MANAGEMENT OF SEXUAL DEVELOPMENTAL DISORDERS

An Essay For Partial Fulfillment For Master Degree
In General Surgery

By

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بسم الله الرحمن الرحيم

DEDICATION

To the soul of my beloved "father" "*may Allah have mercy upon him".*

To my family who shared my ups and downs.

To my kids "Jodie and Mohammed".

And to all of those who care for spreading knowledge, whoever and wherever they are.

LIST OF ABBREVEATIONS

(HHA) axis	Hypothalamic–hypophyseal– adrenal
11OHD	11β-hydroxylasedeficiency
17OHP	17-hydroxyprogesterone
17β-HSD-3	17 β-hydroxysteroid dehydrogenase type III deficiency
21-OHD	Steroid 21-hydroxylase deficiency
3βHSD	3β hydroxysteroid dehydrogenase deficiency
5a-RD-2	5 α- Reductase type 2
A.D.	Anno domini (Latin: years after Christ was born)
ACTH	Adrenocorticotrophic hormone
AIS	Androgen insensitivity syndrome
AMH	Anti Mullerian Hormone
AR	Androgen receptor
ATRX	Alpha thalassimia , mental retardation syndrome. X-Linked gene
B.C.	Before Christ
BI	Behavioral identity
CAH	Congenital adrenal hyperplasia
CAIS	Complete androgen insensitivity syndrome
CGH	Comparative genomic hybridization
CGH	Comparative genomic hybridization
CVS	Chorionic villus sampling
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone Sulphate
DHT	Dihydrotestosterone
dpc	Days post conception
DSD	Disorders of sex development
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth, edition, text revision
ESC	Embryonic stem cells
ESPE	European Society for pediatric Endocrinology
FISH	Fluorescence in-situ hybridization
FSH	Follicle stimulating hormone
GID	Gender identity disorder
GSCs	Germline stem cells
HCG	Human chorionic gonadotropin
hESCs	Human embryonic stem cells
HRT	Hormone replacement therapy
ICD-10	International Classification of Diseases, 10th ed.

I I	Individual identity
INSL3	Insulin-Like factor 3
iPSCs	Induce pluripotent stem cells
LC	Liquid chromatography
LH	Luteinising hormone
LHR	Luteinising hormone receptor
LWPES	Lawson Wilkins Pediatric Endocrine Society
MAGPI	Meatal advancement and glanduloplasty
MAIS	Minimal or mild androgen insensitivity syndrome
MGD	Mixed gonadal dysgenesis
MS/MS	Tandem mass spectrometry
NCAH	Nonclassical congenital adrenal hyperplasia
ODSD	Ovotesticular DSD
PAIS	Partial androgen insensitivity syndrome
PAP	Pyrophosphorolysis –activated polymerization
PGCs	Primordial germ cells
PMDS	Persistant Mullerian duct syndrome
PORD	P450-oxidoreductase deficiency
PUH	Peace upon him
PUM	Partial urogenital sinus mobilization
QF-PCR	Quantitative fluorescent polymerase chain reaction
RBV	Retropubic balloon vaginoplasty
SF-1	steroidogenic factor-1
SHBG	Sex hormone binding globulin
SI	Social identity
SLOS	Smith–Lemli–Opitz syndrome
SRY	Sex determining region on the Y chromosome
SSC	Spermatogonial stem cells
SV	Simple virilizing
SW	Salt-wasting
T	Testosterone
TPIF	Transverse preputial island flap
TRS	Testicular regression syndrome
TUM	Total urogenital sinus mobilization
UDT	Undescended testis
UGS	Urogenital sinus
US	Ultrasonography
WT1	Wilms' tumor-associated gene-1

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INTRODUCTION

The German pathologist Theodore klebs who recognized at autopsy that it was possible for the external genitalia to be discordant with the gonads. Those in whom he found normal ovaries but virilized external genitalia he called, in English translation, female pseudohermaphrodites, whereas those with normal appearing testes but undervirilized genitalia he called male pseudohermaphrodites. In contrast to those, he recognized certain individuals who harbored both an ovary and a testis, which he called true hermaphrodites ***(Aaronson and Aaronson, 2010)***.

Advances in identification of molecular genetics causes of abnormal sex with heightened awareness of ethical issues and patient advocacy concerns necessitate a re-examination of nomenclature ***(Hughes et al., 2006)***.

Terms such as Intersex, pseudohermaphrodites, hermaphrodites, sex reversal are particularly controversial. These terms are perceived as potentially projective by patients and can be confusing to both practitioners and parents ***(Hughes et al., 2006)***.

Consequently, the recommended nomenclature to replace intersex is the umbrella terminology "disorders of sex development" (DSD).This is defined as congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical. However, the nomenclature has no diagnostic purpose other than as a starting point towards the goal. The inclusion of the term congenital within the definition excludes all the condition listed as causes of precocious or delayed puberty. The abbreviation (DSD) is not in common usage for any other “competing” medical disorder ***(Hughes, 2008)***.

There are numerous models of classification to bewilder the reader with the lists of all possible cause of DSD. **No system is perfect**, one of the categories is ‘sex chromosome anomalies’ as these remain a major component of the causes of DSD. The other two categories are the XX, DSD and XY, DSD and are both subdivided according to a primary disorder of gonad development versus a disorder of sex steroid biosynthesis arising from an otherwise more physiologically normal gonad ***(Hughes, 2008)***.

Optimal care for children with DSD requires an experienced multidisciplinary team that is generally found in tertiary care centers.

Ideally the team includes specialties in endocrinology, surgery and / or urology, psychology / psychiatry, gynaecology, genetics, neonatology, social work, nursing and medical ethics ***(Hughes et al., 2006)***.

Hypogonadism is common in patients with dysgenetic gonads, defect in sex steroid biosynthesis and resistance to androgens. Hormonal induction of puberty should attempt to replicate normal pubertal maturation, to induce secondary sexual characteristics, a pubertal growth spurt and optimal bone mineral accumulation using testosterone esters. Females with hypogonadism require oestrogen supplementation to induce pubertal changes and menses ***(Hughes et al., 2006)***.

The genital surgery began since ancient man's first attempts of performing surgery. Trepanation, amputation, incision and circumcision were historical crude attempts at surgery.The bold and imaginative innovations of French, German, English, and American surgeons of the early nineteenth century rescued surgery from the lack of knowledge of previous centuries and charted the way for succession of rapid development ***(Rogers, 1973)***.

Surgeons such as Cooper, Warren, Dupuytren, Dieffenbach, and Mattauer were responsible for a host of new surgical ideas and development of technical tips which in the latter half of the nineteenth century, provided plastic surgery and urological surgery in particular with a new era supply of surgical improvement ***(Rugie and Sykes, 2007)***.

A few years ago it was said that gender assignment could be delayed until later childhood when the child express more clearly his or her individual identity this attitude has a lot of controversies, and it is currently accepted by most practitioners that: the assignment should be done early in life to avoid difficult situations for the parents and the child ***(Vidal et al., 2010)***.

However, (Money and Hampson, 1957) their findings, suggested that most infants are able to discriminate between the sexes by the end of their first year. At two to three years of age, children are able to label themselves correctly and by three, preference for a gender rule emerges. With the onset of the fifth year, they begin to have a sense of gender constancy (Ruble and Martin, 1998). Other factors favouring early intervention are: the threat of cancer in women with XY material in gonads that have not been removed, the great ease with which the surgery can be conducted on children and the finding that the majority of patients

who have had early surgery to relieve their emotional distress are content with their assigned gender as adults ***(Rebelo et al., 2008)***.

The surgical options for vrilized female (46, XX) encompasses three main steps: vaginoplasty, the clitoral plasty and the perineoplasty. The surgical options in undervirilised male (46, XY) aims at repairing a hypospadiac penis, phalloplasty, glanuloplasty and testicular surgery.Or up to total genital reconstruction in both sex ***(Vidal et al., 2010)***.

AIM OF THE WORK

To review different modalities in management of Sexual Developmental Disorders.