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INTEGRATED STUDY MASTER'S THESIS

Differences in Sex Development

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SUMMARY

This work explores the complexities that can arise in sex development, from normal biological processes to developmental deviations that lead to disorders of sex development. Normal biological sex differentiation is determined by hormonal and genetic factors where the sex chromosomes XY and XX determine the path of the first developmental stages. Pivotal genes such as SRY, SOX9, and WNT4 play crucial roles in gonadal development, where ovaries develop in the absence of the Y chromosome and testicles develop in the presence of it. Hormonal regulation, including testosterone and the anti-Mullerian hormone, affects the further formation of the sex organs and secondary sex characteristics.

Gene mutations, hormonal imbalances, or environmental factors can cause deviations in sex development. Disorders of sex development can be classified into three main groups based on the karyotype of the affected individual: Sex chromosomal DSD, 46, XY DSD, and 46, XX DSD.
We discuss in detail sex chromosomal deviations such as Klinefelter's and Turner's syndrome, gonadal deviations such as Swyers syndrome, hormonal deviations such as androgen insensitivity syndrome and 5-alpha reductase deficiency. These conditions can lead to ambiguous sex development, infertility, and medical or psychological challenges.

This work also explores psychosocial and environmental factors such as exposure to endocrine disruptors, the mother's health during pregnancy, and cultural norms that influence gender identity and self-image. Ethical issues surrounding consent, autonomy, and surgical interventions are also discussed, with a focus on person-centered care and a multidisciplinary approach to treating individuals with differences in sex development.

Keywords: Sex differentiation, Disorders of sex development, Diverse Sex Development, Genetics, Hormonal regulation, Klinefelter Syndrome, Turner Syndrome, Androgen insensitivity syndrome, Environmental factors, Ethics, Gender identity.

ABBREVIATIONS

ACTH – Adrenocorticotropic Hormone
ADHD – Attention Deficit Hyperactivity Disorder
AIS – Androgen Insensitivity Syndrome
ALT – Alanine Aminotransferase (liver lab)
AMH – Anti-Müllerian Hormone
AR – Androgen Receptor
AST – Aspartate Aminotransferase (liver)
BMF FAMILY – BCL2-Modifying Factor family
CAH – Congenital Adrenal Hyperplasia
CAIS – Complete Androgen Insensitivity Syndrome
CYP21A2 – Cytochrome P450 Family 21 Subfamily A Member 2
DAZLA – Deleted in Azoospermia-Like
DHH – Desert Hedgehog
DHT – Dihydrotestosterone
DMC1 – DNA Meiotic Recombinase 1
DMRT1 – Doublesex and Mab-3 Related Transcription Factor 1
DSD – Disorders of Sex Development
EMX2 – Empty Spiracles Homeobox 2
FGF9 – Fibroblast Growth Factor 9
FIGa – Factor in the Germline Alpha
FOXL2 – Forkhead Box L2
FSH – Follicle-Stimulating Hormone
FST – Follistatin
HRT – Hormone Replacement Therapy
IGF – Insulin-like Growth Factor
IGF-1 – Insulin-like Growth Factor 1
IGF1R – Insulin-like Growth Factor 1 Receptor
KS – Klinefelter Syndrome
LH – Luteinizing Hormone
LHX – LIM Homeobox
LHX1 – LIM Homeobox 1
LHX9 – LIM Homeobox 9
MAP3KI – Mitogen-Activated Protein Kinase Kinase Kinase 1

MR – Magnetic Resonance

MRI – Magnetic Resonance Imaging

MSH5 – MutS Homolog 5

NOBOX – Newborn Ovary Homeobox Gene

NR5A1 – Nuclear Receptor Subfamily 5 Group A Member 1

PAIS – Partial Androgen Insensitivity Syndrome

PAX2 – Paired Box Gene 2

RPSO1 – R-spondin 1

SF1 – Steroidogenic Factor 1

SOHLH – Spermatogenesis and Oogenesis Specific Basic Helix-Loop-Helix

SOX9 – SRY-Box Transcription Factor 9

SRD5A2 – Steroid 5 Alpha-Reductase 2

SRY – Sex-determining Region Y

STRA8 – Stimulated by Retinoic Acid Gene 8

TDF – Testis-Determining Factor

TGFB – Transforming Growth Factor Beta (alternative notation: TGFb)

TGFb – Transforming Growth Factor Beta

TSH – Thyroid-Stimulating Hormone

UTI – Urinary Tract Infection

VSC – Variations in Sex Characteristics

WNT4 – Wingless-Type MMTV Integration Site Family Member 4

WT1 – Wilms Tumor 1

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1. INTRODUCTION

When genetic, hormonal, or environmental factors deviate from normal sex differentiation, it is called a disorder of sex development. This can lead to medical, reproductive, and psychosocial consequences. Further research in this field is essential to improve the treatment and management of individuals with disorders of sex development.

This study is based on the idea that disorders of sex development are caused by a complex interaction between genetic mutations, hormonal dysfunctions, and external factors. This means that a multidisciplinary approach and individualized treatment plan are fundamental in treating disorders of sex development.

2. NORMAL DEVELOPMENT

Normal sexual development consists of a series of hormonal and genetic factors. It is complex and has many key factors affecting normal growth and development.

In normal human sexual development, female and male individuals have 46 chromosomes. Humans have 22 pairs of autosome chromosomes and one pair of sex chromosomes, which generally for females is XX and for males is XY. [1]

Each parent contributes one chromosome to the offspring to form a pair. [2]

In normal sex development, the mother always passes down an X chromosome to the offspring, whereas the father has an equal chance of passing down either an X or Y chromosome. For the father, it entirely depends on the spermatozoa, if it carries an X or Y chromosome. [3]

2.1 Gonadal differentiation

The presence or absence of the Y chromosome determines either male or female sexual development. [4]

On the Y chromosome's short arm, a gene called the SRY gene is located in what is also called the Sex-determining Region Y. The presence of the Y chromosomes initiates the development of testes, and in the absence of them, gonadal differentiation to female structures takes place. [5]

When the SRY gene is expressed on the Y chromosome, a cascade of genetic events starts.

The activation of the SRY gene regulates another transcription factor, SOX9, which is crucial in the gonadal differentiation of the testes and the development of the Sertoli cells. [6]

2.2 Role of hormones in sex differentiation

The Sertoli cells produce the anti-mullerian hormone, an essential factor in the development of the male gonads. As the name suggests, this hormone stops the development of the Mullerian duct. In the absence of the anti-mullerian hormone, the bipotential gonads differentiate and develop female gonadal structures. [7]

Early in the testis's development, the Leydig cells that arise from the mesenchymal cells produce testosterone, which is a crucial hormone for the differentiation of the Wolffian ducts into male internal structures. [8]

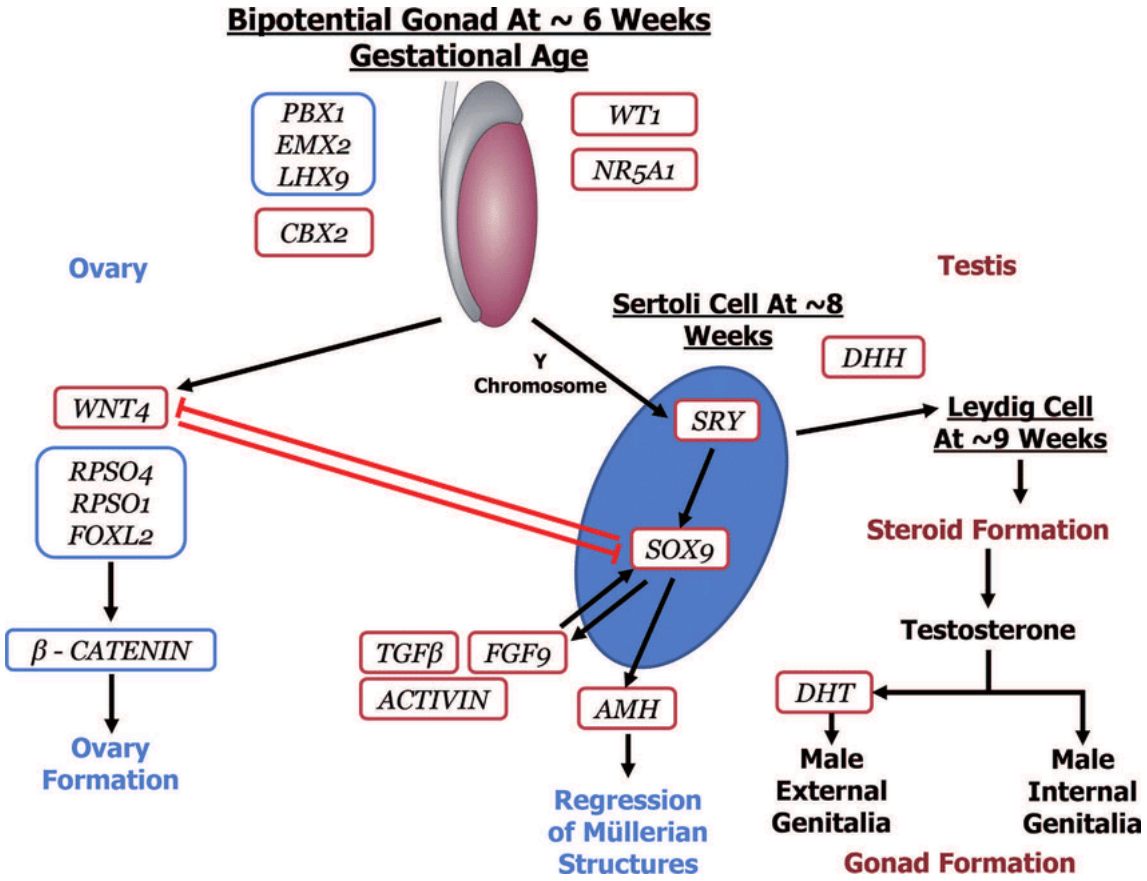

Figure 1: Gonadal differentiation and function. [9]

In the absence of the anti-Mullerian hormone, the bipotential gonad differentiates and initiates the female gonadal development as the Mullerian ducts stay intact as seen in Figure 1. In female sexual development, the Mullerian ducts are what give rise to the female reproductive tract and structures. [10]

The fallopian tubes, which are responsible for carrying eggs, are formed by the upper parts of the Mullerian ducts. [11]
The uterus, which is responsible for holding and nourishing a developing fetus, arises from the caudal parts of the Mullerian ducts that fuse in the midline to form the uterus. [11,13]
The lower part of the uterus narrows down and forms the cervix, which serves as a gateway that regulates access to the uterus. [14,15]
The fusion of the lower part of the Mullerian ducts forms the upper part of the vagina. [11,14]
The lower vagina arises from the urogenital sinus. [16]
As mentioned previously, the differentiation of the bipotential gonads to male gonadal development includes numerous crucial processes, one being the production and secretion of testosterone from the Leydig cells. Testosterone is the hormone that gives rise to the development of the male internal organs and structures, vas deferens, the epididymis, and the seminal vesicle. [17]
Testosterone is converted to a more potent androgen like seen in figure one, called dihydrotestosterone, by the enzyme 5-a reductase. Dihydrotestosterone is responsible for the development of the penis, scrotum and the prostate. [18,19]

2.3 Key stages and timing in normal sex development

2.3.1 Indifferent stage

From day 22-28 the primordial germ cells are migrating from the yolk sac to the hindgut and the formation of the solid wolffian ducts which later forms a lumen occurs. On approximately day 28 the cells migrate to the urogenital ridges.
From day 32-37 in this period the development of the gonadal primordia takes place, and the cells reach the gonadal ridge, the wolffian ducts are growing and the urogenital sinus becomes visible. This period is also marked by the differentiation of the mullerian ducts and the genital tubercle and urethral folds that become visible. [20]

2.3.2 Male specific development

From days 41-44 the differentiation of the seminiferous cords occurs, and the urogenital sinus differentiates into pelvic and phallic parts.
Between days 44-50 within the testes, the seminiferous cords which contain germ cells are formed.
Day 50-60 the AMH starts to get secreted and the Leydig cells are differentiating, thereby causing the cranial parts of the mullerian duct to regress.

At week 9 the production of testosterone by Leydig cells takes place, and this period is marked by the masculinization process of the urogenital sinus and external genitalia. Around week 10 the prostatic buds arise.
By week 12 the seminal vesicles are developed, and the testis is reaching the internal inguinal ring.
At week 14 the male urethral organogenesis is completed.
Week 20 is marked by the formation of the prostatic utricle.
Week 24 is marked by penile growth.
Between weeks 27-30, referred to as the inguinoscrotal phase, it is marked by the testicular descent into the scrotum. [20]

2.3.3 Female specific development

Week 10 is marked by the degeneration of the female wolffian ducts and the meiotic entry of the oocyte in the medulla.
Week 12 is marked by the formation of the vaginal coord and that the primordial follicles start to appear.
Week 16 the development of the primary ovarian follicles occurs.
Week 22 the vaginal canal formation is completed as the vagina reaches the perineum.
Week 24 the graafian follicles becomes visible.
Week 36 is marked by the production of AMH by the secondary and tertiary follicles. [20]

3. NORMAL SEX DEVELOPMENT

3.1 Formation of the urogenital ridge

The intermediate mesoderm gives rise to the urogenital ridges, which are the precursors of the genital organs and urinary tract. The urogenital ridges are formed 30 days after the ovum is fertilized. The urogenital ridges are around 37 days post-fertilization giving rise to the nephrogenic cord and genital ridge. The nephrogenic cord is what later gives rise to the urinary system. The genital ridges are the precursor of the bipotential gonads that either differentiate to form the testis or ovaries. [20]

3.2 Sexual differentiation into male pathway

The first step in male sexual differentiation is the presence of the Y chromosome. The Y chromosome carries a gene called SRY that encodes the testis-determining factor, which is crucial for the differentiation of the bipotential gonad into the male pathway. This cascade of events leads to the further expression of the SOX9 gene. The SOX9 gene is facilitating the development of the testes. The SOX9 gene allows the production of the Sertoli cells and the anti-mullerian hormone, which prevents the differentiation of the bipotential gonad into the female pathway. [21,22]
As the testes develop, male sexual hormones called androgens are produced. Androgens are a group of hormones responsible for the sexual differentiation of male secondary characteristics and the development of the external male genitalia. The male masculinization process can be initiated only by the presence of androgens. The main male androgen is testosterone. [23]
Around a tenth of the testosterone produced is converted to dihydrotestosterone in the presence of the 5-alfa reductase type 2 enzyme. Dihydrotestosterone is responsible for the development of secondary male characteristics. The SRD5A2 gene is responsible for coding the 5 alfa reductase type 2 enzyme, and any deviations in this gene can lead to deficiencies in the 5 alfa reductase type 2 enzyme. A condition related to the mutation in the SRD512 gene is 5 alfa reductase deficiency, a condition where the body does not produce enough androgens and thus the abnormal sex development of males occurs. [23,24]
The transcription factor Doublesex and Mab-3 Related Transcription Factor 1 (DMRT1) are very important for the normal sexual development of 46 XY individuals. In the presence of DMRT1, the Sertoli cells can be differentiated. [25]
The fibroblast growth factor nine is important for regulating and producing the Sertoli cells in the male sex development pathway. The fibroblast growth factor nine (FGF9) allows the testis cords to be formed, which is the structure that gives rise to the seminiferous tubules and promotes sperm production. The fibroblast growth factor nine also interacts with the SOX9 transcription factor which plays a crucial role in the production of Sertoli cells [21]

3.3 Sexual differentiation into female pathway

Ovarian differentiation includes a cascade of multiple factors and processes; it includes molecular and genetic pathways like illustrated in Figure 2. [26]

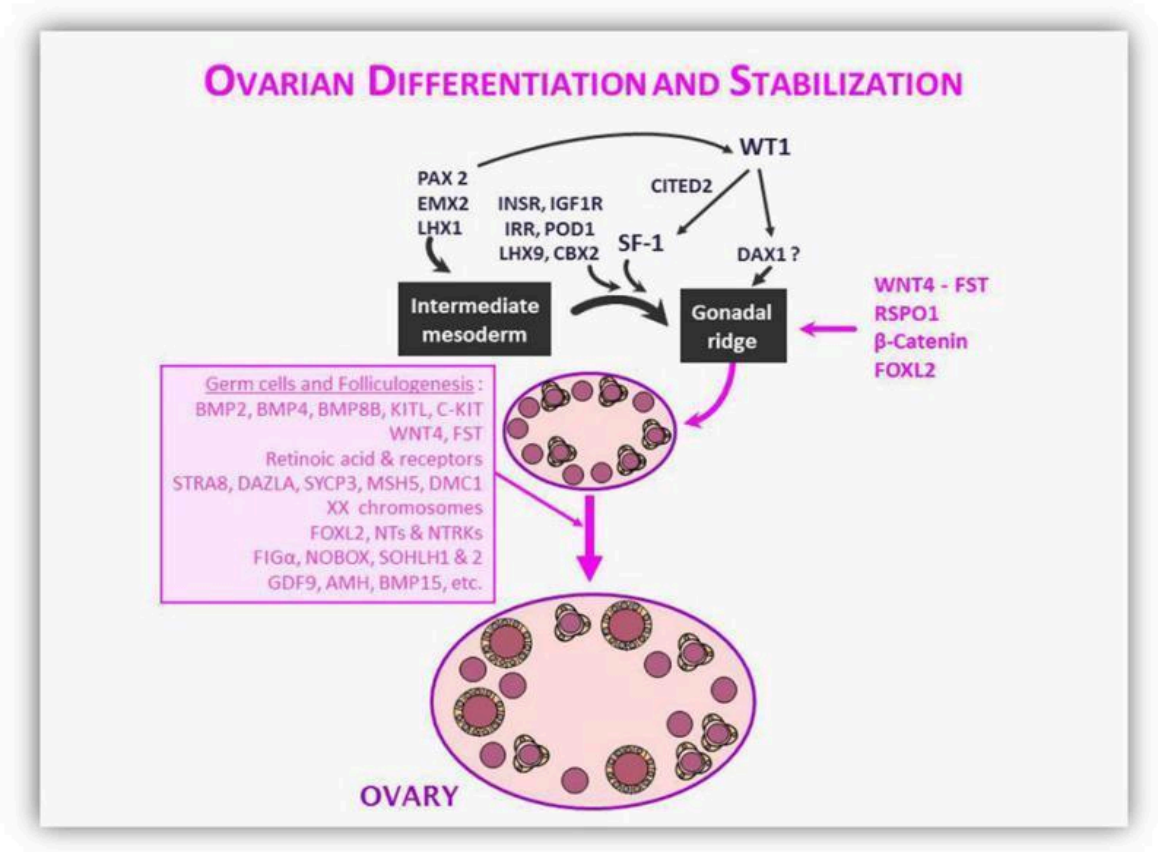

Figure 2: ovarian differentiation and stabilization. [28]

It starts with the differentiation of the intermediate mesoderm to the gonadal ridges, and a series of different transcription factors interplaying, such as the LHX1, EMX2, and PAX2 being expressed. These transcription factors contribute to the formation of the intermediate mesoderm, which gives rise to the gonadal ridge and kidneys. [26]

Gonadal ridge differentiation occurs under the influence of steroidogenic factor 1 (SF1), Wilms tumor 1 (WT1), and LHX9. [26]

For ovarian differentiation to occur, a network of signaling molecules interplays, which is crucial for the normal development of the female pathway. These molecules include the WNT4, B-catenin, FST (follistatin), and RSPO1 (R-spondin 1). [26]

The WNT4 molecule functions to antagonize the expression of SOX9 and the development of the testis, thereby promoting the development of the ovaries. [26]

The B-catenin molecule is stimulating and enhancing the WNT4 molecule.

The FST molecule is acting as an antagonizing factor towards the activins. [27]

The RSPO1 molecule acts as an enhancement factor in the regulation of the WNT4 molecule and promotes differentiation to ovaries. All of these are crucial for the stabilization of the ovary in normal development. [27]

Several factors play key roles in the development of germ cells. We have the BMP family members, the KIT ligand and its receptors, C-KIT, retinoic acid and its receptors, DAZLA, MSH5, STRA8, and DMC1. For normal ovary stabilization, two X chromosomes have to be present. [27]
Multiple factors play crucial roles and are involved in folliculogenesis. These include FOXL2, Neutrophils and their receptors, FIGa (factor in the germline alpha), NOBOX, SOHLH (Spermatogenesis and oogenesis specific basic helix loop helix), family members of TGFB, and antimullerian hormone. [26]

3.4 Genetic factors and hormonal regulation in normal sex development

Human sex chromosomes are what determine the path of our sex development and are based on what sex chromosome is passed down to the offspring from the dad's sperm.
In normal female and male gonadal differences, normal sex development is influenced by several transcription factors, genes, and hormones. [29,30]
For example, the SRY gene, located on the short arm of the Y sex chromosome, initiates male gonadal development by regulating the SOX9 gene. The SOX9 gene antagonizes ovarian formation and thus promotes testis development. [31]
The WNT4 gene serves as a critical promoting factor in the process of female gonadal differentiation and ovarian formation. [32]
Hormones that play a part are, for example, anti-mullerian hormone, which suppresses the formation of Mullerian ducts and promotes testis formation. [33]
Other examples of hormonal influence on normal sex development are pubertal hormones such as testosterone and estrogen, which are responsible for the development of secondary sex characteristics during puberty. [23,24]

3.5 Environmental factors

Environmental factors such as high or low temperatures can alter the normal sex development of the developing child. [35]
Psychosocial factors such as poverty leading to malnutrition can significantly affect normal sex development. Maternal malnutrition is closely connected to maternal stress, as malnutrition can cause psychological stress. Malnutrition can cause improper organ development during pregnancy, alter normal neurodevelopment, reduce immune function, and increase the probability of the child developing chronic diseases in life. [36]

Stress affects the normal sex development of humans, it can affect the circulatory system and cause hypertension which further can lead to preterm labor.
When pregnant women experience more severe forms of stress such as post-traumatic stress syndrome caused by a traumatic event under or before the pregnancy, the risk for preterm labor increases significantly. [36]
A preterm labor can cause pulmonary, cardiological, cerebral, metabolic, and immunological problems for the baby and thus affect normal sex development. [37]
Endocrine-disrupting chemicals has been found to affect the normal sex development of humans. The most common environmental endocrine disrupting chemical is bisphenol A. [38]
We are exposed to Bisphenol A in plastic such as in bottles, metal cans for food, and water pipes. [39]

3.6 Psychological factors

Individual sex development does not only consist of biological processes; hence, it is also influenced by the individual's personal experiences and emotions. The gender identity of individuals starts to develop in childhood and adolescence. The normal sex development of individuals is also influenced by psychological factors such as gender expectations and parental attitudes, which are also closely linked to an individual's gender identity.
Gender identity is defined as an individual's own perception and their sense of belonging as either a girl or boy, or a combination. [40,41]

3.7 Social factors

An example of social factors are medical representation, exposure to sexual content, and norms that can influence individuals' sexual development. Individuals whose cognitive maturity has not yet been reached are susceptible to being affected by medical exposure. [42]

3.8 Changes during puberty and development of secondary characteristics

Puberty or adolescence is a very important period, where many somatic changes including sexual maturation and skeletal growth occur. Changes during puberty include both physical and hormonal transformations. [43,44]

The first clinical sign in boys that indicates gonadal pubertal maturation is testicular growth above 4 cm2 or 4 ml. In girls it is breast development. In approximately 85% of girls, the manifestation of menarche occurs 2 years after breast development. [44]

The female menstrual period occurs approximately at the age of 13 years in in America, late pubertal findings in girls are increased fat mass. [43]

The hypothalamus plays a crucial role in stimulating gonadal functions by secreting gonadotropin-releasing hormone, which leads to increased secretion of pituitary gonadotropins, such as testosterone in males or estradiol in females, and maturation of the spermatogenesis of the ovarian follicle. [43]

Other neuroendocrine factors that control the onset of puberty are cerebral adrenergic or dopamine neurotransmitters, endogenous opioids, and melatonin of the pineal gland. A temporary increase of the luteinizing hormone (LH) is experienced during infancy, which is a key in sexual development. Adrenarche is experienced at the age of 7 to 8, an adrenal maturation that leads to the production of androgens in both males and females.

The final phenotypic outcome of adrenarche is pubarche, apocrine odor and increase in sebum production manifested as oily hair and skin and development of acne. [43,45]

The hormonal changes during puberty lead to the development of secondary sexual characteristics. These characteristics are manifested in girls by breast development, onset of menarche, and enlargement of labia majora and minora. A clear white vaginal discharge before menarche is a typical clinical sign. Growth of pubic and axillary hair development, changes in voice and increase in height, redistribution of adipose tissue to the hips and breasts, and progressive skeletal maturation are seen in girls. [45]

In boys, these changes are seen as changes in the male genitals, pubic, axillary, chest, and facial hair growth, changes in voice, height gowth, muscle mass, and bone maturation. [45]

In girls, the increased level of gonadotropin, which stimulates the ovary to produce estradiol lead to the development of secondary sex characteristics.[45]

Increased levels of estrogen cause the uterus to become pear-shaped in girls, which causes an increase in uterine length and thickness. [45]

In boys, the increased levels of LH stimulate the production of testosterone, while FSH promotes spermatogenesis by acting on Sertoli cells, leading to an increase in testicular volume. The enlargement of the testes can cause the scrotal skin to become thinner and more pigmented. The first ejaculation is experienced 1 year after the testicle growth. Penile growth occurs after testicular growth. The penis grows in length and width, while penile glands and corpus cavernosum also become bigger. [45]

Growth spurt, which is experienced in both girls and boys is caused by interaction between sex steroids estradiol and testosterone, growth hormone, and IGF-1. Increased sex steroids lead to an increase in growth hormone levels, which is followed by an increase in IGF-1. IGF-1 causes somatic growth, such as increased trabecular bone growth. Androgens may also lead to the laryngeal and vocal cords enlargement that causes the voice to become more deep and sometimes this might lead to a temporary “voice cracking”. [45]

Skeletal mass increases significantly in late adolescence, approximately by twofold. The main determinant factors for bone mass are sex steroids, growth hormone, insulin-like growth factors affecting bone and muscle mass, and the 1,25 dihydroxy vitamin D. This vitamin stimulates calcium absorption and retention, and regulates muscle mass by affecting modeling thresholds.
Additionally,
calcium intake is also important for bone development. [46]

4.CLASSIFICATIONS OF DSDs

4.1 Definition of DSDS

Disorders of sexual development (DSD) encompass conditions in which chromosomal, gonadal, or phenotypic traits deviate from typical development. These conditions may lead to variations in the urogenital tract's development and result in reproductive organs and genitalia that do not align with standard female or male characteristics. [47]
An example of such a scenario is that an individual has XY chromosomes but XX genitalia or that an individual with XX chromosomes has male genitalia. [48]

4.2 Evolution of terminology and classification

The evolution of the classification of disorders of sex development dates back to the late eighteen hundreds when the German physician Edwin Klebs described two different types of hermaphroditism. Klebs described developmental deviations in sexual development based on the presence of phenotypic gonadal structures. He classified individuals with both testes and ovaries as true hermaphrodites and individuals with either ovaries or testes as pseudohermaphrodites. [27]
In the year 1931, the German geneticist and biologist Richard Goldschmidt described the term intersex state for individuals with ambiguous sexual structures and traits. Goldschmidt differentiated sexual orientation, specifically homosexuality, from intersex. [27,49]

1949 the Canadian scientist and physician Murray Llewellyn Barr made a pivotal discovery when he identified a marker in cells called sex chromatin, which helps differentiate between 46, XX, and 46, XY chromosomes. The sex chromatin helps distinguish the female chromosomes specifically because of the presence of two pairs of XX chromosomes. In 46 XX individuals, one of the sex chromosomes gets inactivated, leading to the formation of a Barr body, which is a small mass of dense chromatin that can be observed in the inner nuclear membrane of cells. However, in 46, XY individuals the Barr body can normally not be observed due to the absence of the second X chromosome which is that forms the Barr body. [27,50,51]

In 1955, the two scientists Albert Levan and Joe Hon Tjio discovered that humans have 46 chromosomes. They used karyotyping, a method for examining the number and structure of an individual's chromosomes. [52,53]

In the 1960s, an article in the British Medical Journal described a new structure and classification to differentiate different types of developmental deviations, challenging the old classifications and terminology such as hermaphroditism and pseudohermaphroditism. [27,54]

Between 1973 and 1975, pivotal advancements were made in developmental endocrinology and genetics research. Some key genes and proteins were discovered, contributing to a better understanding of the processes in sex differentiation.

Between these years, the H-Y antigen was first discovered, and later, the testis-determining factor gene and the sex-determining region Y were discovered. [27]

The terminology which is used to describe atypical sex development is varying depending on the context today. 2006 the clinical term Disorders of Sex Development (DSD) got introduced and is still widely used in medical contexts [55]

However, this term has been perceived as offensive in some contexts and alternative terminology has been used, terms such as Differences in Sex Development and Diverse Sex Development which are perceived as more patient centered. [56]

The term Variations in Sex Characteristics (VSC) is used widely across Europe as it is perceived as more neutral and not offensive. All these terms aim to describe the same thing in a respectful patient centered manner, however, still maintain scientific clarity. [57]

4.3 Overview of existing classification systems Chicago consensus 2006

The Chicago Consensus on Disorders of Sex Development is a classification established in 2006 by a group of experts. It focuses on the etiology and underlying processes causing deviations in sexual development rather than phenotypical traits.

This classification system has made it possible to approach DSDs in a more standardized way for diagnosis and management. [27]
The Chicago Consensus on Disorders of Sex Development divides DSDs into three main categories: Sex chromosome DSD, 46, XY DSD, and 46, XX DSD.
Disorders of Sex Chromosome Development: This section covers disorders of sex development related to abnormalities in the structure and number of chromosomes in 46, XX, and 46, XY individuals. [27]
46, XY, and 46, XX DSD are further divided into hormonal DSDs and gonadal DSDs. This group of DSDs is categorized based on mutations in genes and important hormonal processes that cause disturbances in development. [27]

5. MAIN DSDs AND THEIR CLINICAL IMPLICATIONS

5.1. Sex chromosome DSDs

This review will discuss the two main and most prevalent chromosomal DSDs in 46, XX, and 46, XY individuals: Klinefelter syndrome for 46, XY, and Turner syndrome for 46, XX individuals. [48]

5.1.1 Turner syndrome

Turner syndrome also called congenital ovarian hypoplasia syndrome, Is a condition characterized by an anomaly in the the sex chromosomes of females. This is also the most prevalent sex chromosomal anomalie in females. It is caused by either the complete or partial absence of one of the X chromosomes. About fifty percent of individuals with Turner syndrome present the karyotype 45,X representing monosomy X, as illustrated in Figure 3, and the remaining fifty percent have a mosaic chromosomal component (45, X with mosaicism). There are a few types of anomalies that can cause the X chromosome to not function normally. These four types are: isochromosome Xq, characterized by two identical copies of the long arm of the chromosome that are connected head to head, ring chromosome where segements of the two copies of the long arm of the X chromosome is missing and partial deletions affecting either the short arm (Xp) or long arm (Xq) of the X chromosome takes place. [58]
Turner syndrome is as common as 10 in 20000 to 10 in 25000 live female births. Some patients with a faint phenotype can be undiagnosed till adulthood. Enhanced clinical understanding and prenatal ultrasound examinations have lead to decreased Turner syndrome prevalence at birth.

This occurs due to the possibility of the mother terminating the pregnancy if the fetus is detected with Turner syndrome in some cases. [54,58]
Studies have shown that social stigma and norms have a role in the decision-making of terminating a pregnancy. [59]
The mosaic type of Turner syndrome can exhibit a broad spectrum of phenotypic clinical features depending on the degree of mosaicism. Some individuals might have more mosaic cells and some less; depending on this, the signs and symptoms differ. [60]
Prenatal screening with amniocentesis or chorionic-villus sampling allows prenatal diagnosis of Turner sydnrome. During prenatal ultrasound, the presence of cardiac abnormalities, cystic hygroma, or fetal hydrops should raise the suspicion of Turner syndrome. The diagnosis needs to get confirmed postnatlly via karyotype analysis. Sometimes the karyotype analysis exhibit normal findings, however if there still is a suspicion of mosaicism, a FISH study could be conducted for diagnosis. [58]
Other tests, in addition to genetic investigations, are also evaluated in the diagnosis of Turner syndrome, including hormonal level analysis and radiological examination. [61,62]
Patients with Turner syndrome may exhibit deviations in the normal ranges of follicular stimulating hormone, Luteinizing hormone, and estrogen levels. [62]
In Turner syndrome, imaging investigations are important to evaluate congenital heart defects, which can be prevalent in individuals with Turner syndrome. Echocardiography and MRI are commonly used. [61]
Turner syndrome is typically not a hereditary condition. When the disease is casued by monosomy X, it usually means that a chromosomal deviation occurred in the cell division, in the formation of the parents reproductive cells. This error results in abnormal number of chromosomes. Mosaic Turner syndrome is also not hereditary, it is also caused by a sporadic chromosomal deviation that takes place early in the fetal development in the process of cell division, resulting in the affected individual cells having two or more cell lines. Some cells can have the normal two sex chromosomes (46, XX), however, it's also possible to have one X chromosome (45, X), partial X chromosome deletions, or even a Y chromosome (46, XY). [58]
The clinical picture of Turner syndrome in childhood is typically characterized by short stature, a webbed neck, a broad chest, and widely spaced nipples. Children with Turner syndrome are typically short in relation to their parents' height. Sometimes, the diagnosis is not made until puberty, when the breasts do not develop or menarche does not begin. [63]
Other symptoms may include a low hairline, problems with teeth, increased moles, small "spoon-shaped" nails, and a short fourth finger or toe. [64]

The eyes are slanted downwards, and they may experience ptosis, strabismus, amblyopia, cataracts, or myopia. [64]

Middle ear infections (otitis media) and glue ears are very common during early childhood. Hearing loss can occur later in life, although it is more severe and often develops earlier than the normal age group. A low set of ears is also a common symptom. [64]

Other associated conditions of Turner syndrome are heart murmur and kidney and urinary tract problems, such as UTIs and high blood pressure. Hypothyroidism is common and needs to be detected early before it causes any possible symptoms. Other associated conditions are hypertension, osteoporosis, scoliosis, diabetes, obesity, and lymphoedema. Some slightly more rare symptoms are Crohn's disease and ulcerative colitis. [64]

Girls with Turner syndrome do not produce an adequate amount of sex hormones. They may not be able to begin sexual development, fully develop breasts, and start their menstruation. If sexual development begins, it is predicted that it most likely will not be complete. [64]

Individuals with Turner syndrome not only suffer from physical challenges but also face social and psychological difficulties. Individuals with Turner syndrome can have developmental delays that lead to behavioral problems and learning difficulties, which might affect their self-esteem. [65]

In teenage years, girls usually present with a delay in puberty and amenorrhea secondary to premature ovarian failure. A characteristic feature of this condition is “Streak gonads”. The streak gonads predominantly consists of connective tissue and have no, or very few atretic follicles.[58]

In children 4 years and older, TSH needs to be evaluated for the screening of autoimmune thyroiditis, and tissue transglutaminase with total IgA is required for the screening of celiac disease. At the age of 10, childreen should be screened for diabetes, hepatic steatosis and renal impairment. The screening consists of laboratory tests to evaluate glucose levels, glycated hemoglobin, liver enzymes such as ALT and AST, and serum creatinine and urinalysis.[58]

In adolescence, elevated follicle-stimulating hormone (FSH) suggests Turner syndrome and very low level of anti-Mullerian hormone (AMH) can be an indication for ovarian failure. Screening includes renal ultrasonography, echocardiography in newborns and children, and MRI in girls and women. [58]

The differential diagnosis for Turner syndrome is a syndrome known as Noonan, it exhibits similarities in terms of clinical findings such as short stature, anomalies in heart and kidneys and a neck that is webbed. The difference is that there are no chromosomal abnormalities in Noonan syndrome. Noonan syndrome can affect both males and females. Genetic testing is important to differentiate between these diseases. [58]

Treatment of Turner syndrome: growth hormone and hormone replacement therapy (HRT).

If breast development is absent, estrogen replacement therapy should be initiated. In cases of elevated gonadotropins or low AMH levels, therapy should begin at the age of 11 to 12. The doses should be started at a small starting dose of one-tenth to one-eighth of the adult replacement dose and progressively increased at 6-month intervals in order support normal pubertal progression until reaching the adult dosage. After achieving the required level of estrogenization and uterine enlargement, progesterone is added cyclically for endometrial protection. [58]
The treatment for cardiac abnormalities should include close blood pressure monitoring. Beta-blockers and ACE inhibitors are the first-line treatments in case of increased blood pressure. [58]

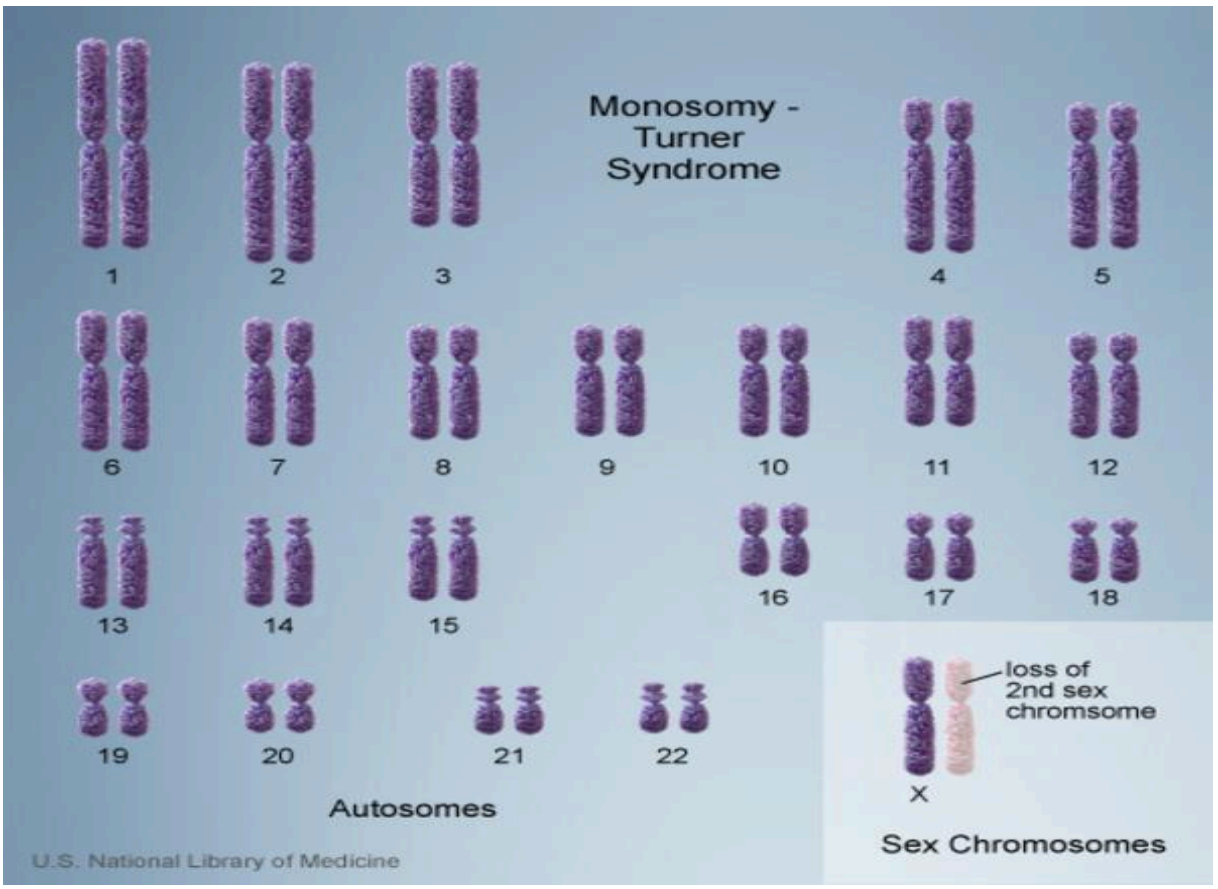

Figure 3: Monosomy (Turner syndrome). [65]

5.1.2 Klinefelter syndrome

Klinefelter syndrome (KS) is a common genetic condition in which phenotypic males have an additional X chromosome. Instead of having the normal genetic composition of 46, XY, males with Klinefelter syndrome acquire the genetic composition of 47, XXY as illustrated in Figure 4. [66]

Klinefelter syndrome occurs in approximately about 1/600 people who are assigned male at birth. [66]

The clinical picture of someone with Klinefelter's syndrome is tall and has long limbs. The mean weight is at the 75th percentile and the head and weight circumference is at the 50th percentile. In childhood, the external genitalia and testes are small (<1.9cm). During adolescence, puberty is not progressing normally. The patient has almost normal external genitalia and pubic hair development, but the testes in rare cases exceed 4ml. The testes are characterized as firm because of the hyalinization and fibrosis. The testosterone ranges are normally within the low to low-ordinary range. Another common clinical. [67]

Patients with Klinefelter's syndrome acquire verbal and behavioral difficulties. Immaturity, shyness, poor judgment and attention deficit hypersensitivity disorder (ADHD) are some of the noted challenges. About 10% of adult males with Klinefelter's syndrome are predicted to have autism spectrum disorder. This excessive affiliation shows the importance of an autism spectrum disorder screening. Some other common problems are: autoimmune disorders, breast cancer, cardiovascular disease, diabetes, increased cholesterol levels, hyperlipidemia, hypertension, hypogonadism, metabolic syndrome, nodular thyroid disease, rheumatoid arthritis, osteopenia, and osteoporosis. [67]

The diagnosis for Klinefelter syndrome is not usually done on fetuses. Chorionic villus sampling or amniocentesis can detect the disease, but it is usually identified while testing for other conditions. [66]

Another testing method usually used for children and adults is karyotype testing, a blood test that shows the number of chromosomes. Neurological testing is also considered important. This way, the child or adult can receive the help they need. [66]

Treatment for someone with Klinefelter syndrome includes hormone replacement therapy and treating other possible symptoms. [66]

People with Klinefelter syndrome have low testosterone levels. This affects the initiation of puberty. In case puberty begins, there is a chance that it will stop or slow down. The low levels of testosterone are due to the inability of testicles to produce testosterone and sperm. In these cases, testosterone injections, gels, patches, or subcutaneous pallets are recommended for children and teenagers. This treatment aims to assist with puberty, including an increase of body and facial hair, voice deepening, increased muscle and bone strength, and improved libido. [66]

Other additional therapies include speech-language therapy, physical therapy, occupational, and emotional, and behavioral, and family therapy. [66]

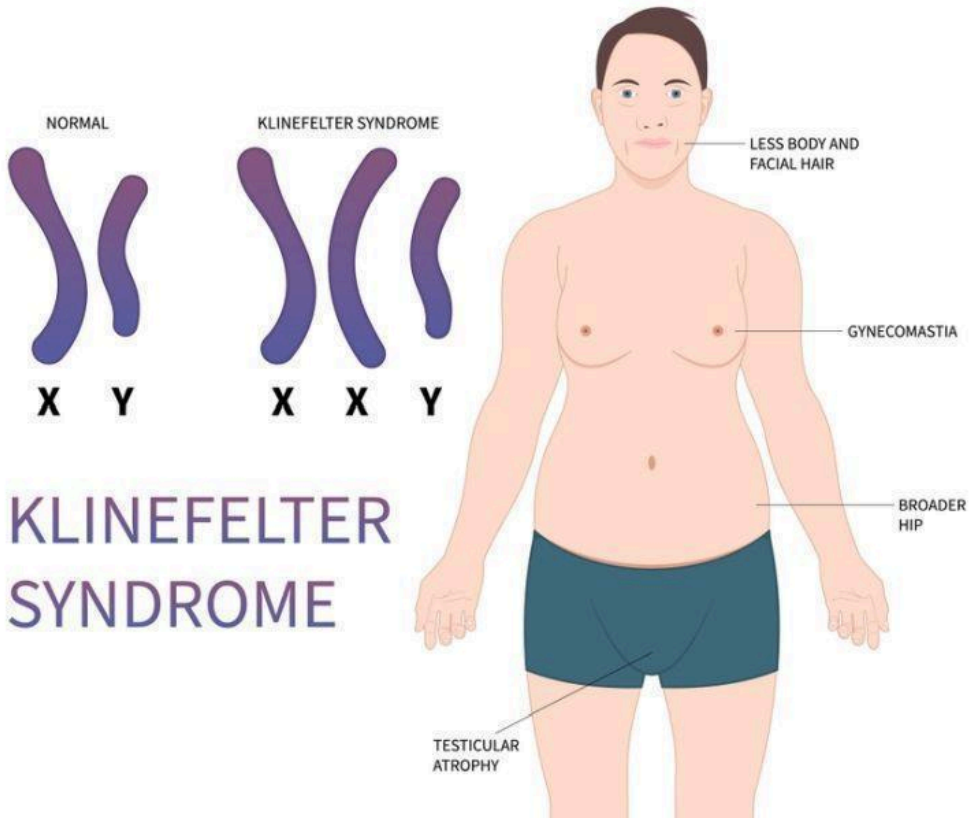

Figure 4: Klinefelter syndrome symptoms. [68]

5.2 Gonadal and hormonal DSDs

5.2.1 Swyer syndrome

Swyer syndrome is a condition that affects XY chromosomally male individuals, and is also called gonadal dysgenesis. The **c**ondition causes a deviation in the normal developmental pattern of XY individuals.

Individuals with this condition follow the female developmental pattern and develop female external genitalia and female internal reproductive organs. [69]

Many individuals only discover and are diagnosed with Swyer syndrome when they reach puberty. The investigation for Swyer syndrome is usually initiated when puberty is not progressing as expected. The diagnostic tests for Swyer syndrome include genetic testing, karyotyping, ultrasound, and magnetic resonance imaging. [70]

Apart from the deviation in development, it's important to note that the gonadal structures are dysfunctional in individuals with Swyer syndrome. This developmental deviation poses many health risks such as the development of gonadoblastoma if not managed.

The incidence of complete gonadal dysgenesis is approximately 13 individuals per every one million. [69]

Some common clinical features of individuals with Swyer syndrome are small breasts, and the development of vagina and uterus. Another very important clinical feature is the absence of menstrual periods. [70]

Although we know a lot about the Swyer Syndrome everything is not clear yet. There is a large patient group where the cause of the syndrome is idiopathic. Here we will discuss the most common causes of the condition. [69]

In approximately 15 % of the population, Swyer syndrome is caused by mutations in the sex-determining gene SRY. The SRY gene is located on the Y chromosome, and it encodes for the development of the male gonads. The mutation of the SRY gene prevents the synthesis of the Testis-Determining Factor protein (TDF), which is crucial for normal male gonadal development. [69]

In approximately one-fifth of individuals with gonadal dysgenesis, a mutation in the MAP3KI (mitogen-activated protein kinase kinase kinase 1) gene is the cause.

The MAP3KI is responsible for signaling the development of the female or male gonads. Usually, the gene increases signaling to encode for female gonadal development, and the opposite is true for the development of male gonads. A disturbance in the signaling of the MAP3KI is the causative factor. [69]

Disgenetic gonads, containing Y-chromosome material, are at risk of developing gonadoblastoma, which is estimated to undergo a malignant transformation in 50-60% of cases, usually to dysgerminoma. Owing to the high risk of malignant tumor formation, streak gonads should be removed as soon as the diagnosis is established. [71]

The management of Swyer syndrome consists of hormone replacement therapy with estrogen to initiate the development of secondary sexual characteristics and long-term combined replacement therapy. The earlier the HRT is initiated, the better the outcomes for the patient. Hormonal replacement therapy is crucial for individuals with Swyer syndrome to be able to develop for example breasts. [72]

Another cause for the Swyer syndrome is mutations in the Desert Hedgehog (DHH) and Nuclear Receptor Subfamily 5 Group A Member 1 gene (NR5A1).

The NR5A1 gene encodes for the synthesis of the protein steroidogenic factor 1 which is important for the regulation of sex hormones.

DHH encodes for the synthesis of a protein called Desert Hedgehog which is crucial for the early development of various bodily structures

The mutation in these genes disturbs the balance and causes abnormal gonadal development. [69]

5.2.2 5-Alpha reductase deficiency

This condition is characterized by individuals with XY chromosomes developing ambiguous external genitalia due to a mutation in the SRD5A gene, as shown in Figure 5. Individuals subject to this condition can showcase a wide variety of phenotypes according to the Prader scale, such as having a micropenis or a penis-like clitoris. [73,74]

The SRD5A gene is responsible for synthesizing the 5-alpha-reductase 2 enzyme, which converts testosterone to dihydrotestosterone (DHT). Dihydrotestosterone is a hormone crucial for the normal sexual development of male sexual characteristics, and the disturbance in this process is the leading cause of 5-alpha-reductase deficiency. [24,75]

Testosterone and dihydrotestosterone have different roles in the development of the male external and internal sexual structures. Testosterone plays a crucial role in the development of the internal genital structures and DHT plays a vital role in the external genitalia development. Individuals with 5-alpha-reductase deficiency usually develop normal internal genitalia however it's important to highlight that DHT plays a role in bodily processes during puberty. [24,75]

This condition is more common in cultures that practice the tradition of marriage between close relatives. This condition is inherited and passed on to the child only if both parents carry the mutated SRD5A2 variant. [24,75]

5-alpha reductase deficiency can be diagnosed by observation of the external genitalia. However, you can also run genetic tests to evaluate variants in the SRDA2 gene and hormonal tests to evaluate dihydrotestosterone and testosterone levels. [24,75]

The treatment of 5-alpha reductase deficiency includes supportive care, hormonal therapy, or surgery. The appropriate treatment is based on each individual's phenotypic trait. It is very important to determine the appropriate treatment before the puberty and the process of masculinization. For instance, surgery to remove the testes might be applicable if the individual has a severe malformation of the male external genitalia.

Reconstructive surgery is also a treatment method that is common among individuals subject to 5-alpha reductase deficiency. [24,75]

Hormonal therapy (HRT) is offered either with estrogens or testosterone. Hormonal therapy with estrogen is the most common treatment because of serious malformations of the male external genitalia. However, HRT with male hormones is also offered in some cases to aid in the developmental processes of XY individuals during puberty. [24,75]

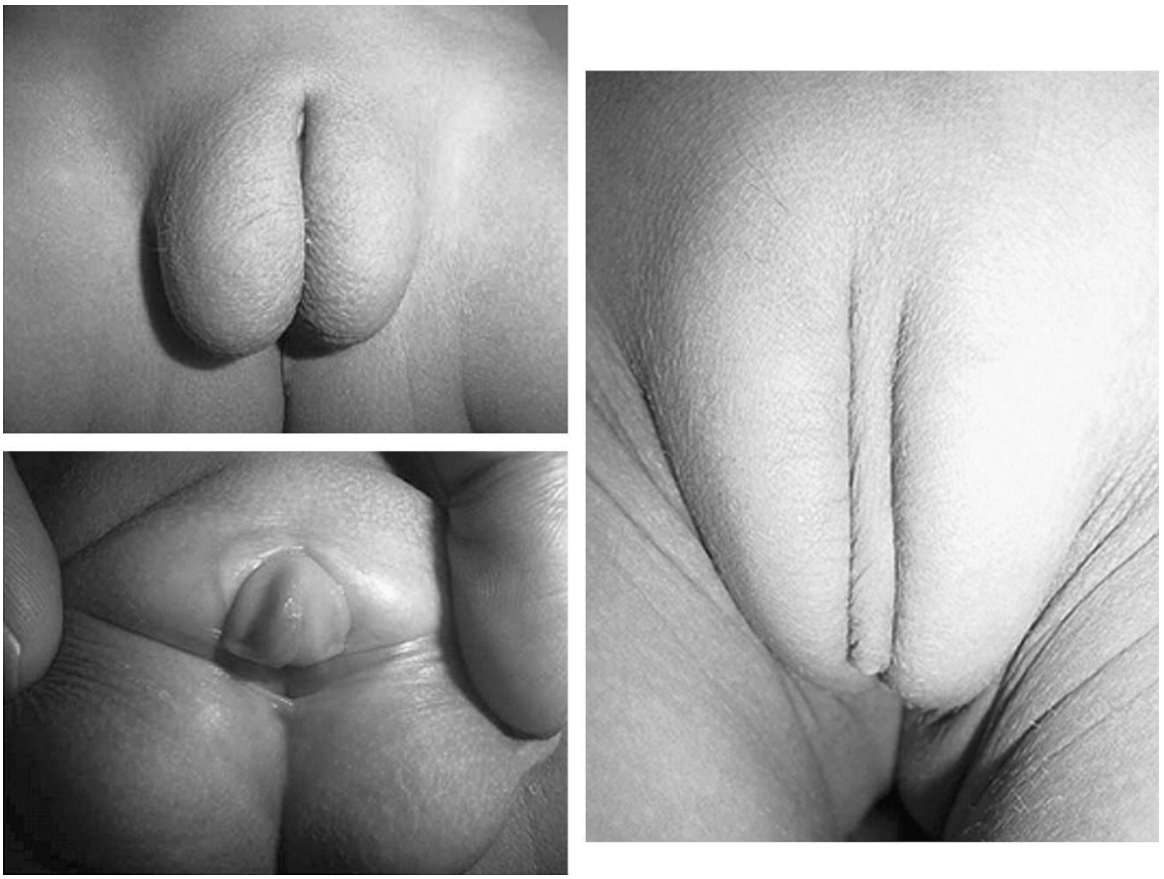

Figure 5: two different patients with ambiguous genitalia, on the left, an eleven-month-old patient, and on the right, a 12-year-old patient upon examination. [76]

5.2.3 Androgen insensitivity syndrome (AIS)

This disorder of sex development affects mainly the development of an individual's genitalia and reproductive systems. [77]

Androgen insensitivity syndrome is a congenital disturbance where the body does not react and respond normally to the male sex hormones due to mutations in the AR gene. The AR gene is located on the X chromosome, and it codes for the androgen receptors. Androgen insensitivity syndrome follows an X-linked recessive inheritance pattern, as illustrated in Figure 6 for better clarity. [77]

There are three different types of androgen insensitivity syndrome and they can be divided into three groups: [77]

Complete androgen insensitivity syndrome (CAIS) means that the body does not react to male sex hormones at all. In the case of complete androgen insensitivity syndrome, a consequence frequently seen in 46, XY individuals is that they follow the genital developmental pattern of female individuals rather than the genital developmental pattern of males.

Individuals with complete androgen insensitivity syndrome only develop external female sex genitalia, however, the development of internal structures such as the testes follows regular 46, XY individuals developmental pattern. [79]

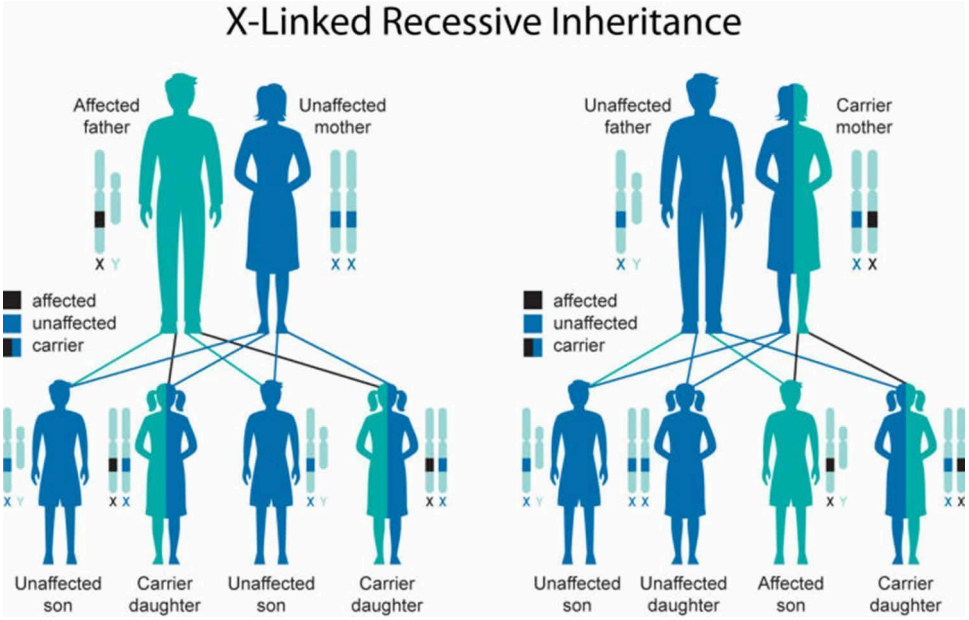

Figure 6: X-linked recessive inheritance. [78]

Individuals with this type of androgen insensitivity syndrome are usually raised as women.
The diagnosis of complete androgen insensitivity syndrome is usually established no earlier than late childhood or during puberty. [80]
Symptoms associated with complete androgen insensitivity syndrome are lack of bodily hair, absence of menstruation, and the complete development of the female external structures.
Diagnostic tests to establish the diagnosis of complete androgen insensitivity syndrome include ultrasound imaging to evaluate and examine the absence or presence of uterus, laboratory tests to evaluate the hormonal levels, and genetic tests to examine the chromosomes. [77]
In partial androgen insensitivity syndrome (PAIS), the body reacts to male sex hormones, but only to a certain extent. The sensitivity is reduced. This type of androgen insensitivity syndrome is characterized by an ambiguity in the external genitals of 46, XY individuals. The external genitalia in partial androgen insensitivity syndrome can exhibit very differently depending on the degree of the insensitivity to androgens. [77]
Individuals with partial androgen insensitivity syndrome may exhibit phenotypes such as an enlarged clitoris that looks like a penis, underdeveloped testicles, or labia, or hypospadias, where the urethral opening is positioned incorrectly. [77]

Although individuals might exhibit very differently depending on the degree of the insensitivity, what all individuals with partial androgen insensitivity have in common is that the development of the external genitalia does not follow the typical developmental patterns of either 46, XX- or 46, XY individuals. [79]

For individuals with Partial androgen insensitivity syndrome problems such as gender identity questions might arise during childhood or adulthood. Because of the ambiguous development of the external genital structures, individuals might not feel an affiliation with either the male or female gender. [79]

In cases of mild androgen insensitivity syndrome, the body has a reduced sensitivity to the male sex hormones. In mild androgen insensitivity syndrome, the insensitivity is not expressed to the same extent as in complete androgen insensitivity syndrome and partial androgen insensitivity syndrome. Individuals with mild androgen insensitivity syndrome usually follow the normal developmental pattern of 46, XY individuals. [77]

The prevalence of complete androgen insensitivity syndrome is challenging to detect in the early stages of development in chromosomally male individuals because they fully follow the developmental pattern of 46, XX individuals externally and exhibit female genitals and appearance. Approximately twenty to fifty in every one million individuals are diagnosed with complete androgen insensitivity. As these individuals exhibit female physical traits, they are usually designated as girls at birth, although being 46, XY. [77]

In contrast to the complete androgen insensitivity syndrome, the partial androgen insensitivity syndrome is much less prevalent, affecting five to seven individuals in every one million people. [80]

The prevalence of mild androgen insensitivity syndrome is unknown due to the mild expression of the syndrome in terms of clinically observable traits in comparison to the CAIS and PAIS. Some experts classify the mild androgen insensitivity syndrome as a form of partial androgen insensitivity syndrome. [81]

To summarise the general diagnostic investigation of androgen insensitivity syndrome consists of a combination of observable findings, hormonal testing, genetic testing such as karyotyping, and radiology to identify the presence or absence of internal sexual structures.

It is important to analyze the levels of testosterone, which is elevated, while luteinizing hormone and follicle-stimulating hormones aare usually within normal limits in androgen insensitivity syndrome. [80]

The prognosis for androgen insensitivity syndrome is usually good and individuals live healthy and normal lives. [81]

The complications associated with androgen insensitivity syndrome are connected to the male gonads. In complete androgen insensitivity syndrome, there is a slightly increased risk of developing testicular tumors, and previously, it was recommended to perform a gonadectomy. The decision to remove the gonads now depends on the patient's wishes after fully informing them about the risks and consequences. In PAIS, there is a high risk of gonadal malignancy, so gonadectomy is usually performed. [82]

Hernias are a possible complication associated with androgen insensitivity syndrome. Since testicles do not descend to the scrotum, they grow internally in the abdomen or inguinal canal, which can lead to inguinal hernias. Surgical interventions can also correct this. [79]

Other complications are for example infertility and psychological difficulties that might arise throughout life related to gender identity and belonging. [77]

Treatment and support for individuals with androgen insensitivity syndrome:

The treatment is very individual and solely depends on the individual’s needs and situation. As previously said, gonadectomy is a prevalent treatment method for androgen insensitivity syndrome. Other surgical interventions focus on correcting genital anomalies.

Providing psychological help is very important for individuals with AIS to deal with questions related to gender identity and gender dysphoria. [80]

Gender identity and gender dysphoria:

46, XY individuals with complete androgen insensitivity syndrome usually identify as women however the situation might be more tricky and complex for individuals with different types of androgen insensitivity syndrome. [79]

Individuals who develop ambiguous external genitals might experience confusion and discomfort with their own bodies. [83]

What can happen is that these individuals can experience gender dysphoria. [79]

Gender dysphoria is when an individual’s gender identity, which means their own sense of their gender does not correspond with the sex they were assigned at birth. [84]

Hormonal therapy is also a treatment for individuals with androgen insensitivity syndrome. For individuals who have undergone a gonadectomy, this is crucial and the estrogen hormone therapy promotes and facilitates the development of the female body. [79]

5.2.4 Congenital adrenal hyperplasia (CAH)

Congenital Adrenal Hyperplasia is a disease that affects the adrenal glands and is a congenital group of diseases. It is caused by genetic abnormalities in the enzymes and proteins that play a role in cortisol synthesis. The CYP21A2 gene, which codes for the enzyme adrenal steroid

21-hydroxylase, is usually mutated. Its function is to convert cholesterol to cortisol within the gland. The adrenal glands above our kidneys produce vital hormones such as aldosterone, androgens, and cortisol. In Congenital Adrenal Hyperplasia, the normal production of these vital hormones is impaired, thus leading to improper functioning of the adrenal glands. [82]

When the CYP21A2 gene is mutated, the pituitary gland releases more ACTH to stimulate cortisol production. A deficiency in the adrenal steroid enzyme causes the overproduction of male sex hormones, and insufficiency of cortisol and aldosterone, which can lead to electrolyte imbalances and hypotension. [85]

Patients may exhibit different clinical features in congenital adrenal hyperplasia depending on the type of congenital adrenal hyperplasia. For the nonclassic type of congenital adrenal hyperplasia, individuals might experience dermatological problems, abnormal hair growth, amenorrhea, oligomenorrhea, infertility, or decreased fertility in males and females. For the classic type of congenital adrenal hyperplasia, women can exhibit ambiguous genitalia and male individuals enlargement of the penis. [86]

In the case of Congenital Adrenal Hyperplasia specifically, the production of cortisol and aldosterone can be decreased due to the lack of the adrenal steroid 21- hydroxylase enzyme, leading to an overproduction of male sex hormones. [86]

Congenital adrenal hyperplasia is passed down to offspring in an autosomal recessive pattern meaning that you need to get a mutated gene from each parent to inherit the disorder. [87]

The increase in androgens as a response to the reduction of cortisol and aldosterone is caused by the increased release of adrenocorticotropic hormone from the pituitary gland.

The insufficient production of aldosterone triggers an overproduction of renin angiotensin II which in turn promotes increased production of male sex hormones. [87]

The diagnosis of congenital adrenal hyperplasia can be established already before birth with diagnostic tests such as amniocentesis and chorionic villus sampling.

After birth diagnostic tests can be performed to evaluate the levels of the enzyme 21-hydroxylase which can identify the classic type of congenital adrenal hyperplasia.

Imagining investigations such as X-rays for the evaluation of bones and ultrasound for the evaluation of internal reproductive organs may be performed. Diagnostic investigations also include genetic testing, blood, and urine tests. [88]

The treatment of congenital adrenal hyperplasia often requires a multidisciplinary approach. Usually, the management starts with a referral to a pediatric endocrinologist for children and adults to an adult endocrinologist. Psychologists and doctors usually work together in the management of CAH. [88]

Pharmacological treatment in CAH aims to replace the hormonal deficiencies caused by the disease and try to control the excess production of male sex hormones. The pharmacological treatment of congenital adrenal hyperplasia consists of aldosterone analogs to restore electrolytes, glucocorticoids to replace cortisol, and salt supplements to stabilize sodium levels. [88]
In the treatment of CAH, regular checkups are crucial to be able to treat the patient correctly as there needs to be a correction in the drug treatment based on the hormone levels that can shift. The classic form of congenital adrenal hyperplasia needs long-term pharmacological treatment, unlike the non-classic type which does not always need to be treated pharmacologically. [88]
Some girls are born with external genitals that are not typical for their gender, and in these cases, reconstructive surgery could be indicated. Reconstructive surgeries are also performed to prevent sexual impairments illustrated in Figure 8. [89]
Congenital Adrenal Hyperplasia can be divided into two main types, classic and non-classic congenital hyperplasia. [85]
The classical form of congenital adrenal hyperplasia is the more severe variant, usually detected upon birth. Girls with the classical variant of congenital adrenal hyperplasia can exhibit abnormal genitalia, such features include enlargement of the clitoris and other deviations in the genitalia. Boys on the other hand do not always show any observable abnormalities on the external genitalia upon birth. In the classical form of CAH both girls and boys can have a reduction in crucial hormones such as cortisol and aldosterone, which in turn can lead to symptoms such as nausea and tiredness. [85]
In the classical variant of congenital adrenal hyperplasia, there is a risk of developing a serious condition called adrenal crisis. An adrenal crisis is a medical emergency in which the body cannot regulate blood pressure, electrolyte balance, and blood glucose levels. Adrenal crisis can cause hypotension, hypoglycemia, diarrhea, and dehydration and requires immediate medical interventions. [85]
The non-classic variant of congenital adrenal hyperplasia is a less severe type of the disease. The classical type does not give physical signs upon birth. It differs from the classical type and is usually diagnosed and detected during childhood or early adulthood. [85]
In girls and boys with the non-classical type of congenital adrenal hyperplasia, early signs of puberty can often be observed. Clinical features that might be exhibited in the classical type of CAH are, for example, premature development of the pubic hair and an acceleration in growth rate. Although an increase in the growth rate can be observed in childhood, the final height of these individuals might be shorter than the average. For girls oligomenorrhea and amenorrhea are common clinical presentations of the diseases. Other clinical features of the nonclassical type of

CAH are hirsutism, hyperpigmentation illustrated in Figure 7, and vocal cord hypertrophy with deepening of the voice. [85]

Infertility is also common among girls and boys with both non-classical and classical congenital adrenal hyperplasia. [85]

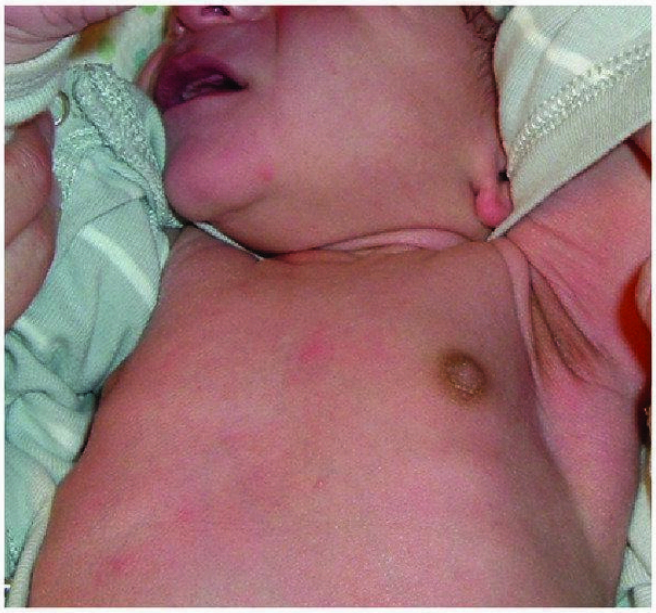

Figure 7: Hyperpigmentation at nipples and axillary in a 10-day-old male infant with salt-wasting congenital hyperplasia due to 21-hydroxylase deficiency. [90]

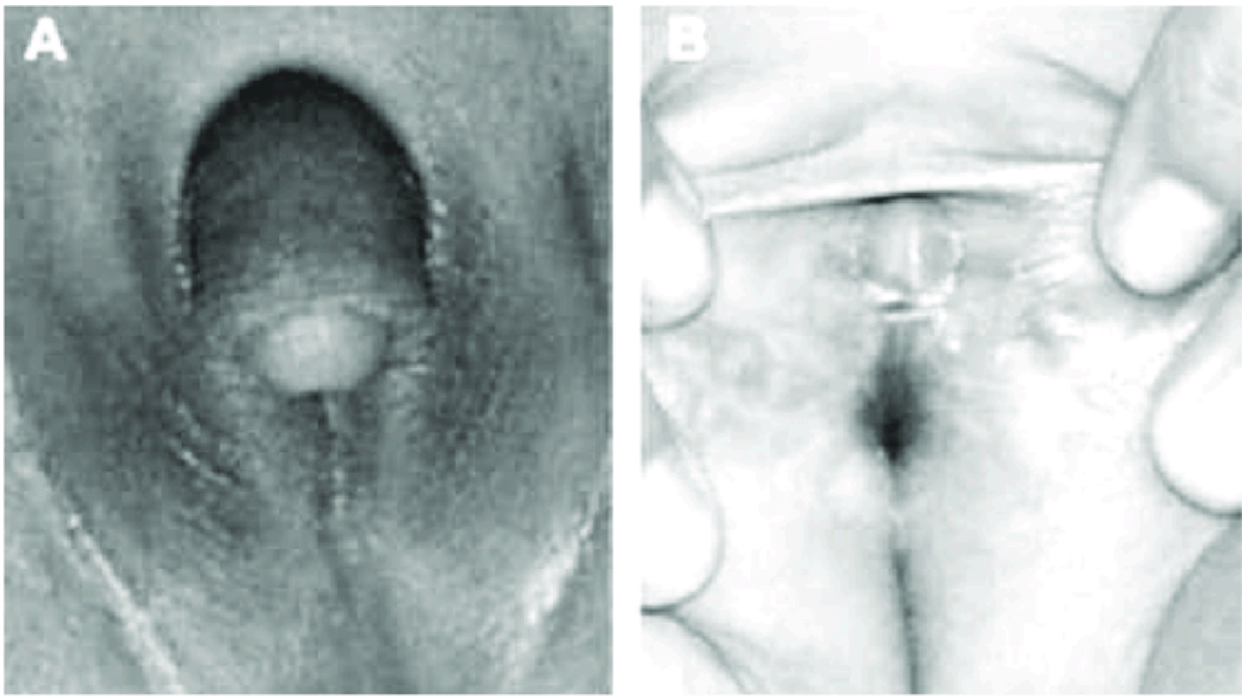

Figure 8: The external genitalia of a patient with congenital adrenal hyperplasia before A and after B genitoplasty-cosmetic results are classified as regular. [91]

6. GENERAL PRINCIPLES OF MANAGEMENT – MULTIDISCIPLINARY APPROACH

According to consensus statement recommendations, the best prognosis and outcomes in the management of individuals with disorders of sex development are achieved through a multidisciplinary approach. According to recommendations, a team of different medical specialties, psychologists, diverse medical personnel, and social workers should work together for the best outcomes. The interplay of social, family, and medical teams is of utmost importance for the outcomes of patients with disorders of sexual development. [92]
Access to proper education for parents about their child´s disorder and how to help their child cope and manage is of utmost importance. [92]

7. ETHICAL PSYCHOLOGICAL AND SOCIAL ASPECTS

7.1 Ethical issues in diagnosis and treatment

Parental Consent is when an individual willingly accepts another individual's suggestions. Autonomy is the idea of an individual having independence and being in control of their own physical destiny. The topic of consent and autonomy is quite controversial in the diagnosis and treatment of disorders of sexual development. Individuals with DSD have been criticizing the ethical aspects concerning the management of disorders of sexual development. [93]
Criticism has been mainly towards the surgeries that are performed on behalf of the parents of children with disorders of sexual development. Some critics mean that no operations should be performed without the consent and autonomy of the child. [93]
Deferred consent is a way to allow individuals to consent and have autonomy in the decision-making of their own body. [93]
Autonomy, the right to an open future, and respecting the child's bodily integrity is an ethical issue concerning the management of disorders of sexual development. The discussion encompasses and highlights the perspective of surgeries that are done without the informed consent and autonomy of the child. [95]
Some ethical considerations for healthcare personnel and families in managing and diagnosing are maleficence and benefits regarding treatment choice.
Beneficience in the context of managing disorders of sex development should consider if the treatment method will overall improve the patient's lifestyle and benefit them.

Nonmaleficence in the context of managing disorders of sex development is the idea of not causing any unnecessary harm. Both maleficence and nonmaleficence in the decision-making of management of patients with disorders of sex development are considered together. [96]
As a method of management of patients with disorders of sexual development shared decision-making is an ethical consideration that should be considered to ensure the best treatment of the patient. This collaborative treatment approach involves healthcare personnel, the family, and the child if possible. [97]
The purpose of surgery in patients with disorders of sex development is to benefit the patients, but there are cases where harm has been caused. [98]
As an example, surgeries such as gonadectomy are performed to reduce the risk of the development of gonadal tumors, as the risk of gonadal tumors is increased in some disorders of sex development. [98]
Ethical considerations surrounding elective surgeries are a controversial topic. Activists argue that it's not in the patient's best interest to always perform surgeries on atypical genitalia. The discussion is that parents might feel pressured and stigmatized and thus act too quickly without the best interest of the child to sign up the child for elective surgery. [98]

7.2 Psychological effects on patients and families

The psychological effects on families and patients in the treatment and diagnosis of disorders of sexual development include the proper education of the child and parents and the approach of the medical personnel. [92]
For parents, it could be a very stressful situation if they have a child with a disorder of sexual development; the uncertainty of their child's gender and future psychosocial development encompasses major decisions that will affect the child's future.
Difficult decisions that parents have to make include decisions regarding surgical interventions and medical treatments that will shape the trajectory of the child's sexual development. [92]
Another stressor for parents is the controversy regarding the treatment options and approaches that should be taken in the management of disorders of sex development. [92]
The healthcare staff's approach to the management of disorders of sexual development is of utmost significance for the patient's self-image and esteem. The psychological outcomes for patients regarding their self-esteem and perception of their physical appearance have shown to be worsened when repeated medical interventions have taken place.

It’s very important for medical personnel to educate individuals with disorders of sex development about the purpose of medical procedures and examinations, as this has been shown to improve psychological outcomes for patients. [92]
A patient’s psychological outcomes and self-perception are strongly connected to family dynamics and a supportive parenting approach. For patients with a safe support network, the prevalence of self-harm and suicidal thoughts is reduced. [92]
Parents with children who have atypical genital appearances might struggle to speak about this with their children, affecting them emotionally. For individuals with atypical genitalia, it can be very difficult to share details about their medical condition with relatives and friends, leading to a feeling of shame. [92]

7.3 Social challenges and cultural implications

A very important social challenge in the management and diagnosis of disorders of sex development that needs to be spoken about is that nonmedical critics oppose medically necessary interventions and label them as elective surgery, making an already complex situation for parents more emotionally distressing and challenging. [92]
Surgeries in the field of disorders of sex development can be classified into urgent surgeries, elective, and cosmetic. Urgent surgeries are performed to prevent permanent disability, including surgeries to make it possible for patients to pass stool. Elective surgeries are surgeries that are not life-threatening but can improve life quality. An example of a cosmetic type of surgery is clitoral reduction surgery, which carries risks of harming genital tissue and adult life sex satisfaction. [92]
Surgeries such as clitoral reduction surgery are usually done in childhood on the initiative of the parents in an attempt to “normalize” the atypical genitalia. However, this can lead to irreversible damage and suffering for the child. Parents have stated that surgeries like early genitoplasty are obvious or necessary for the psychosocial and sexual adaptations of the child. However, irreversible complications occur, and individuals are dissatisfied when they do not have informed consent. [98]
Critics argue that parents do not always have the best outcome for their child in mind when signing up their child for elective surgeries. Critics mean that other factors, such as cultural perceptions of gender, societal stigmatizations, and shame, play major roles in decision-making. [98]

8. CONCLUSION

In this review, the complexity of normal sexual differentiation and the mechanisms that take place are discussed. We review common genetic, structural, and hormonal deviations that can occur in the developmental processes.

The disorders of sex development that are reviewed are Turner syndrome, Androgen Insensitivity Syndrome, Congenital Adrenal Hyperplasia, Klinefelter Syndrome, Swyer Syndrome and 5- alpha reductase deficiency, depicting the broad spectrum of clinical presentation of different disorders of sex development.

Diagnostic tests and methods for various disorders of sex development are reviewed, along with the available radiological, hormonal, and genetic analysis tools used for different conditions.

Treatment options and the importance of an individualized patient-centered approach are discussed. The review is trying to highlight that all patients with disorders of sex development have unique challenges and needs.

Ethical and psychological aspects of disorders of sex development are depicted in the review, highlighting previous terms and classifications. The review highlights the importance of the patient's autonomy and shared decision-making in managing DSDs.

The review also highlights the importance of psychological support and education about DSDs for the family and the patient for optimal patient satisfaction ~~results~~.

This review has shown how unique every case of individuals with disorders of sex development is, the variety and complexity of the management. Just like each case is unique, the approach should be unique to the individual's needs and situation.

The review emphasizes the need for collaboration among healthcare professionals in managing DSDs and highlights the significance of educating the family and the patient to ensure optimal satisfaction.

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