# INTRODUCTION

The term disorders of sexual differentiation (DSDs) are defined as congenital conditions associated with atypical development of chromosomal, gonadal, or anatomical sex ***(Lee et al., 2006).***

Phenotypic sex results from the differentiation of internal ducts and external genitalia under the influence of sex-determining genes and hormones. In one of every 4500 births, the genital appearance is abnormal and it is not possible to decide at first glance the sex of the infant. Disorders of sexual development (DSD) are a very important clinical issue with its different aspects relating to diagnosis, treatment and sex of rearing. The classification of ambiguous genitalia in patients is difficult because similar or identical phenotypes may have several aetiologies ***(Allen, 2009).***

The psychological development of persons with DSD has focused on understanding the influence of atypical sex hormone exposure during steroid-sensitive periods of prenatal brain development on the process of psychosexual differentiation (i.e., gender identity, gender role, and sexual orientation) ***(Hines et al., 2004).***

The psychological and social implications of gender assignment and those relating to treatment are very important and require a multidisciplinary approach with the inclusion of

geneticists, neonatologists, endocrinologists, gynaecologists, psychiatrists, surgeon and social workers in the team. The members of such a team should have a special interest in DSD and possess sufficient experience with this group of patients ***(Reiner, 2005).***

The necessity of psychological counseling emerges in the context of decisions about the timing of interventions, education of the patient and others about medical history (i.e., disclosure), management of potential psychosocial or educational problems that emerge for the child, or when parents need support in understanding the etiology of the child's condition and its implications ***(Sandberg et al.,, 2012).***

# AIM OF THE WORK

***This review aims at:***

Identifying the various causes of DSD, identifying the management strategies for DSD, elucidating the importance of psychological evaluation of patients with DSD during the process of planning the management and reviewing the psychological outcomes of pediatric patients with DSD after management has been done.

# Chapter One

# SEXUAL DEVELOPMENT AND DIFFERENTIATION

Sex is defined as the biological qualities that distinguish between male and female. These qualities are expressed by an individual's chromosomal, gonadal, morphological (internal and external) and hormonal characteristics ***(Stedman, 1982)*.**

Gender is defined as the sex of assignment. Gender can be further partitioned into gender role and gender identity, which refer to the sex of a person assigned by society and the sex of a person assigned by himself respectively ***(Stedman, 1982).***

The jost model formulated by the physiologist Alfred Jost chromosomal (genetic) sex determines gonadal sex, and gonadal sex, in turn, determines phenotypic sex ***(Jost, 1970).*** If a testis develops, the urogenital tract becomes male in character, and if an ovary (or no gonad) is present the urogenital tract is female in character ***(Griffin et al., 2013).***

## Genetic Sex

The genetic sex of an individual is considered to be the first step in sex differentiation. Genetic sex is determined at fertilization, when fusion of an egg and a sperm occurs ***(Migeon and Wisniewski, 1998).***

An egg has a chromosome complement of 23, X and a sperm has a complement of either 23, X or 23, Y ***(Ford and Hamerton, 1956).*** The diploid cell which results from this fusion has either a 46, XX (genetic female) or a 46, XY (genetic male) karyotype ***(Tijo and Levan, 1956).*** Once fusion of parental gametes occurs genetic sex is established for an individual ***(Migeon and Wisniewski, 1998).***

## *Undifferentiated Structures*

During the first 6 weeks of embryonic development the gonadal ridge, germ cells, internal ducts, and external genitalia are bipotential in both 46, XX and 46, XY embryos. Under circumstances of sex differentiation: (1) the bipotential gonadal ridges differentiate into either ovaries or testes; (2) germ cells develop into either oocytes or spermatocytes; (3) one of the two sets of internal ducts develop while the other regresses, and (4) bipotential external genitalia either masculinize or remain feminine. In instances of normal sex differentiation, the undifferentiated structures are complementary to each other regarding classification as male or female ***(Migeon and Wisniewski, 1998).***

## *Gonadal Ridges*

A bipotential gonadal ridge is located medially on the urogenital ridge which can be detected by 5 weeks of gestation ***(Langman, 1969; Jirasek, 1977).***

The gonadal ridge is considered to be a bipotential gonad once germ cells migrate to this structure. Germ cells are formed in the yolk sac and migrate at approximately 5 weeks of embryonic development. They contain a 46, XX or 46, XY complement ***(Jirasek, 1971)*** and undergo mitotic divisions during the process of differentiation, with these divisions occurring in both the fetal testis and ovary ***(Langman, 1969; Witschi, 1948).***

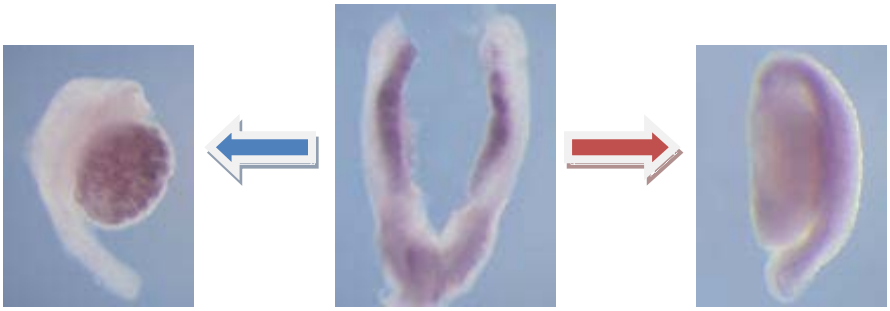


**Fig. (1):** The differentiation of the bipotential genital ridge into a testis and ovary ***(Rao et al., 2013).***

## *Undifferentiated Sex Ducts:*

The 46, XX and 46, XY embryos each possess a set of wolffian ducts as well as a set of müllerian ducts early in development. The wolffian ducts are detected during the 4th gestational week ***(Jirasek, 1977; Josso, 1981)*** and the müllerian ducts appear later, during the 6th gestational week ***(Langman, 1969).***

- **The wolffian (mesonephric) ducts:**

Under the influence of testosterone and mullerian inhibiting substanc (MIS) secreted by the fetal testis, the mesonephric duct becomes the vas deferens by approximately 12 weeks gestation, with the epididymis forming from its testicular end. At the epididymis' superior end, 12–20 efferent ductules persisting from the mesonephros extend toward the testes to meet the rete testis. The degenerated cranial end of the mesonephric duct often leaves a small remnant called the appendix epididymis ***(Rao et al., 2013).***

At 10–13 weeks gestation, testosterone induces the formation of the seminal vesicles from the caudal ends of the mesonephric ducts. The seminal vesicles and vasa deferentia then empty into the prostatic urethra through the ejaculatory ducts at the verumontanum ***(Rao et al., 2013)*** (Fig. 2)

- **The mullerian (para mesonephric) ducts:**

The female fetus has no testis but ovary so there no secretion of testosterone and MIS. Thus the mullerian duct persists. The caudal, fused portions of the paramesonephric ducts form the proximal vagina and the uterus; the more cranial portions form the fallopian tubes, with the conical ends forming the openings to the peritoneum. In females, remnants of the mesonephric ducts form the nonfunctional epoophoron and paroophoron in the mesosalpinx ***(Rao et al., 2013)*** (Fig. 2).

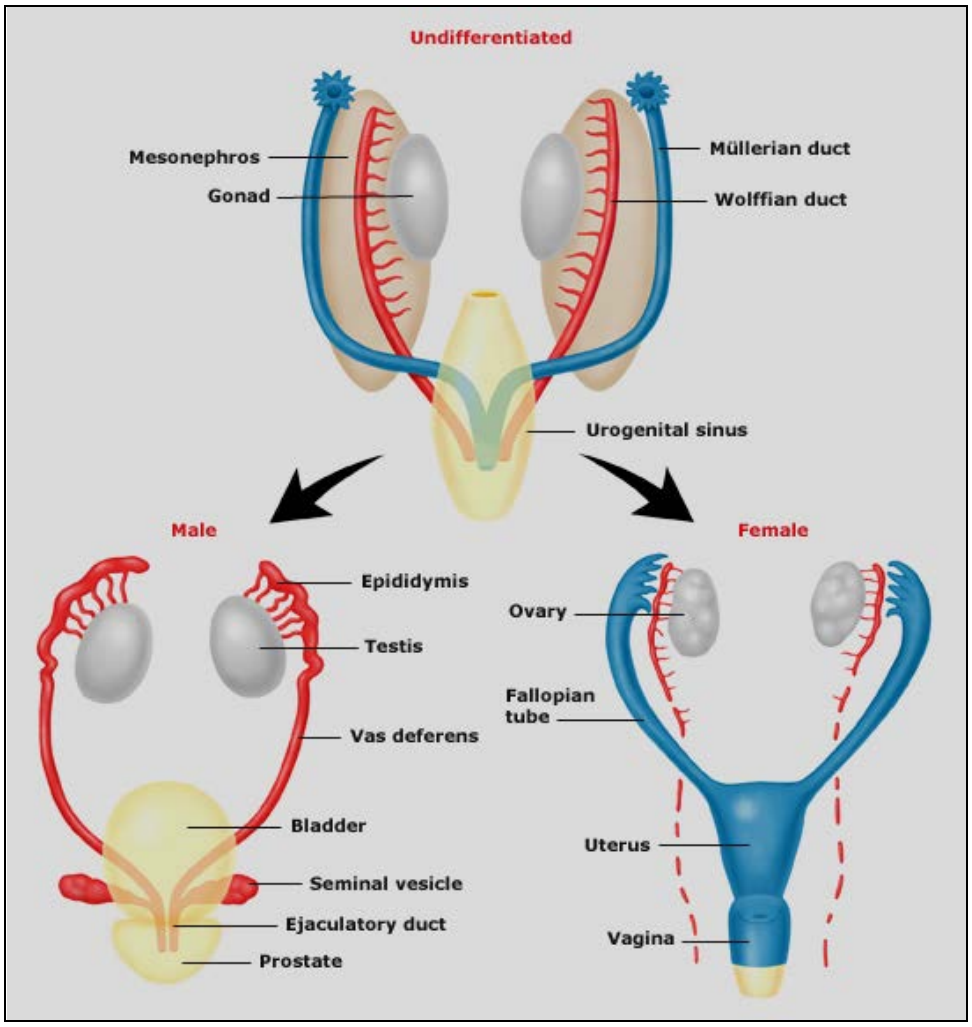


**Fig. (2):** Differentiation of the female and male urogenital tracts ***(Rao et al., 2013).***

In females, the Müllerian ducts give rise to the fallopian tubes, uterus, and upper vagina, and the Wolffian ducts persist in vestigial form. In males, the Wolffian ducts give rise to the epididymides, vasa deferentia, seminal vesicles, and ejaculatory ducts, and the Müllerian ducts regress ***(Rao et al., 2013).***

## *External Genitalia*

The cloacal folds, situated around the cloacal membrane, are detectable at 5 weeks of embryonic development.Tissue destined to form the external genitalia is located at the cranial region of the cloacal folds and separates from the posterior region which will become the anus. This tissue is bipotential, and thus identical in 46, XX and 46, XY embryos until 9 weeks of embryonic development ***(Jirasek, 1977)*** (Fig. 3).

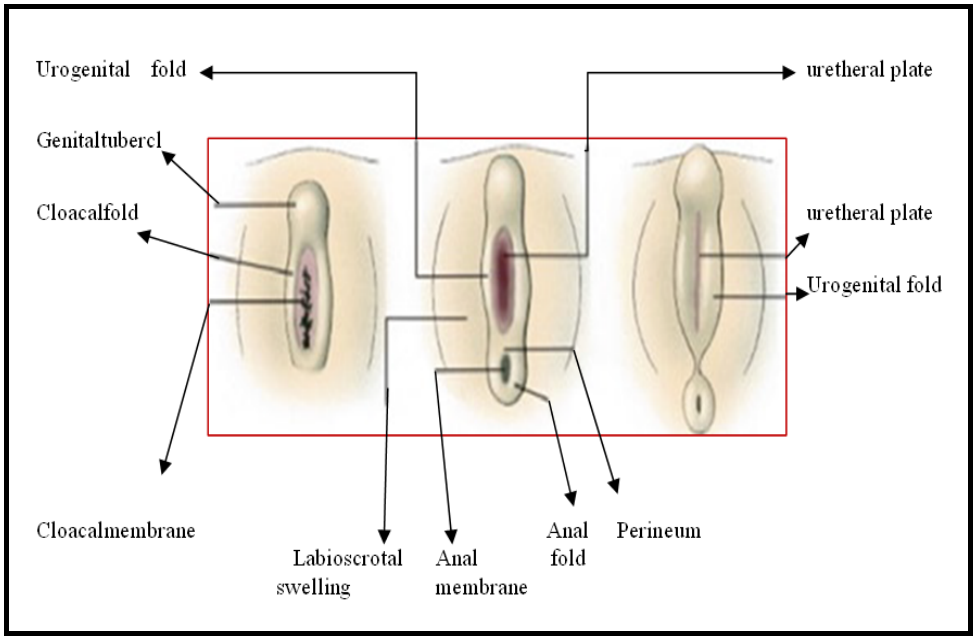


**Fig. (3):** Formation of the male and female external genitalia. Development of the external genitalia during the bipotential stages through 7 weeks gestation ***(Schoenwolf and Larsen, 2009).***

## Side view

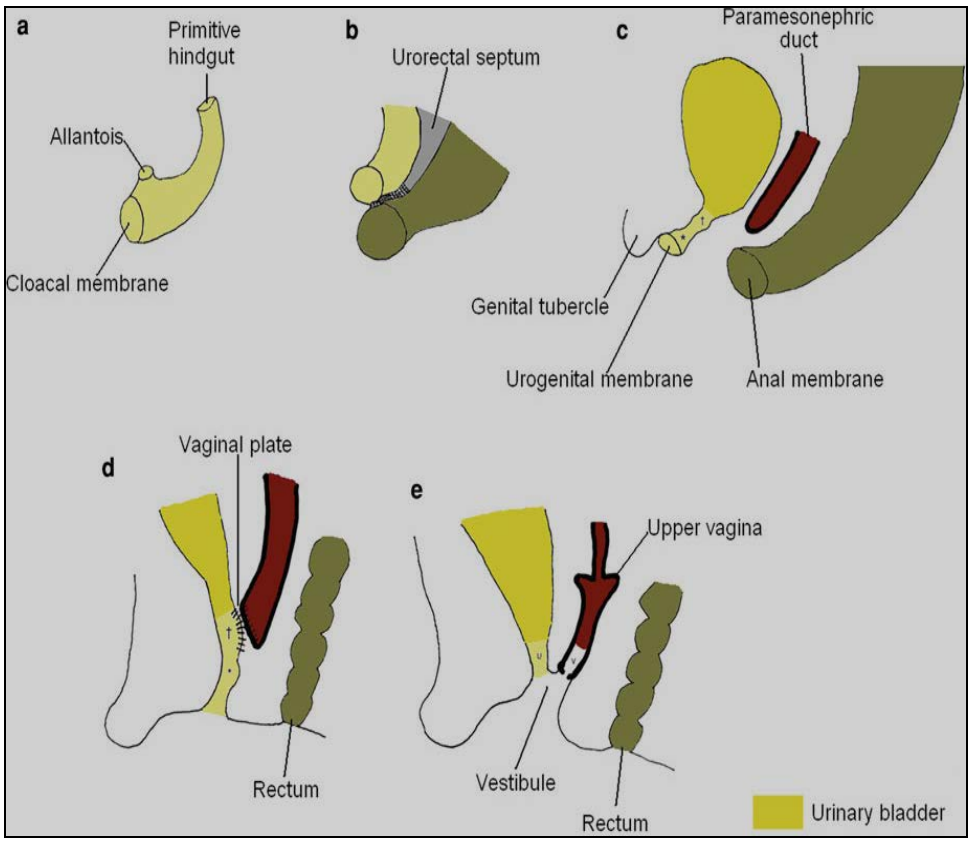


**Fig. (4): Division of the cloaca and differentiation of the female lower genitourinary tract.** a) The cloaca. b) The partition of the cloaca into anorectal and urogenital compartments by the descent of the urorectal septum (4–6 weeks). c) The formation of the genital tubercle and urogenital sinus (UGS). The phallic (*) and cranial (+) portions of the pelvic UGS form the vaginal vestibule and female urethra, respectively. d) Canalisation of the vagina at the vaginal plate onto the UGS (vertical fusion). e) The definitive vaginal vestibule ***(Healey, 2012).***

## Gonadal sex

Gonadal sex determined when the indifferent gonad develops into an ovary or a testis, beginning around week eight and subsequent secretion of hormones by the fetal testes ***(Griffin et al., 2013).***

### *Testis Determination*

The bipotential gonad and associated germ cells develop into a testis containing type-A spermatogonia around 6 weeks of embryonic development if specific influences from the sex determining region of the Y chromosome (SRY), steroidogenic factor-1 (SF-1), and SRY-related HMG-box gene 9(SOX-9) are evident ***(Migeon and Wisniewski, 1998).***

The first of three steps observed in testis determination is the appearance of Sertoli cells which organize themselves into seminiferous tubules and surround the germ cells. Sertoli cells produce (MIS) ***(Magre and Jost, 1984)*** which is necessary to inhibit development of the müllerian duct system. The next step in testis determination from a bipotential gonad is the appearance of Leydig cells ***(Jirasek, 1971; pelliniemi and Niemi, 1969).*** Once Leydig cells are present and stimulated by chorionic gonadotropins early or by fetal pituitary gonadotropins later, the fetal testis is capable of producing testosterone ***(Siiteri and Wilson, 1974).*** The third step in testis determination is differentiation and development of male germ cells. In the testis, germ cells undergo mitotic arrest and

subsequent formation of spermatogonia ***(Migeon and Wisniewski, 1998).***

Two distinct mechanisms exist to explain mitotic arrest of male germ cells: (1) Physical contact between germ cells and Sertoli cells ***(Mclaren, 1988).*** (2) Mitotic inhibiting substance from the seminiferous tubules ***(Byskov et al., 1988).***

## *Genetic Control of Testis Determination*

- The Wilms' tumor gene (WT1) is an important transcription factor for the development of a bipotential gonad upon which testicular or ovarian differentiation occurs ***(Maclean et al., 1997).***
- SF-1is needed for testis determination and mullerian duct regression ***(Smith, 1994)*** as it binds to a regulatory element associated with MIS genes ***(Shen et al., 1994).***
- DAX-1(DSS, AHC, X-linked gene1) is part of the dosage senestive sex Reversal locus-adrenal hypoplasia congenita critical region on the X-chromosome gene1. This gene is expressed in human ovarian tissue, so it is important for the ovarian formation ***(Bardoni et al., 1994).***
- SRY is the locus for the testis-determining factor (TDF), and it is located in a 35-kb segment on the short arm of the Y chromosome ***(Sinclair et al., 1990).***

If a developing embryo possesses a functional SRY gene, the bipotential gonad subsequently develops into a testis then it activates a series of additional so-called downstream genes: Sox9, Sox8, Fgf9, Dmrt1, and Dax1 ***(Wilhelm et al., 2007)*** to promote development of the Leydig cells, Sertoli cells, and the spermatogenic tubules ***(Brennan and Capel, 2004).*** The absence of SRY results in gonadal streaks in individuals with subsequent 46, XY complete gonadal dysgenesis ***(Fechner, 1996).***

SF-1 and DAX-1 expression are detectable prior to SRY expression. It is possible that the role of SRY is to potentiate the transcription of SF-1, which in turn stimulates the expression of male differentiating genes while it suppresses the expression of DAX-1, a stimulant of female-differentiating genes ***(Migeon and Wisniewski, 1998).***

- Autosomal or X chromosome genes also play an important role in testis determination ***(Migeon and Wisniewski, 1998).***

Testicular determination is observed in both 46, XX males and 46, XX true hermaphrodites.Two alternative processes explain this 1) translocation of chromosomal material encoding (TDF) from the Y to the X chromosom, or 2) an autosomal dominant mutation that permits testicular determination in the absence of TDF ***(Gary et al., 1992).***

## *Ovarian Determination*

Formation of oocytes from germ cells is the first step in ovarian determination ***(Jirasek, 1977).*** Folliculogenesis is the second important step in ovarian determination from the original bipotential gonad. The third step is the development of endocrine cells ***(Migeon and Wisniewski, 1998).***In the human fetal ovary, cytochrome P450 aromatase activity is present preceding ovarian differentiation ***(George and Wilson, 1978),*** but it is unclear how or where fetal ovarian tissue produces sex steroid hormones ***(Migeon and Wisniewski, 1998).***

## *Genetic Control of Ovarian Determination*

In both sexes, SF-1 in connection with DAX-1 promotes the development of the bipotential gonad. Later, the absence of SRY in the female fetus results in decreased expression of SF-1. It is interesting that an SF-1 recognition site has been localized in the DAX-1-promoter region, indicating the potential for SF-1 to regulate DAX-1 expression ***(Burris et al., 1995).***The process of ovarian development is believed to involve an active genetic pathway, including R spondin 1 (Rspo1)/Wnt-4/beta-catenin signaling that is repressed by the presence of SRY ***(Griffin et al., 2013).*** Evidence for this comes from experimental studies of mice ***(Vainio et al., 1999)*** and human mutations ***(Biason-Lauber et al., 2004).***

## Hormonal Secretions

### *Anti-Müllerian hormone (AMH)*

Also called Müllerian inhibiting substance (MIS)

AMH is a 145,000 MW glycoprotein homodimer secreted by sertoli cells of fetal testis at about six weeks of development causes regression of the müllerian duct system in males and for influencing testicular formation ***(Josso, 1992).***

AMH is also detected in females, but only after the müllerian ducts are committed to development. The presence of MIS in females and in testes suggests additional functions of MIS in fetal development ***(Josso, 1992).***

It is found that AMH produced by Sertoli cells not only during the period when it is responsible for regression of the Müllerian ducts but also in late pregnancy, after birth, and even, albeit at a much reduced rate, in adulthood ***(Josso et al., 2001).***

AMH is measurable in human serum by ELISA and has diagnostic applications as a marker of prepubertal testicular function in boys ***(Rey et al., 1999),*** of follicular reserve in women ***(Laven et al., 2004)*** and in follow-up of granulosa cell tumors ***(Gustafson et al., 1992).***