Update in management of sexual development disorder

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LIST OF ABBREVIATIONS

ACTH	**Adrenocorticotrophic hormone.**
AMH	**Anti Mullerian hormone.**
BM	**Buccal mucosa.**
CAH	**Congenital adrenal hyperplasia.**
CAI	**Complete androgen insensitivity syndrome**
CGD	**Complete gonadal dysgenesis**
CT	**Computed tomography.**
DHEA	**Dehydroxy-epiandrostendiol.**
DHT	**Di hydro testosterone**
DIEP	**Deep inferior epigastric perforator.**
DOC	**Deoxy-cortisone.**
DSD	**Disorders of sex development.**
D.L.	**Diagnostic laparoscopy.**
FSH	**Follicle stimulating hormone.**
HCG	**Human chorionic gonadotrophin.**
HLA	**human leukocyte antigen**
HSO	**Hystro-salpingeo-oopherectomy.**
HR	**Hypospadias repair.**
HSR	**Hypospadias repair.**
LAIV	**Lap. Assisted ileal vagina**
LH	**Leutinizing hormone.**
LVPE	**Lap vaginal pouch excision**
MGD	**Mixed gonadal dysgenesis.**
MIS	**Müllerian inhibitory substance.**
MPH	**Male pseudohermaphrodite.**
MRKH	**Mayer- Rokitansky- Kuster- Hauser syndrome.**
MRI	**Magnetic resonance imaging.**
PAIS	**Partial androgen insensitivity syndrome**
PCR	**Polymerase chain reaction.**

PGD	**Partial gonadal dysgenesis.**
PMDS	**Persistant Müllerian duct syndrome.**
PST	**Peno scrotal transposition.**
S V	**Simple virilization.**
StAR	**Steroidogenic acute regulatory protein.**
TAIS	**Total androgen insensitivity syndrome.**
TH	**True hermaphrodite.**
US	**Ultra sound imaging.**
UGS	**Urogenital sinus.**
UGSM	**Urogenital sinus mobilization.**
WT-1	**Wilms' tumor type 1**
SF-1	**steroidogenic factor type 1**

List of figures

List of tables

CONTENTS

CONTENTS

INTRODUCTION

The term disorders of sex development (DSD) is a relatively new term in medical terminology that was introduced in 2005. It includes anomalies of the sex chromosomes, the gonads, the reproductive ducts, and the external genitaliaThis term was developed to avoid the impact of the previously used terms like "intersex, pseudohermaphroditism and true hermaphroditism" which are now avoided because of the potentiality for the patient and family to feel ashamed, or stigmatized. **(Dreger *et al.,2005).***

Not only the term intersex is being changed but many other concepts regarding the management of these disorders are being changed in the last few years. These aspects include the proper time of management and who should take the decision and the controversies regarding this aspect. **(Warne et al ., 2005).**

I. Historical background

It is interesting that nearly every old civilization has knowledge of intersex. The original gods in the Egyptian and Indian mythology are half male half female. Ambiguous genitalia have been considered as a birth defect throughout the recorded history. A cuneiform (The type of writing that was used in ancient Iraq) tablet describing it as a problem has been translated.. In the Islamic culture it was presented from both the religious aspect of view using the ward (Khontha) was used to describe this group of people which signifies that the problem was present and identified in the old Arab communities, and also in the Islamic medical literature. In India, the presence of a third sex is culturally accepted since the fifteenth century.Some of our modern ideas of birth defects can be traced to French Anatomist Isidore Geoffroy Saint-Hilaire (1805-1861), who pioneered the field of teratology. **(*Dreger*., 2005).**

II. Development of Terminology

For centuries, people with atypical sex anatomy have been labeled hermaphrodite. **(Feder , and Karkazis .,2008).**

By the late nineteenth century, a consensus emerged in medicine that gonadal histology was the most reliable marker of a person's "true sex" and that there were three classificatory types of hermaphroditism: male pseudohermaphroditism, describing the presence of testes and genital ambiguity, female pseudohermaphroditism, when ovaries are the present gonads and true hermaphroditism when both gonads are present.**(Dreger .,1998).**

The term intersex has a more recent history. It was first applied to sexual ambiguity in moths in the early twentieth century.(**Goldschmidt .,2008).**

Clinicians gradually adopted the term to refer to sexual ambiguity in humans, but its use over the intervening century has been inconsistent and variable.**(Williams .,2008).**

During the second half of the twentieth century, as medical techniques were refined and medical specialization became more defined, diagnostic terms proliferated and were mapped onto the earlier hermaphrodite taxonomy. Thus, androgen insensitivity syndrome, for example, was understood more generally as a case of male pseudohermaphroditism. By the end of the twentieth century, intersex was widely used in the medical literature as a synonym for hermaphrodite, and the older taxonomy based on hermaphroditism and the newer diagnoses of specific conditions coexisted.**(Feder,andKarkazis .,2008).**

The use of the term intersex became newly contentious beginning in the 1990s, when activists appropriated the term for their own use.

Newly politicized and no longer restricted to medicine, intersex came to mean many things to different people. Because activists were interested in bringing together people who shared similar treatment and life experiences, they made use of the term intersex to refer to any condition in which reproductive or sexual anatomy does not conform to typical understandings of male and female. Thus, they often included conditions such as Turner syndrome and hypospadias that clinicians would not locate within the older taxonomy **(Hughes.,2006).**

Many people and perhaps the majority of parents of people affected with these conditions resisted the imputation of identity associated with intersex. They felt it did not apply to those conditions for which gender assignment is straight forward or to those people who had undergone genital surgery (whose "intersexuality" had been "corrected"). The term intersex has been viewed as stigmatizing by many doctors and parents and by some of the individuals who have these conditions **(Kessler.,1998)** .

The United state and European endocrinological societies convened a meeting to revisit the standard of care for intersex, providing an opportunity for advocates of the change in nomenclature to argue for a formal change and for announcing it in a consensus statement. Those at the meeting settled on "Disorders of Sex Development" as a terminology.(***Cohen*** **et al., 1993).**

The new nomenclature aims to circumvent the fraught history of the terms hermaphrodite and intersex. The term brings a welcome clarification that it is a medical condition, not an identity. The critical move is the recommendation that DSD be used together with a system based on clinically descriptive terms, for example, "androgen insensitivity syndrome"and "CAH" (**Hughes.,2006).**

AIM OF THE WORK

The aim of the present study is to evaluate disorders of sex development and to build up a policy for the management of these cases and the different surgical intervention modalities.

Normal Sex differentiation

Anatomy of normal sex differentiation

a. Male sex differentiation

i. Testicular differentiation:

The gonadal primordium is represented by the gonadal ridge, which is progressively colonized by extraembryonic primordial germ cells. The first recognizable event of testicular differentiation, at 7 weeks' gestation, is the development of primordial Sertoli cells, which aggregate to form seminiferous tubules and produce Anti Müllerian Hormone (AMH), also called Mullerian-Inhibiting Substance. Leydig cells differentiate at 8 weeks' gestation and increase until 12 to 14 weeks, when they begin to degenerate. At birth, few remain in the interstitial tissue; the Leydig cell population reappears at puberty. **(New, and Josso.,2004).**

ii. Somatic sex differentiation:

After gonadal differentiation, the internal reproductive tract consists of two pairs of ducts: the wolffian ducts and the müllerian ducts. In males, müllerian duct regression begins at 8 weeks and is more or less complete at 10 to 12 weeks. The wolffian ducts develop into the vasa deferentia, epididymides, and seminal vesicles. Prostatic buds develop around the opening of the ducts at 10 to 11 weeks, and fusion of outgrowths of the urogenital sinus forms the prostatic utricle in the male equivalent of the vagina. At 10 weeks' gestation, elongation of the genital tubercle and fusion of the urethral folds over the urethral groove lead to formation of the penile urethra, whereas the genital swellings move posteriorly and fuse to form the scrotum. Male anatomic development is completed by 90 days' gestation, but penile growth occurs mainly between 20 weeks and term, at a time when, paradoxically, serum testosterone levels are declining. Several other growth factors are also involved. **(MacLaughlin, Donahoe.,2004)** .

b. Female sex differentiation

i. Ovarian differentiation:

Slower than the testis to differentiate initially, the fetal ovary eventually reaches a more advanced stage of maturation. At 12 to 13 weeks' gestation, some oogonia located in the deepest layer of the cortex have entered the meiotic prophase. By 7 months' gestation, all germ cells have entered or completed the meiotic prophase. Fetal granulosa cells produce estrogen at the same developmental stage at which fetal testes produce testosterone, but ovarian production of AMH can be demonstrated only after birth. The ovarian hormones do not play a role in the differentiation of sex till puberty. **(Biason-Lauber .,2010).**

ii. Somatic sex differentiation:

Female fetal sex differentiation is characterized by degeneration of the wolffian ducts at 10 weeks, whereas the müllerian ducts develop into fallopian tubes, uterus, and the upper part of the vagina. The vagina differentiates at the level of the mullerian tubercle, between the openings of the wolffian ducts where the prostatic utricle forms in males. Whereas in males the prostatic utricle opens just beneath the neck of the bladder, in females, the lower end of the vagina slides down the posterior wall of the urethra to acquire a separate opening on the body surface. Feminization of the external genitalia begins with formation of the dorsal commissure between the genital swellings, which in the female do not migrate posteriorly or fuse and give rise to the labia majora. Because the genital folds do not fuse, they become the labia minora, and the genital tubercle becomes the clitoris. In the female, these steps occur in the absence of hormonal stimulation but the signaling molecule WNT4 is required for the initial formation of the mullerian ducts**.(Ottolenghi et al.,2005).**

1. Mechanisms of sex differentiation

a . Genetics of sex determination

SRY and its partners:

Testicular differentiation is usually called sex determination because it determines whether testicular hormones, responsible for subsequent somatic sex differentiation, will be produced. Sex determination in mammals is governed primarily by SRY, a transcription factor expressed by Sertoli cells and encoded by a gene located on the Y chromosome. **(MacLaughlin and Donahoe ., 2004).**

reversed females, and conversely, translocation of SRY on an X chromosome leads to maleness in XX individuals. However, normal SRY transcripts, although necessary, do not guarantee normal testicular differentiation. SRY target genes, not yet identified, are probably important and, in addition to SRY, many other transcription factors are required for testicular development and often for other functions as well. For example, mutations of Wilms' tumor type 1 (WT-1) gene lead to Wilms' tumor and renal insufficiency, SO X-9 mutations are associated with campomelic dysplasia. The orphan nuclear receptors steroidogenic factor type 1 (SF-1), also known as FTZ-F1, and DAX-1, also known as Ahch, are required for normal adrenal and pituitary development. As shown in the mouse, Dax-1 acts in a dose-dependent manner to repress SRY and is also necessary to the integrity of testicular germinal epithelium. Chromosomal location of genes involved in sex determination is shown in Figure 1**. (Houmart et al,.2009).**

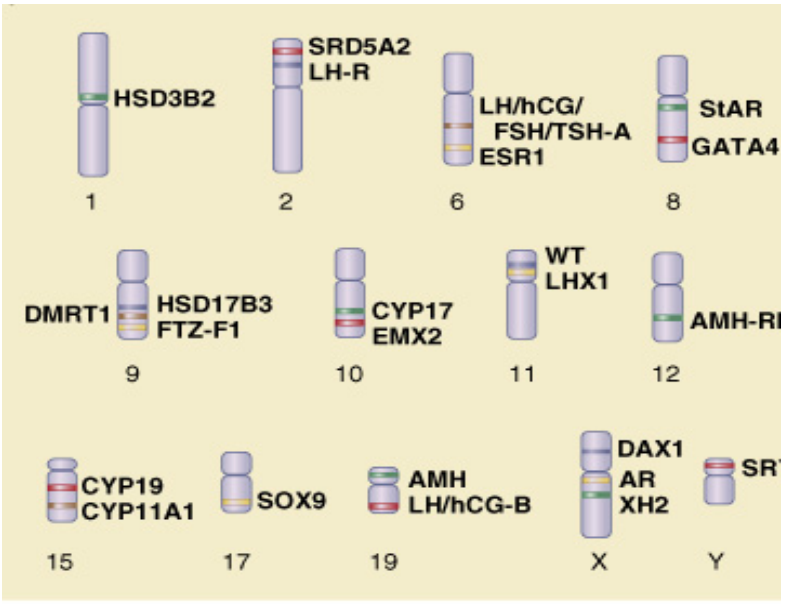

Figure 1: Chromosomal location of genes involved in sex determination and differentiation ***(Houmart et al,.2009).***

b. biosynthesis and action of testicular hormones

Virilization of the reproductive tract is mediated by AMH and testosterone; in their absence or inactivity, female differentiation proceeds unimpeded (Fig. 2). AMH, a glycoprotein synthesized by immature Sertoli and postnatal granulosa cells, is responsible for müllerian regression. The gene, located on chromosome 19, is a member of the transforming growth factor-β (TGF-β) family and acts via a type II AMH receptor whose gene is located on chromosome 12q13. For signaling, AMH uses three type I receptors of the bone morphogenetic protein family, ALK2, 3, and 6, all activating cytoplasmic effectors SMADs 1 and 5**. (Edson et al.,2009).**