

**Male Pseudohermaphroditism  
Evaluation in Egyptian Children**

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**To my beloved  
Parents  
Wife  
Son**

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## **Abstract**

In this study we present the profile of **33** cases with 46, XY DSD. The aim of this work was the proper diagnosis and classification of these cases. The age of the studied cases ranged from **8** days to **29** years. +ve consanguinity was noticed in **(84.8%)**, clinical, hormonal, radiological and sometimes molecular study were done for the patients. The results showed that **15.1%** of the patients had disorders of testicular development , **48.4%** had disorder in Androgen action and **33.3%** had disorders in Androgen synthesis.

### **Key Words:**

- **Ambiguous genitalia**
- **DSD.**
- **Molecular study.**

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## Abbreviations

- **3 $\beta$ HS II D:** 3beta Hydroxysteroid Dehydrogenase type II Deficiency
- **5 $\alpha$ R:**5 alpha reductase
- **5 $\alpha$ RD:** 5 alpha reductase deficiency
- **17 $\beta$ -HSD type 3 Deficiency:**17 beta hydroxy steroid dehydrogenase type 3 defeciciency.
- **AD:** Autosomal dominant
- **AGD:** Abnormal gonadal differentiation
- **AHC:** Adrenal hypoplasia congenital
- **AIS:** Androgen insensitivity syndrome
- **AMH:** Anti-Mullerian hormone
- **AMH-RII:** AMH-receptor type II .
- **AR:** Autosomal recessive
- **AR:** Androgen receptor
- **ARE:** Androgen response elements.
- **ASD:**Abnormal sexual development
- **ATRX:**Alpha-thalassemia/mental retardation syndrome X- linked
- **AZF:** Azoospermia factor
- **BMP:** Bone morphogenetic protein
- **CAIS:** Complete androgen insensitivity syndrome
- **C-AMP:** Cyclic adenosine monophosphate
- **CFTR:** Cystic fibrosis transmembrane conductance regulator.
- **COL2A1:** First intron of the human type II collagen gene.
- **CSF2RA:** Colony-stimulating factor 2 receptor alpha.
- **CYP11A1:** Cytochrome P450 cholesterol side-chain. cleavage enzyme (P450SCC) .
- **CYP 17:** Cytochrome P450 17-hydroxylase .
- **CYP19:** Cytochrome P450 aromatase .
- **DAX1:**Dosage Sensitive Sex reversal-AHC critical region X chromosome gene 1
- **DAZ :**Deleted in azoospermia

- **DBD:** Putative DNA binding domain
- **DDS:**Denys-Drash syndrome
- **DES :**Diethyl-stilbestrol
- **DHT:** Dihydrotestosterone
- **DMD:**Duchenne muscular dystrophy
- **DPC:** Days post-coitum.
- **DSD:**Diorders of sexual development
- **DSS:** Dosage sensitive sex reversal
- **E2:** Estradiol
- **ESR1 :** Estrogen receptor alpha.
- **ESR2 :** Estrogen receptor beta.
- **ETRS:**Embryonic testicular regression syndrome.
- **FISH:** Fluorescent in situ hybridisation
- **FGF9:** Fibroblast growth factor 9.
- **FPH:** Female Pseudohermaphroditism
- **FRA-X :**Fragile X syndrome
- **FS:**Frasier syndrome
- **FSH:** Follicle Stimulating Hormone
- **FSH-A:**a- subunit of FSH.
- **GK:** Glycerol kinase
- **hCG:** Human chorionic gonadotrophins.
- **hCG-A:** a-subunit of hCG.
- **hCG-B:** b-subunit of hCG.
- **HGF:** Hepatocyte growth factor.
- **HMG:** High-mobility group box sequence.
- **HSD3B:** 3 $\beta$ -hydroxysteroid dehydrogenase .
- **HSD17B:** 17 $\beta$ -hydroxysteroid dehydrogenase.
- **HY:** Histocompatibility antigen Y.
- **Igf1r:** Insulin-like growth factor receptor 1.
- **IL3RA:** Interleukin 3 receptor alpha
- **IL9R:** Interleukin 9 receptor
- **INSL3:** Insulin-like growth factor 3.
- **Ir :** Insulin receptor.
- **Irr :** Insulin-related receptor.
- **Kal1:** Kallmann syndrome 1

- **KTS** : Lysine, threonine and serine
- **LBD** :Ligand –binding domain
- **LH**: Lutenizing Hormone
- **LH -A** : a-subunit of LH.
- **LH -B** : b-subunit of LH .
- **LH-R** : Luteinizing hormone receptor .
- **MGD**: Mixed gonadal dysgenesis
- **MIS**:Mullerian Inhibiting Substance
- **MISR**: Mullerian inhibiting substance receptor.
- **MPH**:Male Pseudohermaphroditism
- **mRNA**:Messenger RNA
- **MURCS**:Mullerian hypoplasia/aplasia, renal agenesis and cervicothoracic somite dysplasia.
- **NGFs**: Nerve growth factors.
- **NR5A1**:Nuclear receptor subfamily type 5, group A, member 1 gene
- **NROB1**: Nuclear receptor subfamily O,group B,member 1
- **OMIM**:Online Mendellian Inheritance in Man
- **POR** : P450 oxido-reductase
- **PAR**: Pseudo-autosomal regions
- **PAIS**: Partial androgen insensitivity syndrome.
- **PDGFs**: Platelet derived growth factors .
- **POLA**: DNA polymerase alpha.
- **PMDS** :Persistant Mullerian Duct Syndrome
- **RBMV**: RNA-binding motif protein Y chromosome
- **RIA**:Radio Immuno Assay
- **SHOX**: Short stature homeo box
- **SF-1**:Steriodogenic factor-1
- **Shh**:Sonic hedgehog
- **SOX**: SRY-related HMG box
- **SRD5A1/A2**: 5 $\alpha$ -reductase types 1 and 2 .
- **SRY**: Sex-determining region Y chromosome
- **USP9Y**: Ubiquitin-specific protease 9 Y chromosome
- **StAR**: The acute steroidogenesis regulatory protein
- **T**: Testosterone



- **TDF:** Testis Determining Factor
- **TF:** Transcription factor
- **TGF- $\beta$ :** Transforming growth factor- $\beta$ .
- **TSH:** Thyroid stimulating hormone.
- **TSH-A:**  $\alpha$ -subunit of TSH
- **VMH:** Ventromedial hypothalamic nucleus
- **WAGR:** Wilm's tumor, aniridia, genital abnormality, mental retardation.
- **WT1 :** Wilm's tumor suppressor gene
- **XIST:** X inactivation-specific transcript
- **ZFX:** Zinc finger protein X-linked
- **ZFY:** Zinc finger protein Y-linked

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## INTRODUCTION

Sexual differentiation is a complex process which results in a newborn baby who is either male or female. If errors in development occur, sexual development is abnormal and the sex organs of the baby are malformed. In such cases, individuals may develop both male and female characteristics. This is referred to as intersexuality. *(Hughes 2002)*

Abnormal sexual development (ASD) resulting in the birth of an infant with ambiguous genitalia, is a medical and social emergency.

This group of disorders, previously termed as intersex, is not an uncommon disease in Egypt; a study has reported an incidence of one newborn with ambiguous genitalia per 3000 livebirths *(Temtam, et al 1998)*.

The spectrum of the underlying intersex disorders comprises a majority of heritable monogenic diseases that spectrum has been broadly categorized into three main groups: Sex chromosome DSD, 46, XY DSD and 46, XX DSD. *(Hughes et al., 2006)*

As disorders of sexual differentiation (DSD) represent a group of entities, heterogeneous in their etiopathogenesis and clinical manifestations, the newborn with abnormal genital development presents a difficult diagnostic and treatment challenge for the pediatrician providing care.

Establishing a precise diagnosis in DSD (for proper gender assignment) is just as important as in other chronic medical conditions to minimize medical, psychological and social complications. *(Lee et al.,2006)*

### **Aim of the work**

- The study aims at proper diagnosis and classification of cases of 46, XY DSD in order to reach an etiological diagnosis.
- Genetic evaluation in correlation to phenotype of patients with 46, XY DSD.

## Background and Review of literature

### DEFINITION

- The term 'intersex' refers to "conditions in which chromosomal sex is inconsistent with phenotypic sex, or in which the phenotype is not classifiable as either male or female ". (*Sax 2002*)
- Recently the term "disorders of sex development" (DSD) was proposed which is defined as congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. (*Hughes et al.,2006*)
- Male pseudohermaphroditism (MPH) is defined broadly as incomplete masculinization of the external genitalia in a male (46XY) karyotype. (*Migeon 1980*).
- A more recent definition for Male pseudohermaphroditism (MPH) defines it as the abnormal development of genitalia in an individual with a 46, XY chromosome complement and testicular tissue (*Meau-Petit et al., 2005*).

### INCIDENCE

- In 1975 Hamerton et al, estimated that the incidence of genital ambiguity that results in the child's sex being uncertain is 1 per 4500 (*Hamerton et al.,1975*)
- Dreger suggests that the incidence of intersex conditions is 1 in 1,500 live births. (*Dreger 1998*)
- According to the highest estimates (*Blackless et. al., 2000*) that 2 percent of live births exhibit some degree of sexual ambiguity, and that between 0.1% and 0.2% of live births are ambiguous enough

to become the subject of specialist medical attention, including surgery to disguise their sexual ambiguity.

- Other sources (*Sax 2002*) create a narrower definition of "true intersexual conditions" and estimate the incidence as far lower, at approximately 0.018% (one in each 5500 newborn)
- Professor Peter Koopman from the University of Queensland suggests that intersex disorders are surprisingly common. "About 4% of live births are affected by these disorders, which can result in infertility, genital abnormalities, gender mis-assignment and long-term psychological trauma" (*UQ News July 2004 p6*).
- The Medical Examiner (<http://slate.msn.com/id/2102006>) suggests that each year about 1 in 2,000 children is born with ambiguous looking genitalia.
- In the statement of the international consensus conference on intersex it was estimated that genital anomalies occur in 1 in 4500 births (*Hughes et al.,2006*)
- DSD is not an uncommon disease in Egypt. A study has reported an incidence of one newborn with ambiguous genitalia per 3000 livebirths (*Temtamy, et al 1998*).
- In Egypt, 5  $\alpha$ -reductase deficiency (5 $\alpha$ RD) and Androgen Insensitivity syndrome have been the two most frequently reported etiologies constituting 64% among 46, XY DSD cases (*Mazen et al, 1996*).