?'*, justifying in a way the discomfort she experienced during intercourse.

It is clear that defining 'success' is not a sinecure and that many scenarios common in clinical practice pose a challenge [28]. For instance, if a woman is deemed physically capable of vaginal intercourse, but has never done so, is she then considered a success? Or when she does engage in sexual intercourse, but experiences no sexual pleasure, does she represent then a successful case? Or what to think about success in the case of a woman with CAH who was really unhappy with the cosmetic result, although she could have sexual intercourse? Or another scenario where a man is having sexual intercourse but with precocious ejaculation and with discomfort, could he count as success?

Masters and Johnson, the grandparents of modern sex therapy, advised couples not to have intercourse in the first place, when this was a source of anxiety and difficulty [88]. The 'ban' on intercourse was suggested to remove the pressure and a sense of 'failure' and lead to a re-discovering of a range of non-coital and non-genital sexual activities together. One of the participants even suggested the importance of the latter and to 'sensate focus'⁸: *"as a man, you have the feeling that everything has to do with your penis. It's not. It's also about kissing and touching and hugging."* Instead, typical advice for instance for women who underwent vaginal dilation or surgery is that they *must* engage in regular intercourse or dilate indefinitely. The effects of this on the sexual experiences of women and her partner have never been really discussed or examined, but they might be counterproductive [28]. However, because of the way both patients and clinicians currently approach situations where sexual difficulties are reported, it becomes difficult to clarify whether the problems are due to a poor or failed

⁸ A term introduced by Masters and Johnson, i.e. to focus attention inward on the sensory aspects of a sexual experience rather than outward on sexual performance [88].

reconstruction, to psychological barriers or to both (see also *Figure 1*). In general, it remains difficult to determine the relative contributions of physical and psychological factors in sexual difficulties in these groups of patients. Physical contributory factors may be an insufficiently large introitus or insufficient vaginal volume, numbing of the genital area, scarring and reduced stretch, vaginal dryness or maybe also an absence of libido due to androgen deficiency in some DSDs with an androgen action and synthesis deficiency. Lay criticism has also highlighted other factors including poor communication, humiliating encounters with health professionals (including medical photography, or clinicians being unable to hide their curiosity about non-typical aspects of the anatomy), but also inadequate psychological support [28,29,65]. Two other important aspects, however, also deserve some further attention: the influence of pornography and the sex industry, and the cherished principle of choice in our society and in cosmetic surgery in particular.

6.2.2.3 McSex and Individual choice

"I had plenty of reasons to have self-confidence, but I was lacking it because I didn't have a penis. And you cannot accept it, because look at the commercials, just look everywhere, it's all about sex."

Sex is everywhere in the consumer-oriented West, and we seem more sexually active and sexually conscious than any other generation [89]. Images of genitalia - although highly selective and/or subjected to digital enhancement- are exceedingly visible due to the increased availability and acceptability of pornography. Internet provided us furthermore the entry to multiple identities, numerous sexual partners and recreational methods –if we want to. Is this perceived as even more confrontational for men and women who feel limited in their sexual expression choices? 'Choice' can be fundamental to the ways we perceive ourselves, to our cultural values, and to how we theorize our actions and the actions of others, both consciously and unconsciously [90]. The question is however how real or viable all the options can be, when societal norms and expectations effectively mandate one course of action over another, the choice for 'the norm' [91].

"You compare yourself and the biggest problem is pornography. There you see penises and somehow in your subconsciousness you think that this 20cm penis is normal. And you think that women like it. And if you read that these pornographic stars have to take painkillers sometimes, to make the movies, because it hurts so much, then you realize, but I mean, you don't know."

Feminist contributions, with autonomy and personal choice of the subject at its heart, appear to be drowned out by the powerful messages that are now influencing more and more women to have their standard genitals surgically enhanced [28,92,93]. Hymen reconstruction has existed for a long time, but 'tidying up' of the labia, injecting or suctioning of fat in different genital regions are only a few of the many newer additions in genital redesigning for 'normal' women [94]⁹. Likewise, the growth in the number of 'normal' men asking for surgical penile enhancement is worrisome [83]¹⁰. To date, there is no evidence to support the frequently made claim that sexual and/or psychological transformations will (or should) occur through cosmetic genital surgery [93].

In sum, although surgery is a domain where people are framed positively as making individual choices about their lives and framed as empowering by the media, people's desires to achieve 'normality' through surgery do raise questions about (individual) 'choice' [90]. Moreover, within the current make-over culture, and because surgical solutions are rendered a possibility, there is a social imperative towards taking up possible 'improvements' to one's body – as to become something better. The likely effect is that cosmetic genital surgery will continue to increase in popularity, with more people 'choosing' it [90]. It seems vital that the level of debate about cosmetic surgery in general be kept broad and critical, because there remain troubling concerns related to areas such as ethics and choice, pathologization and medicalization [93] – with possible implications for the future (surgical) management and acceptance of individuals with an 'atypical' genital anatomy.

⁹ Why do so many women seek Female Genital Cosmetic Surgery (FGCS)? Both esthetic and/or functional concerns have been reported [94]. Esthetic concerns appear primarily linked to a dislike of some very specific aspect of vulval appearance, particularly the visibility of labia minora, or their shape, color, or asymmetry [94]. Reported functional concerns relate to vaginal 'laxity' during intercourse or discomfort or irritation from the labia when exercising, wearing tight clothing, or during intercourse. Psychological concerns (e.g., sexual or social embarrassment) are also noted as a reason why women seek surgery [90,93,95]

¹⁰ Many men overestimate the size of the 'normal' penis and consequently feel inadequate about their own [96]. Worries about the length of the penis are, amongst others, attributed to the fact that in homosocial situations, such as changing-rooms, other men are seen frontally; apparently, the other person's penis looks larger because a man sees his own penis only from above. Looking down from above causes what visual artists refer to as 'perspective shortening'. Hence, the penis looks shorter than it actually is [97]. An additional problem is that men on the whole do not feel comfortable to raise the issue of penis size in conversations with others, resulting in little or no feedback on the perceived problem, and thus no opportunity to correct blurred ideas or thoughts [83,97]. Furthermore, many advertisements overtly suggest that women's sexual satisfaction greatly depends on penis size [98], despite research evidence of the contrary [99-101]. Kinsey et al. had already established that very few women actually become sexually aroused by looking at a penis [102]. Masters and Johnson speculated in 1966 that penis size should also not predict women's sexual pleasure or orgasm likelihood during intercourse - given the vagina's elasticity and its allegedly poor innervation [37] - , but there is evidence that the chances of experiencing a vaginal orgasm are greater with a longer penis. In contrast, penis size is unrelated to frequencies of other sexual behaviors, including clitoral orgasm [103]. Indeed, it may be just this type of information that is most helpful to patients. Education for patients about physiological needs of a penis for sexual pleasure, and partner expectations may help men accept the penis they were born with. But as Kilmartin observed, as long as men continue to equate penis size with masculinity, they will continue to feel unnecessary sexual anxiety (p. 219)[104].

6.3 Clinical implications

6.3.1 A pendulum motion between cosmetic and functional outcomes

One of the recommendations of the Consensus Statement is that emphasis of surgical intervention in *all* cases should be on functional outcome rather than strictly on cosmetic appearance [24,26]. Some interesting findings are further added to this debate.

First, a review of the literature as well as the studies in this thesis, point in the direction that indeed often a trade-off between functionality and esthetics seems to be in order, as past and current surgical techniques could or still cannot guarantee both¹¹. In the majority of the women with CAH for instance, medical and surgical therapy appeared to provide near satisfactory physical and genital appearance; however the frequency and importance of self-reported sexual dysfunction was problematic and highly impairing (e.g. as in [35]). Similarly, in women with MRKH or CAIS, despite a near-normal genital appearance after surgical treatment, sexual distress and difficulties were highly common (e.g. as in [105]). Other studies have indicated that women with CAIS and pure gonadal dysgenesis, who have female-looking external genitalia, were in general more satisfied with the appearance of their external genitalia and sexual quality of life than women with clitoris hypertrophy or ambiguous genitalia (as in PAIS, 17 β HSD or 5 α RD), but perhaps because they had significantly less genital surgery affecting functional and cosmetic outcomes [79,106]. In contrast, in men with DSD, there was high dissatisfaction with penile appearance, causing great distress, however, the majority did not seem to experience significantly more functional problems compared to non-affected men (e.g. as in [23]). Similarly in adolescents with DSD, boys, but not girls, with DSD had a more negative body image. Sexual activities for boys did not differ from controls, while girls had less experience [107]. It is also striking that women with DSD (e.g. PAIS or GD) were less satisfied with their overall sex life and less engaging in sexual activity than men with the same DSD diagnoses [23,108,109], despite sex-corrective surgery in both groups.

The observed gender differences may be related to gender-specific differences in socialization. Boys are still more encouraged to show sexual interest and behavior than girls [79]. Gender-specific social influences on the sexual quality of life of persons with DSD have been minimally discussed so far and should be given more attention in future studies. However, the above mirror image certainly also challenges the role of cosmetics besides sexual function in decision making about surgical interventions, as the perceived importance of both esthetics and functionality seem to differ between men and women.

If a trade-off needs to be made, would men for instance appreciate a non-functional, but esthetically pretty penis more than a functioning, but no so attractive penis? All of the men

¹¹ And even if they would, they do not take the ethical dilemma surrounding DSD treatment away [11]

who had phalloplasty surgery would do it again, even if they had decreased genital sensation. This issue needs further consideration and long-term outcome data are highly needed, especially because one of the blocks to accepting evidence of poor outcomes of for instance feminizing surgery has been the difficulty of accessing a non-treated sample for comparison. Will cosmetic anomalies left uncorrected have an impact on psychosexual well-being? In that respect it is informative to further evaluate if children with clitoral hypertrophy, in which feminizing surgery is postponed because of the current conservative approach, will eventually opt for genital surgery. On the other hand, it is argued that we cannot yet know whether improvements in surgical techniques in the last decade will yield improvements in cosmesis and functional outcomes. Most adult women with CAH for instance typically underwent relatively unsophisticated surgical procedures that are no longer used, also reflected in the variable outcomes in terms of cosmesis, function, and patient satisfaction in the literature. However, we do tentatively suggest that *all* genital surgery in DSD must not be completely reviled. It can have a place in the medical treatment of certain DSD conditions, given that patients are fully informed on the consequences, and that their expectations are realistic and informed¹². More specifically, the few reports in the literature suggest that phalloplasty might be a promising technique, but highlight that it remains an experimental treatment for the indication of micropenis. The pendulum (com)motion between surgery or non-surgery certainly is to be continued.

Second, the subjective perception of genitals is more defining for sexual wellbeing than their objective appearance (e.g. as in [105]). Moreover, the concordance in ratings between patients and clinicians is variable (**Chapter 2, 3**, as in [73]). As might be expected, when it comes to later sexual satisfaction, the patients' genital image is more important than outcome assessment by surgeons. The relationships between 'objective' and perceived genital anatomy and sexual function remain to be further investigated, but a negative perception or expectation might further strengthen sexual dysfunction and vice versa (**Chapter 3**). Therapists treating men or women with sexual dysfunction would be wise to assess patients' perceptions of penis size or vaginal outlook importance as a potential source of sexual anxiety. Genital image measures, such as the Self -Assessment of Sexual Anatomy and Sexual Function Questionnaire (female and male version) would increase communication with surgeons about areas of dissatisfaction and allow for effective counseling. In general, healthcare professionals need to be aware of potential sexual impacts should changes occur to the penis, vagina or clitoris following medical treatments or their complications .

In general, in men and women struggling with this subjective 'atypical' genital image and the pressure to conform, having 'successful' sex (i.e. intercourse) might resolve some of the psychological issues associated with atypical genitalia. However, sex always represents a high risk, as it also could confirm all their fears of 'being abnormal' in case of failure. Precisely because of a negative genital image and/or unrealistic and idealized portrayals of sex, some men and women who have not taken the risk yet to get sexually involved are extra vulnerable.

¹² We cannot underestimate to what extent medical and surgical intervention is the primary means of demonstrating caring for many clinicians, patients and family members [11]. But as the history of intersex and DSD showed us, there are certainly other ways to care for people [11].

Psychological barriers are heightened, with a possible withdrawal from potential opportunities of sexual expression. These men and women can stay in this perpetual state of conflict for years (...and so you just keep postponing your sexuality). Others have described spectating¹³ of their own performance and their partners' reactions (...can you feel it, is it different compared to others?). Problems become self-fulfilling [28, 37, 88].

6.3.2 Overcoming psychological barriers

"You come in here and you feel like your sex life is destroyed for 100%, and you have this operation where 100% of your sex life will depend on. This is bullshit [...] It's like 30%. It's a lot, but 70% are other things."

Perhaps the main implication of this doctoral thesis is that (surgical or non-surgical) 'correction' of a genital anomaly does not necessarily 'correct' or affect the patient's self-image. One participant described it as *'desillusion, because I could still not deal with the image that I had of myself. I was seriously depressed, had to break up with my girlfriend because I felt I had nothing to offer her.*

However, both men and women were reluctant to ask for professional support. Might this reluctance have been part of a greater feeling of isolation from all sources of information and understanding about their condition and its effects? Or by the fear to be 'disqualified' for certain genital treatment practices when they admit to experience emotional difficulties? Or have we failed in addressing their social, psychological and developmental needs?

6.3.2.1 Psychology and its connotation

One of the recommendations of the Consensus Statement included that psychosocial care provided by mental health staff with expertise in DSD should be an integral part of management, recognizing that diagnosis and medical intervention are not the sole focus of treatment. In a recent follow-up study of practices in Europe following the consensus statement, the call for psychological support was in most centers answered [110]. Interestingly, the report also suggests that, while 100% of the parents who were charged with the daunting process of

¹³ 'Spectating', introduced by Masters and Johnson, refers to focusing on and evaluating oneself from a third person perspective during sexual activity. This focus of attention outward on sexual performance rather than inward on the sensory aspects of a sexual experience (i.e., sensate focus) is believed to have deleterious effects on sexual performance [88].

gender assignment were offered psychological support, only about 80% took advantage of the proposed service. While the reasons for this discrepancy are not entirely clear, it is possible that the emotionally charged nature of the process may make it difficult for parents to integrate fully various components of their circumstances. Further, the prospect of involving additional specialists in the process may be overwhelming [26]. In addition, there might be a wish to keep the treatment process strictly 'medical' as 'psychological' support could have certain connotations.

"No, not psychologists. If you come to me and say you are a psychologist, I go away. Because you feel again like a patient. You feel abnormal."

In clinical practice, when the issue of psychological support is brought up, immediate resistance is likely to occur. People will basically say, *"I don't want to talk about this now."*

But when is it that they do want to talk about it? They don't want to talk about it with family, because it may upset them. They don't want to talk about it with friends, when they just want to relax. They don't want to talk about it in the workplace or at school, because it's too controversial. Essentially, there really is no appropriate time to talk about it -- which is what a **secret** is.

It might be taken for granted how difficult it is for most people to actually make the decision to seek out help for intimate issues, mental health or sexuality concerns. It is not like anybody *wants* to go see a psychologist or therapist. It's not the type of thing someone wakes up in the morning and says, "Wow, I have been missing something in my life. I would love to chat to a stranger about my innermost personal fears, thoughts, and feelings and see exactly how screwed up I really am." In fact, most people think just the opposite about almost any health or mental health appointment. It's just not something you want to deal with [111].

There are no easy ways to 'get over' this fear and anxiety. Such anxiety is a normal part of life, and the psychological therapy journey might indeed be a scary journey of (self)discovery. Politely asking people if they want to take up psychological support has been shown to result in refusal. However, the best evidenced-based treatment for avoidance is exposure. Therefore, when people decline, they should be offered even more psychological support. Familiarity with the team psychologist might reduce confusion related to the notion that psychosocial support is needed/required and people cannot handle it on their own. Recognition of the psychological components of DSD care does not represent a presumption of psychological disorder, but rather an acknowledgment of the possible impact (as in other chronic conditions) on the patient's psychological development and the wider family adaptation [112]. Psychological counseling should be a mandatory, additional service, integrated in the multidisciplinary care offered, in an attempt to 'normalize' DSD conditions and focused on the prevention of difficulties throughout medical care [112].

The context of patients' lives and their social support is known to be a crucial factor in long-term psychosocial outcomes of many chronic medical conditions [113]. Thus, ideally, where appropriate, patients and parents should be encouraged to access support from their personal contexts. Families can act as interpreters, caretakers, support systems and buffers [66]. However, because of the specific intimate character of the involved conditions, asking for and receiving community support¹⁴ implicitly means giving up (part of the) privacy, which new parents of a child with a DSD not always want to do [58] (Figure 2), nor adolescents or young adults in their pursuit of formulating a social and sexual identity, possibly leading to social isolation. Therefore, 'anonymous' psychological support in different formats (e.g. with professionals or through internet platforms and peer support groups) can be of high value.

"I didn't feel judged and it was someone different... In the beginning it was strange, what was I going to say? (laughs). But she made me comfortable and she was really nice and I felt relieved. She helped me not trying to hide it. It's not something that has to be hidden."

Disclosure decision depending on:

1. Worries about stigma, rumors and gossip
2. Perceived ability of parents to accurately explain DSD to others and/or have their child's condition understood
3. Preserve the child's right to make decisions about disclosure
4. Personal comfort in talking to others about anatomical aspects of the condition (i.e. genitalia)



Figure 2. Parents' decisions and experiences with sharing DSD-related information (adapted from [58]).

¹⁴ In counseling families about sharing information concerning their child's DSD diagnosis with the wider community, Cohen-Kettenis rightly posed the question 'Is living a "normal" life with a secret more harmful than living a life without secrets but with a reasonable chance for stigma or shame?' (p. 328) [114]. However, secrecy may also carry a reasonable chance for stigma and shame (e.g. [65]).

Despite the clinical knowledge concerning the psychological demands of DSD, very little direct information is however available in the mainstream literature to conceptualize psychological practice in this field [115]. Also, it is difficult to articulate psychological-therapeutic input in much detail as one model cannot fit all [116]. Individualized care and psychological methods should perhaps reflect 'technical eclecticism', whereby the integration of therapy models is at the level of techniques rather than theory [116,117].

A Psycho-education and sensitive information delivery

In order for patients to have greater control of their treatment, they need to become more expert about their own condition and attendant difficulties [28]. *It's like a book and it's heavy. You have to carry the book, it's a problem... But you can also say 'I simply read it' and get the knowledge out of it*, implying that we should give affected individuals correct information on their condition.

Historically, withholding information about diagnosis and treatment to competent children, adolescents and parents was mainstream. From a paternalistic view, the goal has been for the patient to remain insulated from shock and despair subsequent to learning his/her circumstance [26]. However, such an approach has been shown to actually foster the development of negative psychological responses [65]. In the current climate, the question is less whether or not to disclose medical information, but more when and how to disclose [26].

Debate regarding the 'right' time to give information to children is ongoing. The tension evolves around the age at which information can be meaningfully understood, balanced against the impact of delivering possible painful information during the vulnerable teenage years [112]. It is suggested that children should know about their condition before adolescence, when a developing sexuality and changing parent-child relationships are evident and a child's desire to minimize difference and conform to a group is amplified [118]. This desire to conform can also increase the pressure of surgery, seeking to eradicate difference as soon as possible [112]. Based on models of children's cognitive development (e.g. Piaget, Kohlberg) [119, 120], it has become clear that from age 12 and onwards children are able to develop the ability to think in conceptual terms and may understand the more complex nature of their condition. Before this age, simplified information can already be given on biological and psychological aspects of normal sex differentiation. Children sometimes have a clearer technical understanding of their condition and treatment than their doctors or parents realize and can endure considerable distress, which might be intensified when there is a lack of access to direct discussions with an understanding doctor or parent [121]. In the sparse published guidance, disclosure of the chromosomal pattern (e.g. in XY women) is generally recommended to be given when the child is around the age of 14 years [122]. However, it may be that giving this information earlier would allow children to integrate this into their developing constructs of male and female and hence their self-concept, rather than having to accommodate the information later when constructs are already more fixed [112]. Some adults with a DSD advised that the sooner one is able to deal with the full psychological impact of the condition, the sooner one can get the immediate

trauma over with and the sooner one can get on with one's life [65]. Others advised that a phased truthful approach can also work, meaning a strategy in which each piece of information given is in itself truthful, so that there is no need for backtracking at a later stage (e.g. Saying 'malformed ovaries' in stead of 'testicular tissue' can lead to anger and distrust if a teenager later finds out about her XY chromosomes) [123].

Furthermore, disclosure of fundamental and potentially stigmatizing information is a difficult process and must be considered carefully [58]. Families and patients have different beliefs and values, which need to be taken into account when considering the impact and meaning of information (e.g. cultural or individual values attached to infertility). Specific phrases used to explain an underlying condition may still be remembered many years after they were said and can continue to cause discomfort [65]. Professional clinical language has been shown to positively or negatively influence a patient's experience of the diagnosis [124].

Lastly, sensitive and responsible disclosure also means that patients and significant others are not left to contemplate the implications of disclosure without support. High levels of emotional distress are correlated with increased cognitive confusion [59]. When irreversible interventions are proposed, it is essential that the emotional distress is addressed first (e.g. by opportunities for parents to speak to other parents who have lived through similar experiences) to ensure that cognitive impairment does not compromise decision-making. Real collaboration in treatment decisions (and true and meaningful informed consent), is reliant upon an effective communication *process* between the physician, patient and family [125]. This process requires time and a flexible open approach in line with patients' and families' differing needs. Therefore, repeat opportunities for questions and discussions are needed, to allow time to adjust to the diagnosis and to ensure that patients (or surrogates) understand the immediate and long-term implications of medical interventions and alternatives and are able to make decisions with the support of health care providers [56].

B Psychological counseling

Fostering a positive self-identity

As with all of medicine, it is of vital importance to remember that patients are individual people who happen to have a disease or disorder, rather than a person intertwined with or defined by the disorder [26].

"In the beginning I really thought I was not like the others. I cannot have children, I cannot have intercourse. I'm abnormal. But now it's completely different. I am this person, I have friends, a good boyfriend, a good relationship with my family, I'm happy. I don't see this as something that defines me."

For some, an important task might be to distinguish between ‘living the condition’ and “living with the condition” [28]. Some coping mechanisms, such as downward social comparisons (e.g. *“there is cancer and I’m still alive”*) should be discussed. They can help people to enhance well-being and self-esteem, but may also become problematic if people identify too closely with the ‘worse’ world they compare themselves with [66].

For others, it means providing support to develop adequate communications skills for explaining body differences in social and sexual contexts, which are of major concern for many adolescent and adult patients [65,78]. Some DSD diagnoses are associated with body differences that are internal (e.g. absent womb), and/or external but concealable (e.g. micropenis) and/or or external and visible (e.g. hirsutism). Bodily differences and experiences can have a formative influence on a person’s psychological development and identity experience [126, 127]. Although recent research appears to suggest that the majority of people with a DSD see their experience of gender as being adequately represented by a binary model, for some, it also means being able within a safe environment (of psychological therapy) to explore the spectrum of gender identities and gender experiences that transcend the male/female dichotomy [126]¹⁵. In addition, patients should be able to grieve for their losses associated with the diagnosis and consider the implications for their identity, for instance regarding the infertility issue. Infertility can become central to a person’s identity [66].

Although group work has been suggested to be effective for negotiating identity and facilitating positive psychological changes [128, 129], certainly not all participants involved in this research were advocates of the idea. To date, there exists no patient support group in Belgium, only in the Netherlands. Whereas the support groups in the Netherlands have a lot of ‘supporters’, Belgian patients seem somewhat more reserved in joining the Dutch group, or setting up a Belgian initiative and sharing common concerns. Perhaps cultural differences play a role here. However, one- on-one contact was said to be helpful, but was mainly limited to subjects related to the shared condition [65].

“Support groups? Feels like AA meetings.

They give you a label and precisely then you feel something is wrong with you.”

Addressing barriers in relationships and intimacy

Whilst it is important to de-focus on penile-vaginal intercourse and to discuss sexual intimacy in broader terms, the importance of vaginal sex is of course culturally reinforced and will remain an important aspect of clinical management for some time. However, patients may need to develop a more questioning attitude towards some dominant discourses of sex and sexuality, which can be installed by using richer vocabularies and drawing on alternative discourses, and by using a positive language [28,106].

¹⁵ ‘Mixed’ two-gender identities (i.e. the experience of both male and female identification at different times) as well as third and undecided gender roles have all been described by participants (and in particular participants with GD, salt wasting CAH and ovotesticular DSD), even though the majority were satisfied with their gender assignment [126].

*"Not just say 'you have a pump now'. No!
'You have a penis, which functions. Enjoy it!'"*

In psycho-sexual counseling, a defocus from 'normal sex' and an increased emphasis on sensuality and pleasure can encourage people to become more open to opportunities for good-enough sexual enjoyment and relating. Therapeutic exploration might focus on an exploration of sexual likes and dislikes and interaction skills in social and sexual situations [115]. It should also focus on expanding awareness of variations in male and female sexualities and undermining assumptions that all genitalia look the same and that partners are highly knowledgeable about the structure, function and appearance of genitalia [28].

*"When I didn't have a vagina... there were other ways to have
pleasure, other ways than intercourse. It's so wrong for us to think
that we can't have a sexual life."*

Facilitating informed choice in medical treatment

The advent of internet and its 'anonymous' forums has patients given the confidence to express some of their concerns. Many good websites and initiatives exist, providing the patient with updated information on some of the specifics of their condition and its management and where to find help (e.g. DSDNederland.nl, dsdfamilies.org). However, as the quote below illustrates,

*"There is so much information on the internet, but it's negative!
I really wonder why? Do they want to exaggerate their situation?"*

the overload of (negative) information might still be overwhelming. Within a context of counseling and education that target psychological wellbeing and sexual awareness, information needs respectful consideration and clarification where incorrect or misleading information has been gained. This also might open the discussion regarding the different treatments options, including the choice of no treatment, based on all information sources, possibly reaching a more informed and hopefully positive decision for the patient.

C The role of time

Psychological support should parallel all key stages of medical intervention, and is best considered as a process (and not an event). This is also in recognition of the different stages of adjustment to the diagnosis and the temporo-developmental factors (e.g. peers starting to have children, can re-install psychological distress related to infertility, or parents fearing physical,

social, or emotional changes when their child enters puberty and adolescence) [66,78]. Planned episodes of medical care may not coincide with an individual's needs at particular points in time and, therefore, ideally the family and affected individual will also need to be able to initiate contact as and when it feels appropriate to them [130].

TABLE 1

Common clinical concerns, helpful strategies and pitfalls in clinical work with adults who have DSD's (based on [10, 28, 36, 65-67, 78, 116, 117, 127, 132, 133]).

Concerns
Self-disclosure to partners, friends and family (what, when and how)
Participation in sex to be 'normal', with less focus on pleasure
Loss of control and choice
Sexual anxiety, passivity, fear of rejection
Compromised gender, sense of damaged self
Avoidance or idealization of relationships
Loneliness and social isolation
Changes in life goals or expectations following diagnosis
Public intimate medical examinations
Getting full information on condition
Genital aversion through treatment
Beliefs that sexual lives can only be the doctor's (surgeon) makings, indicating an absence of problem solving
Strategies
Explore and question assumptions about 'normal' and 'sex'
Assess genital and body image
Pleasure talk
Increase control over social and sexual situations
Be transparent, humble and empathic
Be realistic about limits of treatment, entertaining the possibility that surgery might damage the very thing that it tries to fix – appearance and normal sexual function
Facilitate least invasive treatment options
Deliver information sensitively
Let patient set agenda in counseling to increase control
Make time – despite brief therapy- to let them tell their story and grieve losses
Consult with multi-disciplinary team
Emotional support
Encourage social contact, including peer support
Anxiety and pain management

Strategies
To ensure good psychologist/patient communication by:
Discussing treatment goals and treatment choice with patients, and maximizing informed decision-making.
Being responsive to the inherent power imbalance within the psychologist/patient relationship.

Pitfalls
Lack of knowledge on conditions
Focusing on anatomy solely, rather than emotional experience of patient
Not knowing one's feelings about DSD
Not consulting with multi-disciplinary team or supervision about possible counter-transference
Presuppositions that a vagina or penis of certain dimensions are pre-conditions for 'sex', as they only reinforce the idea of penile-vaginal intercourse as only valid avenue for sexual satisfaction

Table 1 summarizes common clinical concerns, helpful strategies and some pitfalls in clinical work with adolescents and adults who have a DSD. Clinical psychology has been critiqued for pathologizing, individualizing and categorizing suffering and human distress [39], not in the least the Diagnostic and Statistical Manual of Mental Disorders (DSM) and some of its narratives (e.g. Sexual dysfunction or heterosexual dysfunction? [131]). Alternative approaches to assess sexual (dys)function, can consist of assessing sexuality dimensions and developmental trajectories of gender positioning of the self and gender(s) of the preferred partners besides body perceptions, relationship aspirations and attitudes relating to sexual practices and experiences [39]. Psychotherapy should perhaps also be defined differently [39]. Psychotherapy is usually seen as helping the client fit in with other people by reducing the behaviors, thoughts, and feelings that separate the individual from the world of ordinary life. However, it can also be seen as helping the patient accept his or her individuality, the ways we all sometimes fail to meet our own or other people's expectations, and occasionally rise above them [39]. In Liao's model [39], there is a shift from a model of 'correction' to 'adaptation'; a model in which difference can be tolerable and acceptance is possible; in which surgery can be an option and subject to interrogation, but evidence (and not observation) is crucial; in which work with patients and families explores meaning and increases their expertise; in which sharing tasks with multidisciplinary team members leads to an optimal information delivery, research designs and interpretation of data. Such a collaborative clinical care framework will hopefully lead to more perceived control, optimal physical health and psychosexual wellbeing (as defined by the person) and a positive self-evaluation.

6.3.3 Recommendations for vaginal dilation therapy

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Already briefly touched upon in **Chapter 4**, an individual-based approach with skillful evaluation and negotiation with the patient can help to prevent failure, limited compliance, treatment drop-out and loss of confidence in the vaginal reconstruction process. As compliance affects the success of vaginal dilation therapy as first-line technique, it is extremely influential in clinical decision making [134]. Therefore, a set of clinical care recommendations is proposed, including a self-management model of vaginal dilator treatment, based on a health belief model of behavior change [135], and on therapeutic interventions within a framework of behavioral and cognitive psychology, and motivational interviewing [136]. Merely informing people of sexual-health practices rarely results in behavior change (e.g. sexually transmitted disease prevention or reproductive cancer screening) [137]. Encouraging women to adopt the practice of using vaginal dilators is similarly difficult. *Figure 3* illustrates how an information-motivation-behavior skill model of behavior change would incorporate the influencing factors identified in this doctoral thesis. This model can offer useful pointers for understanding compliance difficulties with vaginal dilation, suggesting that vaginal dilator use can be increased by providing stronger cues to action, emphasizing the benefits, overcoming the barriers and minimizing the perceived threat, while accounting for modifying factors.

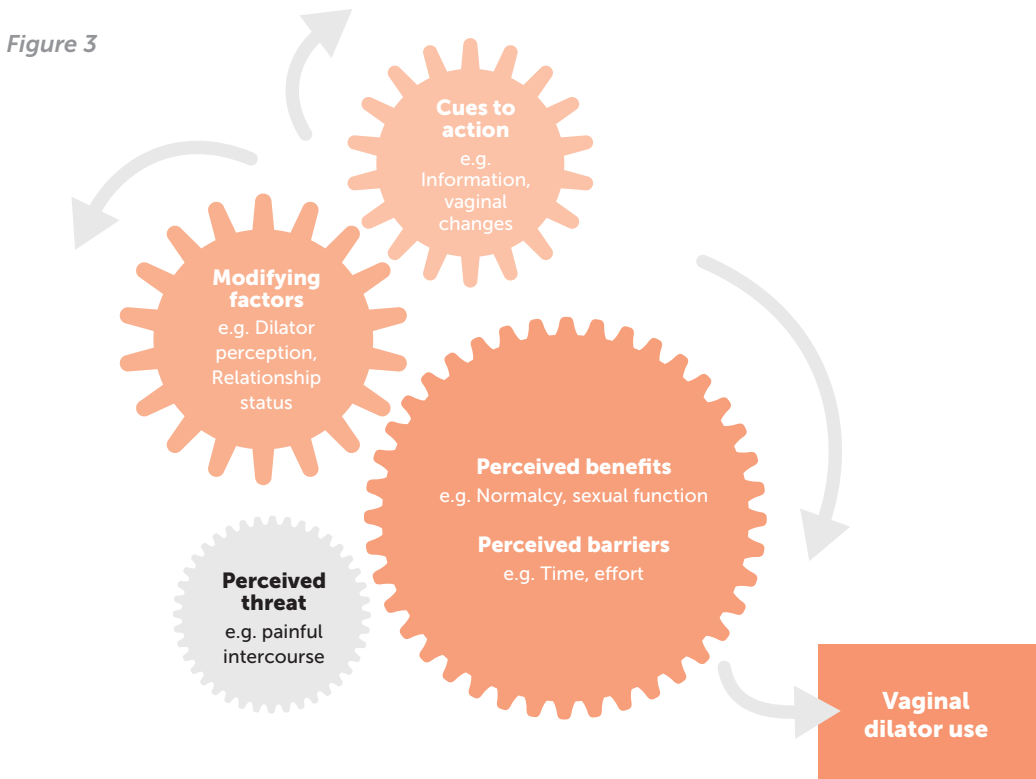


Figure 3. Determinants of vaginal dilator use.

Information: additional information (e.g. information leaflets, websites) and (rebranded) psycho-educational support (e.g. the possibility of phoning/emailing physiotherapist with questions, contact with peers through chat or email) can be provided, resulting in certainty about vaginal dilator use. Standardized and easy-to-follow instructions may boost patient's confidence to correctly use the dilators.

Dilator provision: Ideally, dilators should be purchased at the hospital pharmacy, websites or directly from the healthcare team, rather than going to an adult sex shop. By making the dilators as accessible as possible, women's discomfort with the devices is potentially minimized.

Vaginal changes through personal experience or medical examination: Regular check-ups by clinicians and personal experience of anatomical and functional success can act as confirmation of the efficacy of dilators and increase the frequency of dilator use. Close follow-up consultations are therefore an important forum for maintaining compliance. Asking patients to keep a record (e.g. diary chart) of the frequency and ease of their dilation use and setting goals for size progression may help women and clinicians to assess the further benefit of dilation treatment over time. However, as vaginal size in non-sexual situations can be a poor predictor of pleasurable intercourse upon sexual arousal, clinicians should reduce the level of preoccupation with vaginal size solely and also emphasize enjoyment and pleasure, also through not-penetrative activities.

Dilator perception: Young women may experience embarrassment when being introduced to dilator treatment, as a dilator can be perceived as a sexualized object [138]. A conversation with the gynecologist/physiotherapist and/or sexologist/psychologist directly assessing uneasiness with the vaginal dilator and addressing any potential embarrassment may help women reframe their perception from a 'sex toy' to a more neutral, rehabilitative tool. Moreover, it is common for younger women to be quite appalled by the idea of inserting an instrument in the vulvar region. It may be that, despite concerns about amenorrhea, the woman might not have explored her genital area or even has developed a phobic reaction [139]. For some women, negative perceptions of the genitals may also be exaggerated by an idealization of 'normal'; and negative social comparisons may raise the anxiety further [28]. The highly selective popular images of female genitalia represent an unnaturally narrow range instead of recognizing natural variation between women [91,140]. It is necessary to explore the nature and extent of these negative social comparisons, aversion or fears (including pain), to offer information and reassurance and estimate the impact of remaining anxiety on adherence to therapy.

Diagnosis adjustment: The most significant recommendation is the need to be sensitive to the strong emotional reactions some women may have. Due to the intimate nature of the syndromes

associated with vaginal agenesis (including the fertility issue), women may experience a range of symptoms consistent with posttraumatic stress in reaction to the diagnosis and use of dilators. Thus, in addition to inquiring women about their adherence to vaginal dilation treatment, health care providers should also inquire about distress associated with the matters discussed. Dilation treatment must be delayed in the presence of psychological disorders such as depression, as they are likely to mitigate against adherence and therefore treatment outcome [139].

Maximizing support: psychological research in chronic diseases suggests that successful self-management can be enhanced by the availability of social support [113]. Thus, ideally, where appropriate, patients should be encouraged to access support from their personal contexts. However, because of the nature of the syndrome, many women feel they cannot talk about it with their family or friends and wish to hear about other patients' experiences in dilation treatment. Support can also be provided by clinical services, discussed above, and groups can provide a useful resource to share concerns or motivate each other during treatment. Regular appointments with a clinical psychologist or nurse specialist and/or physiotherapist can provide future opportunities for addressing anxiety and for problem-solving practical difficulties [28].

Timing of treatment: Vaginal dilation treatment should be planned on an individual basis as there is considerable variation in social and psychological development. This may also be influenced by cultural or religious beliefs. However, it is suggested that dilator treatment should not be started before the age of 16 years, as younger women might be less familiar with their genitalia and might therefore be less capable of dealing with treatment or have less motivation to remain active in the treatment process over a period of months. It has been shown that adherence is reduced in adolescence [139]. Every failed attempt at dilation might also jeopardize success of further attempts, including postsurgery dilation if the patient decides to undergo vaginoplasty. There are also differing opinions about whether treatment should be delayed until a woman is in a relationship or whether treatment is best completed before forming personal relationships and women have decided to become sexually active. Current relationship status did appear to have influence on the motivation and frequency of dilator use. Women who were not in a current relationship, but who were highly motivated to start sexual activity, had fewer appointments and shorter treatment durations. This suggests that confidence to begin intercourse may be established during the treatment process and in a sense may form part of the treatment.

Perceived benefits and barriers: empathetically and non-judgmental exploring the benefits of dilator use (e.g. sexual function is possible by achieving greater vaginal length, aspirations of normalcy regarding sexual anatomy and sexual relationships) and overcoming the barriers (e.g. need for discretion, lack of time, effort, negative experience (e.g. having a sense that it is not 'right' or 'natural' to touch her genitals or treatment triggers flashbacks to previous traumatic experiences such as embarrassing examinations or unsuccessful attempts at intercourse, pain), should be tailored to each woman's reasons for adhering or not adhering to dilator treatment [133]. The extent of a positive attitude towards treatment is thought to be influential upon compliance and the perceived efficacy (i.e. personal beliefs of how likely it is dilation will work) will be central to a woman's motivation to repeat the exercises regularly [139]. Improving information provision, providing examples of other women's dilator use, or helping women

plan to incorporate the dilator use in their daily routine, as well as providing dilators in attractive packaging could help women maintain discretion and feel more comfortable with the dilators, as well as build confidence in her ability to perform dilation [133].

Perceived threat: pain and the susceptibility to loss of vaginal depth. Women are advised to maintain dilation or have regular sexual intercourse, although it was suggested that this recommendation might be counterproductive in some women experiencing sexual difficulties (see *supra*). The way women react to the pain that comes with dilation (or with intercourse), will significantly influence compliance. Anxiety can lead to more anticipation of pain, thereby exacerbating the pain by intensifying muscular spasms. Psychological pain management techniques in the treatment of dyspareunia associated with other gynecological conditions such as vulvar vestibulitis, might be useful [141]. Effective techniques include helping patients become more aware of their thoughts and emotions in relations to anticipation and experience of pain. Further cognitive techniques modify the elicited thoughts and emotions (see *Figure 1*). Relaxation training can be a useful adjunct in reducing muscular tension and pain management, and can come in many forms (e.g. biofeedback, Kegel's pelvic exercises, respiratory training, yoga).

6.3.4 Recommendations for the psychosocial management of DSD conditions involving penile deficiency

Supporting the parents— by providing them with correct information on the specific DSD condition involved and emotional support—is an essential first step, as informed and supported parents will hopefully equip their children with knowledge and resilience so that they can take over the responsibility for their own health and wellbeing as they grow up [59, 142]. Patients and parents should in any case be encouraged to maximize social support from their personal contexts, which can provide a buffer against the demanding and possibly adverse diagnosis related events along the way. Offering patients as well as parents the possibility to get in touch with support groups or affected peers can additionally be empowering and reduce possible social isolation and inhibition, especially during adolescence, when communication and mutual support between close family members is (more) likely to be affected.

Further professional counseling will be guided by the stresses perceived by the patient (and those close to him), and available strategies for coping with the psychological challenges imposed by the condition and treatment. Specific psychosocial domains that need consideration are the assault on the sense of self and body image (i.e. the penis being an organ associated with self-esteem, sexuality, fertility, and psychosocial-masculinity issues). Asking boys and men about other aspects of their lives will also remind them that there is an identity beyond that of being a patient with DSD.

In addition, hormonal and surgical treatment options - both hypospadias repair (if needed) and its timing, as well as possible phalloplasty - and their likely psychosexual effects need further

exploration [143]. Patients (or parents) should be given sufficient time before the initiation of any treatment to psychologically process the information. In particular, clinicians may be under huge pressure from parents or adolescents to make the penis larger. The problem may be worse if pediatricians have avoided discussing penile size and have implied that something definitely can be done, if not by hormonal treatment in childhood, then definitely when the patient grows up. Young men with a micropenis may arrive at an adult clinic with unrealistic expectations [68]. To prevent later disappointment or difficulties, the multidisciplinary management team needs to truthfully inform the involved parties about treatment risks and benefits and continuously address and educate about psychosexual function, in an age-appropriate way. Understanding children's and teenage cognitive skills is critical to providing the optimal care and in further informed decision-making processes. For instance, 15 to 17-year-olds may typically understand the possibility of negative consequences of the risks involved in phalloplasty procedures, but will perceive them as unlikely to occur. Those 18-years-old and older often understand the risks and that they apply to them [144].

Recommendations for the further content of discussions about sexual matters are included in [Table 2](#). Psychosexual counseling of young men should always proceed from an understanding of their life contexts (e.g. age, living conditions, partner status) and then include questions about prior sexual experiences, level of sexual desire, frequency of self-stimulation or sex with partner, quality of erections and ability to reach orgasm and ejaculate semen, and whether they experience pain during sexual activity [143]. Giving details on penile anatomy may help their perception of structure and sexual function [145]. Some specific standardized visual tools, such as the Self-Assessment of Genital Anatomy and Sexual Function –Male version (SAGAS-M), might pinpoint specific (genital) areas of concern and can be useful to guide the consultations [146]. It should be emphasized that genital size as such is not related to sexual function or satisfaction. Because most men by early teenage years have already viewed pornography, it is also worth mentioning that the men depicted in pornography are often selected and photographed in ways to overemphasize size. Health-care providers offering concrete information and healthy dialogues about penile matters can allow an otherwise already self-conscious teenager the chance to develop a realistic, healthy body and penile image [145]. Rather than focusing solely on building knowledge on sexuality topics, however, clinicians should further help young men problem solve (e.g. use of sexual positions that are easiest for patient, applying relaxation techniques when being tense), and communicate more effectively (e.g. about sexual likes and dislikes, or about the diagnosis). In some cases, brief cognitive behavioral therapies (CBT) and techniques, to address body/penile image concerns or feelings of discreditment (as men) can be of extra value [78,147-149]. Restraining thoughts, which produce undesirable behaviors and feelings, are replaced by enhancing self-affirming thoughts, backed up by adequate stress and coping strategies. This enables patients to become more skilled in problem solving, as well as become more focused on (and therefore being able to recognize) other physical sensations (see also [Figure 1](#)). CBT is generally short term and proven to be successful for men with other penile conditions, such as penile cancer, or small penis syndrome (i.e. a fear-fuelled subjective perception that the penis is considerably smaller than average, in some cases part of a body dismorphic disorder) [150].

TABLE 2

Recommendations for education and psychosocial support of patients with micropenis or penile deficiency [115, 147, 151].

Technique	
Ask, advise, assess, assist, arrange follow-up (the 5 A's)	
Content	
1.	Discuss sexual status and clarify expectations of possible treatment (hormonal and/or surgical, including phalloplasty)
2.	Discuss possible sexual changes, review side effects and potential management
3.	Individualize needs assessment and personalize care
4.	Encourage open communication with possible partner, promoting couples' mutual coping and support processes
5.	Include nongenital foreplay to minimize performance pressure
6.	Focus on pleasure/arousal rather than orgasm to limit performance pressure, explain relation of penile size to sexual ability and satisfaction
7.	Use sexual positions that are physically easiest, possibly avoiding pain, bodily tension and inhibition of arousal
8.	Consider sex therapy with appropriate professional
9.	Provide possibility to talk to affected peers or support group
10.	Apply objective, validated tools to assess patient satisfaction and the impact of psychotherapy, education, and counseling

Lastly, if the patient decides to proceed to phalloplasty surgery, close collaboration with surgeons who have experience with transsexual individuals is essential, as the same techniques for female-to-male gender reassignment are applied. Based on the current status of science, phalloplasty surgery for micropenis or penile deficiency conditions is still experimental and should be limited to research or university institutions with extensive clinical experience and supervising ethics committees [147]. Great care must be taken when selecting men for such phalloplasty surgery since there is the danger that a small but functioning penis will be changed to a large but relatively inert one [68]. Well-informed, and counseled patients are aware of the risks involved. Routine data collection on patients' experiences is further recognized as the key marker of care quality and can inform service improvement strategies [115]. Finally, psychosocial adjustment to the diagnosis is an extended process and does not end with the completion of treatment. Men should be given the opportunity to receive support and long-term follow up, beyond the treatment period.

6.4 Limitations

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Without some understanding of what is happening and why, physicians, patients, parents and others cannot thoroughly evaluate current practices and devise ways to improve treatment. The main aim of this doctoral thesis was to provide a snapshot of some of the past and current (and future) treatment practices, its efficacy and long-term impact. By using a qualitative, mixed-methods approach, and giving affected persons a voice, valuable and richer insights into their *lived* treatment experience were hopefully offered.

However, participants were only recruited from several hospital clinics, making the scope of some of the conducted research limited and less generalizable. The range of recruitment sources, including support groups, should be broadened. By adopting a quantitative and standardized methodology we were able to compare the results with those of non-affected men and women and some other medical conditions (e.g. hypospadias). However, sample sizes and power to detect differences, remained small. That so little research, in general, has been dedicated to examining associations between sociodemographic (e.g., age, assigned gender, current gender role), psychosocial (e.g., traumatic experiences, attachment to parents) and medical aspects (e.g., diagnosis, treatment measures) and psychosexual wellbeing is partly because small sample sizes do not enable association analyses. Further collaborative national and international projects (such as iDSD), working according to standardized research protocols ensuring high-quality outcome data, are highly welcome [152].

This doctoral thesis also falls short of a discussion of endocrine treatment and prevention of aspects of DSD. For example, the issue of gonadal management, which is an important area of further decision making in some specific DSD conditions and possibly adding to the experienced distress, is not further considered. The goals of gonadal management are to preserve gonadal function (sex hormone production in accord with sex of rearing and fertility) and avoid gonadal malignancy, which may exceed 30% in some conditions [153]. The approach varies depending on the underlying DSD and its manifestation. As a general rule, Y chromosome bearing gonads that remain within the abdomen will function poorly from a reproductive standpoint and are at high risk for malignancy [154]. Such gonads are either removed or, depending on their functional capacity, brought into the scrotum. Müllerian structures of a significant size in individuals raised male may also require removal, whilst smaller Müllerian remnants can be left in situ as usually they do not cause significant problems [130]. Extirpation of gonads in complete (pure) gonadal dysgenesis, PAIS raised female, DSD due to WT1 mutations (e.g. Denys-Drash and Frasier syndromes) is generally recommended before pubertal age. The exception is CAIS, where retention of gonads through puberty is acceptable so spontaneous puberty can be experienced. Although the risk of malignancy is not precisely known, especially at an adult age it is significantly lower than the risk with dysgenetic gonads [154]¹⁶.

¹⁶ For instance, it is estimated that the risk of gonadal malignancy in CAIS is less than 1% compared to approximately 25% for women with complete gonadal dysgenesis [153].

Furthermore, recent reports challenge the need to perform gonadectomy at all, since there have been anecdotal reports of loss of libido following gonadectomy, concerns about long-term hormonal replacement and even the potential of the gonads harboring viable germ cells - cells within the ovary or testis that eventually develop into eggs or sperm- that could be used for procreation with future advanced technology [155]. Optimal modalities of surveillance and screening intervals for gonadal tumors remain to be defined [153].

More research is needed to assess the effects of psychological counseling and education and to delineate factors associated with differential psychological and sexual outcomes. Further qualitative psychology studies are needed to improve our understanding of patients' and parents' perspectives and their lived experience. Some also suggest it would be worthwhile investigating the explicit and implicit psychological gender models not only of affected persons but also of clinical professionals working with them [156]. In addition, it is important for all services to further audit the effects of (genital) treatment on sexual experience and wellbeing along a number of different dimensions such as quality of intimate relationships, partner-independent sexual activities [149], or predictors of persisting gender dysphoria [114], by using an improved research methodology. Standardized psychometric instruments designed for a normative sample may not be well designed to detect the specific distresses experienced by affected individuals. Some psychologists have already responded to this problem with better tailored instruments e.g. for assessing pediatric penile perception [157] and for assessing health-related quality of life [158]. What is still needed, includes decision aid tools e.g. for facilitating disclosure and shared decision-making processes and screening tools to help identify parents who may have more substantial coping issues and may require particular psychological support [114]. Prospective outcomes studies, in which a baseline psychological assessment of emotional wellbeing and sexual quality of life can be compared with post-treatment assessments on the short and long term, are paramount. Theoretical formulations of psychological questions should be included to address gaps of psychological knowledge in living with atypical genitalia [116].

On the note of research however, it is worth reminding that because conditions associated with atypical genital characteristics are relatively rare -, whilst the number of questions that need answering is large- the same group of people may have to participate in one research project after another [28]. The quest for knowledge in order to assist these people may actually reinforce the message that they are 'interesting', with all the negative connotations attached. An additional responsibility must be assumed to strike a balance between repeatedly investigating the small populations and tangible achievements for those populations [116]¹⁷.

Further participant-centered psychological research might, for example, include projects that investigate family members' relationships to the condition in question, factors that can affect personal adjustment and the impact of genetic testing on family relationships. Patient-driven

¹⁷ As Liao & Simmonds remark, it is peculiar that academics, journalists and program makers alike assume that the only way to understand DSD is via research on affected people. It is as if the non-DSD world has nothing to do with how DSD is experienced. Public engagement about DSD via research and interventions with non-affected populations should also become a key psychosocial focus in the future [115]

research will hopefully give patients the control and minimize potential negative effects; it will hopefully also lead to even more positive changes in clinical services for DSD in the future.

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" You can make us a good car, but we have to drive it ourselves.

Meaning, give us self-confidence. [...] But you have to let the person go.

And you have to see how he falls down, and stands up again.

But with the self-confidence, he can do it."

Future perspectives: 6.5 reasons for optimism

Since medical management of DSD came under criticism over a decade ago, there have been a number of attempts by the medical community to respond to the criticism. Before Chicago, none of these attempts had been very successful. The Chicago Consensus conference did a better job of including and listening to patient advocates and also benefited from much more diversity of discipline and geography than previous attempts [159]. *Figure 4* summarizes some of the successes of the meeting and the clinical standard of care translated in the Consensus Statement on Management of Intersex Disorders [24, 160]. Perhaps the most remarkable product of the Statement, is the complete overhaul and adoption of a new medical lexicon pertaining to DSD. Such a rapid uptake is unparalleled in clinical medicine [26]¹⁸. By updating the medical nomenclature, DSD was brought into line with other genetic and endocrine disorders, and with a hope and expectation that these conditions would be brought as well into the mainstream of evidence-based medicine [159]. Furthermore, the role of psychologists has been emphasized, not only to assess potential psychosocial/ psychosexual outcomes, but also to offer immediate support to families in distress [26]. Peer and parent support for many chronic medical conditions is widely accepted, and DSDs, being lifelong conditions which affect developmental tasks at many stages of life, are no exception [159]¹⁹.

After the meeting, however, the call for more efforts remains open. The skills of qualified mental health professionals and professionals in the field need to be further built, and recent initiatives including e-learning portals [162] and e-consultations as platform for expert advice [163] are very valuable towards reaching this goal. Second, the call for establishing patient registries in the context of longitudinal and prospective studies has been responded by the European Union

¹⁸ DSD terminology is not uniformly accepted by those whose bodies the terminology describes, but most affected are familiar with the term, indicating how prevalent DSD has become [161].

¹⁹ In the wake of the consensus conference, a non-profit organisation –Accord Alliance– was created with the mission to ‘promote comprehensive and integrated approaches to care that enhance the health and well-being of people and families affected by DSD by fostering collaboration among all stakeholders’ [160]. Together with DSD syndrome-specific advocacy and support organisations, the active involvement of these stakeholders augurs well for constructive collaborations among ‘consumers’, health care providers, representatives of health care organisations and researchers [160]



Figure 4. Successes at the 2005 Chicago conference and the clinical standard of care translated in the Consensus Statement (adapted from [24, 159]).

Commission and many countries [164, 165], but further collaborative and international projects on the pathophysiology and natural course of DSD remain essential. Third, investigations of the effects of low-cost psychological interventions on self-evaluation, stress and distress, relationship and sexual experiences and adherence to medically essential treatments, are

critically important in the DSD field [115]. Fourth, as the protocol for case management becomes a part of routine practice, it seems appropriate to turn to the meta-cognitive task of assessing how we think about and disclose the diagnosis of DSD to patients and their families in the earliest stages of interaction. To explicate the process and incorporate a best practices protocol should be a new focus for improving patient care [26]. In addition, decision aid tools, assisting parents and patients to better understand the biological basis of DSD and the importance of their family and cultural preferences in shaping treatment decisions, should be developed [159]. Finally, the challenge remains to establish a productive dialogue between neuropsychology and psychosocial approaches: for psychosocial research to incorporate new understandings from hormonal and genetic research as they come to light, and for neuropsychological studies to more fully take into account diverse and psychosocial factors that may impact on the very conceptualization of gender and gendered well-being [62].

Evidence-based standardization of diagnostic and treatment (medical, surgical and behavioral health) protocols will hopefully be associated with higher rates of definitively diagnosed DSD, reduced variation in clinical practice, and enhanced patient/family health care experiences [159]. An evidence-based practice is supported by drawing critically on available research evidence. Keeping up to date with recent literature and advances, and contributing to the knowledge of pathophysiological mechanisms, molecular diagnoses and DSD health psychology. Openness, critical awareness and reflexivity can be encouraged by utilizing peer support, regular peer reviews and supervision [117].

Conclusion

Disorders of sex development present a unique challenge, both diagnostically and in terms of acute and longer-term management. DSD can present to many different healthcare professionals and at different ages. Whilst the majority of infants with DSD present with genital ambiguity at or shortly after birth, an increasing number of individuals are identified either prenatally or during childhood and adolescence. Adults diagnosed with DSD will sometimes present through infertility clinics. Therefore, an awareness of these potential diagnoses, appropriate terminology and the need to involve specialist services early is required by all practitioners. These are relatively rare conditions requiring a holistic and multidisciplinary approach from the outset (*Figure 5*) [160].

Many individuals with DSD will, at some point, require genital treatment or reconstructive surgery, especially when functionality remains being characterized in terms of successful penile-vaginal intercourse. Whilst there is agreement that genital procedures should only be performed by clinicians and surgeons with specific expertise working within the context of a specialist multidisciplinary team, there is ongoing debate as to both the timing of treatment/surgery and which procedure should be chosen. Despite the increasing number of publications on this topic, evidence-based guidelines are lacking beyond expert recommendations [69, 152]. The following recommendations for genital treatment of certain DSD conditions are based on the findings in this dissertation; however, they do not define optimal treatment for any specific individual, and every person with DSD has aspects of his/her condition that need an individualized approach.

We believe that vaginal dilation therapy constitutes the first-line treatment for the majority of women with vaginal hypoplasia, and that phalloplasty in male patients with a DSD offers perspectives when these men are extremely dissatisfied with their penile size and sexual function (i.e. possibilities for sexual intercourse). The optimal time to perform vaginal dilation therapy (or vaginoplasty if vaginal dilation therapy fails) and phalloplasty, is after puberty. As

young adults, patients will be more sexually mature and motivated to undergo such procedures and well-informed and counseled patients are aware of the risks involved. No specific recommendations can be made regarding the type or 'right' timing of vaginoplasty and/or clitoroplasty (if necessary) in women with ambiguous genitalia, nor hypospadias repair in men with DSD. It remains surprisingly difficult to quantify the numbers and types for surgeries for girls and women with CAH as a group, and from country to country. Each study of this type should shed further light on practices and experiences. It seems, however, that femizing genitoplasty may in many cases be deferred to adolescence, with the exception in some severe cases, in which genital ambiguity signals severe hormonal dysfunction and a necessity of early surgery to avoid urinary tract infections. Even in the most experienced of hands, there is often a need for re-intervention and a surgical risk of damage to clitoral sensation and future orgasmic capacity. Likewise, parents need to be aware that severe hypospadias in DSD often requires multiple surgeries and may be associated with problems such as scar tissue formation, affecting both genital sensitivity and cosmetic appraisal, which should not be underestimated in boys and men with DSD. In general, choices should always depend on individual characteristics and detailed discussions with the patient (and, as applicable, the parents) regarding perceptions of advantages and disadvantages of the various approaches. The goals of genital treatment/surgery and, in particular their consequences for sexual function and satisfaction –as defined by the patient- need to be explicitly addressed.

Finally, it can be questioned that treatment, research, and critics still often focus mainly on the consequences of genital surgery and efficacy of medical interventions. Critical but constructive in-depth discussion about what constitutes professional treatment and support of persons and families affected by DSD is timely and needed [168]. The importance of a psychologist, or similar professional, in the management of DSD is not about pathologizing DSD, but rather the recognition of the exceptional personal and social challenges that a diagnosis of DSD presents [130]. Psychological support and intervention should remain an integral part of care,

and is most effectively provided within this multidisciplinary approach, in which all the different actors have the same goals: more social acceptance of DSD and empowerment of individuals and their family to successfully address challenges as they arise. However, the results in this dissertation also suggest that additional experience has to be gained concerning the format of acceptable and efficient psychological care and how to integrate this in the regular medical follow-up. Furthermore, it is essential that there is a seamless pathway of transition, from pediatric through adolescent and into adult services. This will not only serve to optimize the clinical care of individuals with DSD, but it will also ensure that both short- and long-term outcome data are collected and translated into better future management strategies.

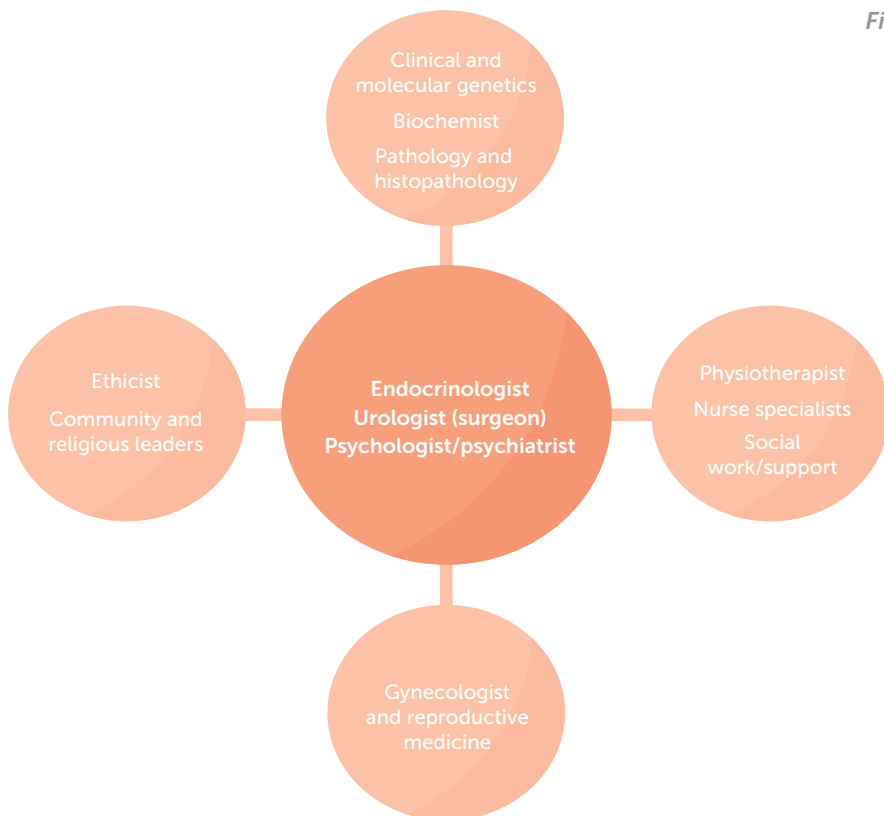


Figure 5

Figure 5. An overview of the multidisciplinary team (adapted from [130]).

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Afterplay

Many researchers have found that researching 'taboo', 'private' or 'sensitive' subjects can be problematic. Research on sex is a prime example and sexology has 'suffered the slings and arrows of ridicule and delegitimation because of its risqué subject matter (p.192) [86]. In this case, the topic disturbs the constructed division between 'public' and 'private', and because of the charged nature of the topic, the writer risks association with the unseemly role of voyeur [166].

When I have to talk about my research, I find myself oscillating between a devil-may-care attitude and a sense of dis-ease. I am not embarrassed by the topic, but I certainly feel the social code or pressure of not talking about 'private parts' with strangers or acquaintances. What is also interesting is, that by not talking about it, I somewhat imagine the dialogue partner to be protected from being in the possibly uncomfortable position of having to respond – 'that their jaws would (metaphorically) drop, and I would single-handedly rob them of all the interactional tools of social convention' (p.368) [166]. I also admit making judgments about whether people can 'handle' the information, which obviously leads to omissions. I refer to this as the 'grandparent-friendly' version – a completely stripped-down version that excludes every detail. I say 'I evaluate the psychological outcome of different urological and gynecological treatments', which doesn't put 'sex' on the agenda, nor 'genitalia', thereby blocking the possibility of unwanted comments. Although I want to de-stabilize the status quo, my own experiences could be analyzed as serious difficulties with breaching taboos and social conventions [166].

Despite my embarrassment and omissions, I have told many different people about my research. The responses have ranged from fascination and interest to horror and complete disbelief. When it comes to the subject of sex and genitalia, or something of which we have 'hands-on' experience, we all have opinions and why not? We can all claim to be sexperts. But myths, assumptions and preconceptions take hold, even when there is rational evidence to the contrary [167].

Methods of scientific inquiry are a useful template for finding out what is true and false in the realm of human society and sexuality. In recent years, a large number of researchers from different disciplines have systematically looked into an area of human experience previously assumed to be untestable, whilst sharing their methods. It becomes harder and harder to pass off opinion and unverifiable stories as proof [167]. The results of this new generation of studies can be controversial, because they have the power to contradict our assumptions. But challenges are good. Being able to re-examine what we think about the truth is one of the hallmarks of good science and of human achievement. So let's further explore the intimate geography, but more importantly: let's keep the conversation going.

Summary

Intersex/ction

It is estimated that one in every four thousand five-hundred people is born with genitals, gonads and genetic material sufficiently equivocal to make doctors and parents wonder to which sex they belong. Disorders of Sex Development (DSD), standing at the intersection of sex and gender, have from the beginning been understood to be a 'problem'. Within this doctoral dissertation we want to address how these problematic bodies are regarded and medically treated today, as both a binary gender ideal and anxiety over uncertainty persist. The body, to paraphrase the feminist artist Barbara Kruger (1989) remains a battleground.

Chapter 1 provides the reader with basic information about the process of typical sex determination and differentiation. We characterize the biological factors responsible for the development of an undifferentiated, bipotential—or should we say multipotential?—embryo into a human being with either a male or a female appearance. We further explore the early and current medical responses to variations in genital anatomy as medical practice cannot be understood apart from the broader culture in which it is embedded. The treatment paradigm determined by John Money and colleagues in the 1950's has dominated the DSD field for over 50 years. The postulates of their approach are summarized as 1) individuals are psychosexual neutral at birth and gender identity arises primarily from psychosocial rearing (nurture) and not biology (nature) and 2) a healthy psychosexual development and psychosocial adjustment is dependent on the appearance of the genitals (i.e. adequate penis for boys, a vagina and no easily noticeable clitoris for girls). If penises are determined to be inadequate for successful adjustment as males, then patients are assigned as females. Diminishing genital incongruity in infancy is essential so that parents can rear unambiguously identified children. In the last decade activists, former surgical patients surgeons, and scholars have come forward to reject any 'fix' based on social concerns rather than medical necessity. The current dissertation is a collection of clinical outcomes studies, providing a snapshot of some of the current genital treatment practices, its efficacy and long-term impact, guided by the voice of affected persons.

In Chapter 2, satisfaction with medical management and genital surgery is examined, with special emphasis on functional and cosmetic outcomes in three groups of patients: 1) women with 46, XX DSD and congenital adrenal hyperplasia, in which genital appearance is often masculinized because of prenatal exposure to androgens. Severity of masculinization at birth is related to a higher number of genital surgeries (i.e. clitoral reduction and vaginoplasty) and an earlier age at surgery, which is associated with worse cosmetic and functional outcomes, 2) in women with vaginal hypoplasia (i.e. 46, XX Mayer-Rokitansky-Küster-Hauser Syndrome and 46, XY Complete Androgen Insensitivity Syndrome), in which women who had a surgical vaginoplasty procedure to enlarge the vagina for sexual contact, report more functional problems, complications and genital cosmesis issues, compared to women who had followed nonsurgical vaginal dilation therapy and 3) in men with 46, XY DSD and multiple hypospadias repair in childhood, who report more dissatisfaction with their genital appearance compared to control men, and in whom a penile length of at least 6 to 7 cm seems to constitute a premise for successful sexual contact.

Chapter 3 examines in more detail the influence of the perception of genital image and genital sensitivity and its implications for sexual functionality outcomes in a large sample of women without DSD and a history of genital surgery. As the clitoris is perceived as the most sensitive genital area for sexual pleasure and orgasm experience - consistent with maximum nerve density in this area-, surgery to the clitoris could disrupt neurological pathways and compromise erotic sensation.

Chapter 4 further focuses on the efficiency of vaginal dilator treatment as first line technique in women with vaginal hypoplasia. A review of the literature indicates that in at least 75% of the women dilation therapy can normalize vaginal length and sexual function. Start vaginal length is not an exclusive criterion for obtaining success. The available evidence suggests further that continued dilation is needed to maintain patency in periods of coital inactivity. The

role of psychological counseling in optimizing treatment outcomes remains however unclear. Moreover, in a prospective study it is further underlined that continued follow-up (>1 year) is necessary to fully evaluate the impact of treatment on both anatomical and functional success. Although the majority of women have pleasurable sex and a vaginal length within normal ranges, emotional difficulties relating to infertility and disclosure with others remain significant, and necessitates continued psychological counseling.

In Chapter 5 the importance of penile length for sexual wellbeing is further evaluated and a new treatment strategy for men with DSD examined. In an updated review, it is shown that a micropenis (stretched penile length < 2.5 cm at birth or <7cm in adults) can jeopardize sexual quality of life and that the current hormonal and surgical lengthening procedures, including hypospadias repair, have no or limited effect on penile length. Phalloplasty, principally used in the transgender population, can be transferred to 46, XY men with DSD and micropenis, and has promising results. However, there are limitations, such as urethral complications, and patient expectations need to be realistic. Psychological barriers for engaging in sexual activity remain at least as high as the physical ones, underlining the importance of continued and appropriate psychological counseling also in this group of patients.

Chapter 6 finally aims to contribute to the actual process of re-thinking the clinical management of patients with DSD, with a specific focus on how the shifting understandings and approaches can provide a basis for optimized medical and genital treatment care. Perhaps the main implication of this doctoral thesis is that surgical or non-surgical 'correction' of a genital anomaly does not 'correct' or affect the patient's self-image nor genital image. Despite high levels of emotional distress, many refuse psychological support. Additional experience has to be gained regarding the optimal format of psychological support within an overall multidisciplinary approach and how to integrate it effectively in the medical follow-up, making a firm commitment to address the socio-emotional dimensions and not just sexual anatomy. The

thesis concludes with some implications for clinical practice, including a theory-based model of vaginal dilator treatment and strategies to facilitate compliance, and recommendations for the psychosexual management of men with penile deficiency, and offers future perspectives on *successful* research.

Nederlandstalige samenvatting

Geslachtsoffers

Bent u een man of een vrouw? U kunt die vraag ongetwijfeld met stelligheid beantwoorden. Maar het is niet voor iedereen zo eenduidig. Eén op 4500 mensen wordt geboren met geslachtsorganen, geslachtsklieren of genetisch materiaal dat in die mate dubbelzinnig is dat het bij dokters en ouders tot twijfel over het geslacht leidt. Dit proefschrift beschrijft hoe aangeboren stoornissen van de geslachtsontwikkeling (Disorders of Sex Development, DSD) in het verleden en heden medisch worden behandeld. Bijzondere aandacht gaat uit naar de genitale en heelkundige behandelingen, om een bijdrage te kunnen leveren aan actuele pogingen om het medisch beleid bij deze patiënten te herzien en in overeenstemming te brengen met de vraag van patiënten voor een meer terughoudend beleid met betrekking tot heelkundige interventies, waar mogelijk.

In Hoofdstuk 1 wordt kort het fundamentele proces van seksedeterminatie en differentiatie geschetst, met de belangrijkste biologische factoren die verantwoordelijk zijn voor de ontwikkeling van een ongedifferentieerd embryo in een menselijk wezen met een vrouwelijk of mannelijk (genitaal) uiterlijk. De huidige medische praktijken en responsen op variaties in genitale anatomie worden verder geëxploreerd en gekaderd binnen een historisch-culturele context die op verschillende manieren de binaire standaard van man/vrouw heeft proberen te waarborgen. Het behandelingsparadigma opgesteld door John Money en collega's in de jaren '50 heeft het DSD-veld meer dan 50 jaar gedomineerd. Binnen dit paradigma wordt gesteld dat psychologisch en seksueel welzijn kan bereikt worden, wanneer kinderen ondubbelzinnig opgevoed worden als meisje of als jongen, en wanneer een ambigu genitaal uiterlijk operatief wordt gecorrigeerd in lijn met het gekozen geslacht. Dit beleid is in het laatste decennium fel betwist door patiënten, chirurgen en academici die genitale correcties gebaseerd op een sociale bekommernis, eerder dan een medische noodzaak, in vraag stellen. Dit proefschrift bestaat uit een verzameling van klinische outcome studies waarin de lange termijn impact van enkele genitale, medische praktijken op psychologisch en seksueel vlak wordt uitgediept, met de stem van patiënten als leidraad.

In Hoofdstuk 2 wordt de tevredenheid met het functionele en cosmetische resultaat na genitale heelkunde geëvalueerd binnen drie groepen van patiënten: 1) vrouwen met 46, XX DSD en congenitale adrenale hyperplasie, waarbij het genitale uiterlijk vaak is vermannelijkt omwille van een prenatale blootstelling aan androgenen. De ernst van de graad van vermannelijking is geassocieerd met meer genitale operaties (clitorisverkleining en vaginoplastie) en een jongere leeftijd waarop genitale heelkunde wordt uitgevoerd, en wordt in verband gebracht met een verminderd cosmetisch en functioneel resultaat 2) in vrouwen met vaginale hypoplasie (i.e. 46, XX Mayer-Rokitansky-Küster-Hauser Syndroom en 46, XY Compleet Androgeen Ongevoeligheidssyndroom) waarbij operatieve vaginoplastie technieken om de vagina te vergroten voor seksueel contact, geassocieerd zijn met meer seksuele en cosmetische problemen in vergelijking met vrouwen die een conservatieve vaginale dilatatiebehandeling hebben ondergaan en 3) in mannen met 46, XY DSD en hypospadie correctie in de kindertijd, die in vergelijking met een controlegroep mannen meer ontevredenheid rapporteren met betrekking tot hun genitale uiterlijk en waarbij een peniele lengte van minstens 6 tot 7 cm een voorwaarde lijkt in te houden voor succesvol seksueel contact.

Hoofdstuk 3 spitst zich verder toe op het belang van de perceptie van het genitaal uiterlijk en sensitiviteit en de implicaties daarvan op het seksueel functioneren in een grote groep vrouwen zonder DSD en een voorgeschiedenis van genitale heelkunde. Daarbij wordt het belang van de clitoris voor seksueel plezier en orgasmebeleving verder bevestigd, met mogelijks nefaste gevolgen indien zenuwverbindingen worden aangetast met clitorale heelkunde.

Hoofdstuk 4 onderzoekt of een vaginale dilatatiebehandeling in vrouwen met vaginale hypoplasie verder efficiënt en waardevol is als eerstelijnsstechniek. Een overzicht van de literatuur geeft aan dat in ten minste 75% van de vrouwen met dilatatie een normale vaginale lengte en functioneel succes kan bekomen worden, en dat de start lengte niet van invloed is op het anatomische eindresultaat. De rol van psychologische hulpverlening in het optimaliseren

van de resultaten blijft evenwel onduidelijk. In een prospectieve studie wordt verder het belang aangegeven van lange termijn follow-up van deze vrouwen, omdat ondanks plezierige seks en een normale vaginale lengte, emotionele moeilijkheden gerelateerd aan infertiliteit en het delen van de diagnose met anderen, blijven spelen.

In Hoofdstuk 5 wordt het belang van peniele lengte op het seksueel functioneren verder bestudeerd en een nieuwe behandelingsstrategie voor mannen met DSD onderzocht. In een overzichtsartikel is aangetoond dat een micropenis (een gestrekte lengte < 7cm bij een volwassen man) het psychoseksueel welzijn van mannen in gevaar kan brengen, en dat de huidige medische behandelingen, zowel hormonale als heelkundige ingrepen niet of beperkt in staat zijn om de penis te verlengen. Een falloplastie - ingreep, die momenteel vooral uitgevoerd bij transgenderpatiënten, levert ook beloftevolle resultaten bij mannen met een micropenis, maar complicaties zijn reëel. De psychologische barrières met betrekking tot het ondernemen van seksuele activiteit blijven aanzienlijk, wat het belang van gepaste psychologische ondersteuning ook bij deze groep patiënten verder benadrukt.

Hoofdstuk 6 geeft ten slotte een samenvattende bespreking weer van de belangrijkste bevindingen met als doel een bijdrage te leveren aan een geoptimaliseerd zorgbeleid. Het onderzoek gepresenteerd in deze doctoraatsthesis heeft als belangrijkste implicatie dat een heelkundige of niet-heelkundige 'correctie' van een genitale anomalie niet per definitie leidt tot een 'correctie' van het zelfbeeld noch genitale zelfbeeld van de patiënt. Ondanks de hoge mate van emotionele distress die deze patiënten ervaren, wordt psychologische hulp vaak geweigerd. De vorm en de manier waarop psychologische hulpverlening in de toekomst moet georganiseerd en geïntegreerd worden in de medische follow-up, verdient verder aandacht. Dit proefschrift besluit met verdere implicaties voor de klinische praktijk, met onder meer praktische aanbevelingen voor vaginale dilatatie therapie en het psychoseksueel beleid van mannen met een micropenis, en biedt toekomstige perspectieven voor *sucsexvol* onderzoek.

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300

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*Joint first authorship

Curriculum Vitae

Nina Callens was born on the 5th of May 1986, in Brussels, Belgium. She graduated from Sint-Jan Berchmanscollege, Brussels in 2004 and started her study Psychology at the Free University of Brussels. During her masters, she developed a special interest for patients with Disorders of Sex Development and conducted research on the influence of prenatal androgen exposure on psychosexual development in girls with congenital adrenal hyperplasia, at Cambridge University, UK, under the direction of Prof. dr. Melissa Hines. In 2009, she graduated summa cum laude in Biological and Clinical Psychology, with the scripton entitled 'The Missing Vagina Monologues and Beyond: Psychosexual Functioning after Vaginal Substitution Treatments for Vaginal Hypoplasia', under the direction of Prof. dr. Martine Cools, dr. Griet De Cuypere, and dr. Arianne Dessens, in collaboration with Ghent University, Belgium and Erasmus Medical Centre Rotterdam- Sophia's Children's Hospital, the Netherlands. The latter research project ultimately resulted in the appointment as a PhD candidate at the Department of Pediatric Endocrinology at Ghent University Hospital, Belgium, under the direction of Prof. dr. Martine Cools and Prof. dr. Piet Hoebeke, and in further collaboration with Erasmus Medical Centre Rotterdam, the Netherlands under the direction of dr. Arianne Dessens and Prof. dr. Stenvert Drop. During her PhD program, she also collaborated with Prof. dr. Ira Haraldsen at Rikshospitalet Oslo, Norway, for the Sex on Brain European Research Study, and focused in particular on the neurocognitive functioning of girls with precocious puberty under GnRH_a analogue treatment. She plans to continue working on different research projects relating to sexuality and genital sensitivity, both in patients with and without Disorders of Sex Development, and to start a clinical postdoctoral fellowship in Pediatric Psychology at Michigan University, Ann Arbor, USA, under the supervision of Prof. dr. David Sandberg.

Notes

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THE PAST

THE PRESENT, THE FUTURE

GENITAL TREATMENT PRACTICES
IN DISORDERS OF SEX DEVELOPMENT

UNDER SCRUTINY