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# "HYPOSPADIAS" ITS EMBRYOLOGICAL BASIS AND CLINICAL IMPORTANCE

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**ABSTRACT**

Hypospadias is a congenital anomaly that is presented in both male and female newborn as the External Urethral Meatus opens ventral to its normal position. This birth defect of the Urogenital Tract is found more common in males; and the main contributing factors are subcategorized mainly into Genetic, Hormonal and Environmental factors. The incidence of this anomaly varies around the globe but a raise in its rate of occurrence within the past two decades has been detected, suggested to the increase of several Endocrine Disrupters that mimics the action of Estrogen affecting the normal development of the embryo during gestation.



## Introduction

Hypospadias is a congenital anomaly or a birth defect (an in utero embryological development abnormality) that involves the position of the External Meatus (orifice) of the Urethra which is the membranous tube that extends from the neck of the Urinary Bladder to the tip of the Penis (Glans Penis) in case of Males or to the Urogenital Vestibule just below the Clitoris in case of Females. In Hypospadias (Hypo- means below normal, +spadias Greek for slit or fissure) [1] the outer opening of the Urethra is below or inferior to the normal position [2].

In Females, Hypospadias is illustrated when the Urethra opens to the Vaginal Cavity, due to a defect in the closer and fusion of the Urethral Folds with a failure in the development of the Urethrovaginal Septum [3].

In Males the Hypospadias is illustrated also due to a failure in the proper fusion of the Urethral Folds [4]. It is represented in the positioning of the Urinary Meatus on the underside or the Ventrum of the Penis instead of its tip normally [5]. It has different variations that pertain to the exact location of the Urethral Opening. Those variations include the opening being present on the neck of the bulb or the Glans, further more below on the shaft of the Penis, even more retreated near to the base of Penis, in or below the Scrotum and eventually in the Perineum [6]. A curving of the Penis that gives it a hooked appearance may or may not occur because of Hypospadias condition and it is mainly manifested by the Penis erection, such medical condition is known as **Chordee (Fig-1)** [5].

Frequently, the Prepuce or the Foreskin fails to encircle the entire glans Penis leaving the ventral side of it exposed forming a "Dorsal Hood" like structure [7].

Hypospadias condition variations in the Male are categorized into separate degrees from Mild to Severe (Fig-2). The Mild degree includes the Glanular, Subcoronal and Distal Shaft Hypospadias. This degree is also called a 1st degree or Primary Hypospadias and its reparative surgery is often simple and has a highest success indicator [6, 8]. In the more Severe degrees it involves the Midshaft, Proximal Shaft, Penoscrotal and Scrotal Hypospadias which are considered as a 2nd degree or Secondary Hypospadias; and last but not least the Perineal Hypospadias which is considered a 3rd degree or Tertiary Hypospadias [6, 8].

The more advanced the degree is the more complicated the surgical intervention is and the more sessions of surgical operations is required in order to completely and successfully correct the urethral deformity [6].

## Incidence

Hypospadias is a common congenital anomaly in males that occurs approximately in 1 out of 200-300 newborn cases. In females Hypospadias condition is less common with a rate of one in 500,000 newborn cases [5]. An increase of Hypospadias incidences has been detected in the recent decades (15-20 years) [4] up to 2-4% more of newborn cases in some regions around the world [6].

For an example in a 2 year prospective study in Netherlands the rate of Hypospadias was found to be 38 in 10000 newborn cases, a number that is 6 times higher than previously recorded [9].

Also it is important to mention that Hypospadias incidence rates varies across the globe from one country to another ranging from 1 in 3840 newborn cases in Mexico to 1 in 384 newborn cases in Scandinavia 'in both males and females' (Fig-3) [8]. The cause of the increase in Hypospadias reported cases is unknown yet it is suggested to be related to some environmental changes that led to the increase of Environmental Estrogens that may disrupt the normal Endocrine hormonal function during the intrauterine embryonic development [10].

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**Fig 1. Male midshaft Hypospadias with Chordee.**

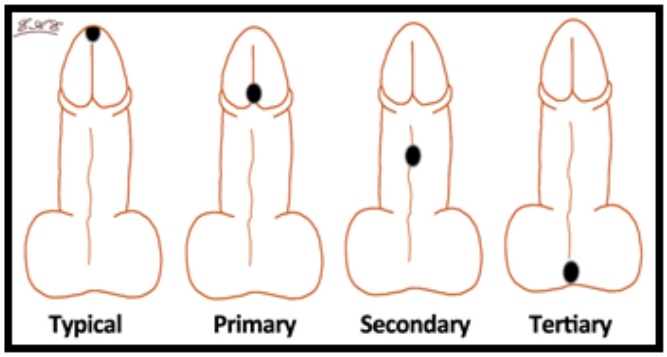



**Fig 2. Hypospadias degrees in male.**

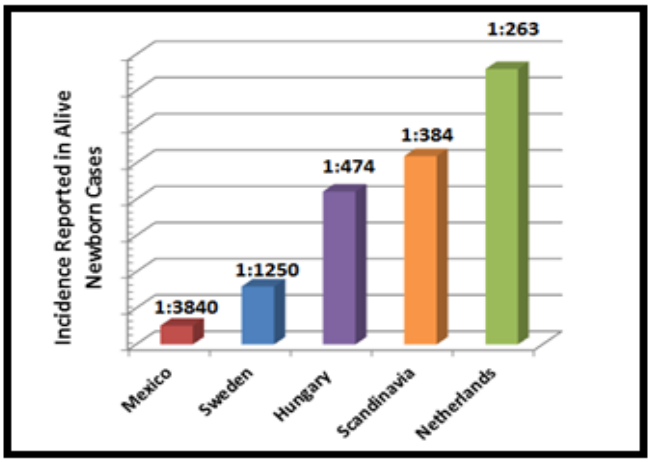



**Fig 3. This diagram shows the geographical variance of reported incidences of Hypospadias cases [8].**

**Ontogenesis of the normal development of the Urethra in Males and Females**

The embryological development of the Urethra varies somewhat between the human male and female **(Fig-9)**. It all starts with the development of the **Cloaca** from the Hindgut portion of the Gut Tube [4, 11]. As within the end of the 3rd week of gestation the Embryonic Gastrula undergoes a lateral folding that transforms the shape of the embryo from a flat disk into a cylindrical shape [12]. Resulting from this folding the Endodermal layer of cells forms a tube that is called the Gut Tube which maintains in the caudal portion of it a connection with the Allantoic diverticulum or the Allantois. This connection forms the Cloaca.

Then, between the 4th and the 6th week of Gestation, the Cloaca undergoes a partitioning made by the Urorectal Septum which is an ingrowth of Splanchic or Visceral Mesoderm cells forming one upper fold (Tourneux) located frontally and two lateral folds (Rathke) located nearby the Cloacal Membrane (Fig-4) [13].

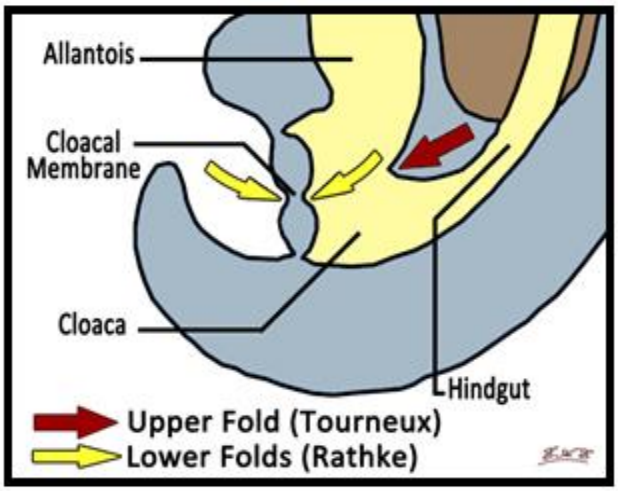



**Fig 4. The initiation of the development of the Urorectal Septum during the 4th week of gestation.**

The Tourneux's Fold grows caudally towards the Rathke's Lateral Folds to fuse eventually at the median level. The result of the Cloacal division is the Primitive Urogenital Sinus and The Anorectal Canal (Fig-5) [13].

We are concerned now with the Urogenital Sinus, as it receives its opening tributaries from the Mesonephric Ducts which originate from the Intermediate Mesoderm, the Urogenital Sinus is now definitive below the level of the ducts opening and it is structurally divided into a Pelvic and a Phallic parts. While above that level the Vesicourethral Canal is formed [14].

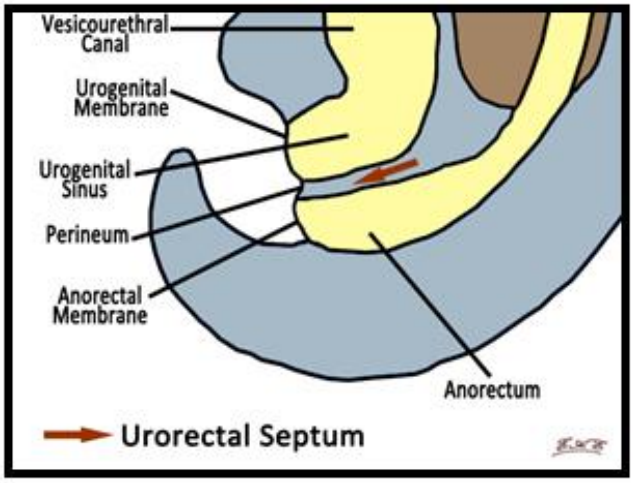



**Fig 5. The separation of the Cloaca by the Urorectal Septum roughly in the 8th week of gestation.**

In females, the Urethra is formed in its superior aspect from the Vesicourethral Canal. The inferior aspect of the female urethra develops from the Pelvic part of the Definitive Urogenital Sinus. In the posterior aspect of the Urethral canal, the extension of the Trigon of the Bladder which is derived from the absorption and fusion of the Mesonephric Ducts is the source of the urethral development. The remainder portion of the Pelvic part and the entire Phallic part of the Definitive Urogenital Sinus contributes to the formation of the Urogenital Vestibule (Fig-6) [14, 15].

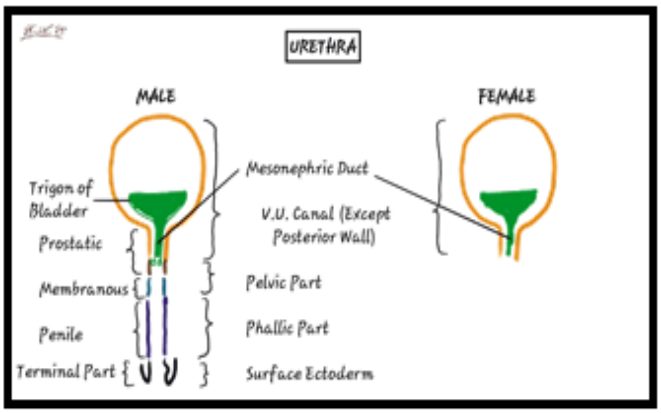



**Fig 6. The source of development of different parts of the Urethra in Human Male and Female.**

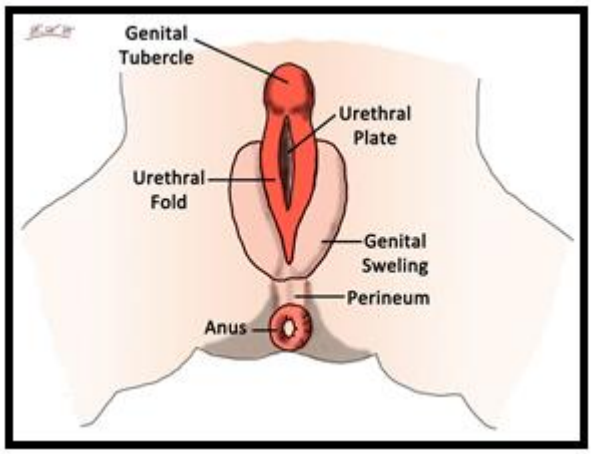



**Fig 7. The progress of the development of the Penile Urethra of Human Male in the 10th week of gestation.**

In case of Males, the Primitive Urethra up to the opening of the ejaculatory ducts into the Prostatic part of the Urethra is derived from the Vesicourethral Canal except for its posterior aspect - as it was explained before - it is derived from the Mesonephric Ducts endothelial absorption. The remainder of the Prostatic Urethra plus the Membranous Urethra are derived from the Pelvic Part of the Definitive Urogenital Sinus. While the Phallic Part of the Definitive Urogenital Sinus extends accompanying the protruding growth of the Genital Tubercle stretching with it the Urethral Plate of the Phallic Part of the Urethra during the formation of the Penile Shaft (the Phallus) (Fig-6&7) [14, 16].

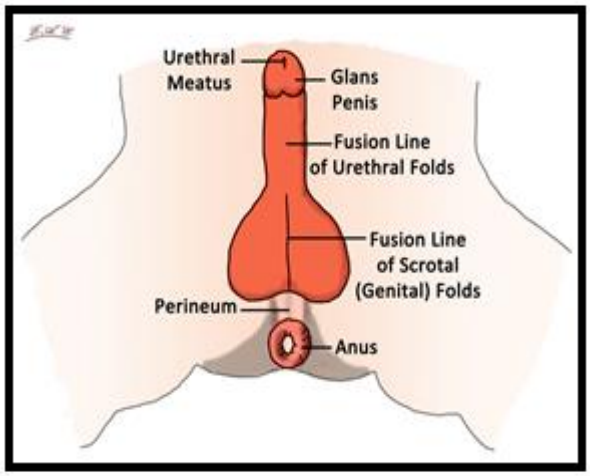



**Fig 8. The Fusion of the Urethral Folds and the terminal positioning of the External Urethral Meatus in the 13th week of gestation.**

At the end of the 3rd month of gestation the Urethral Folds around the Urethral Plate close up and fuse to form eventually the Penile or the Spongy Urethra that ends at the Glans Penis (the Tip of the Penis) contributed by the Surface Ectoderm in its terminal part via a Short Ectodermal Cord that grows to merge with the Penile Urethra during the 4th month of Gestation (Fig-8) [16].

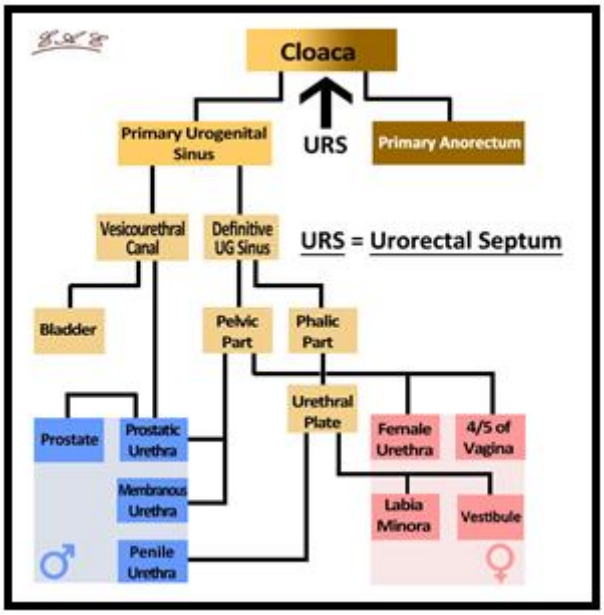



**Fig-9: Embryological Development Scheme of Urogenital Tract in a Human Male and Female.**

**Embryological basis for "Hypospadias" anomaly in Male and Female**

Female Hypospadias occurs when the distal meatus of the Urethra opens into the anterior wall of the Vagina [17]. This anomaly has two major presentations. The first presentation is when the Urethra opens into the proximal part of the anterior wall of the vaginal canal, near by the cervix of the Uterus, in which this abnormal connection is thought to be resulted from a differentiation failure or defect during the development of the Wolffian or the Mesonephric Ducts that constitutes the posterior aspect of the wall of the Female Urethra. This presentation is called a Female Proximal Hypospadias and is considered as a severe type of Female Hypospadias (Fig-10) [18].

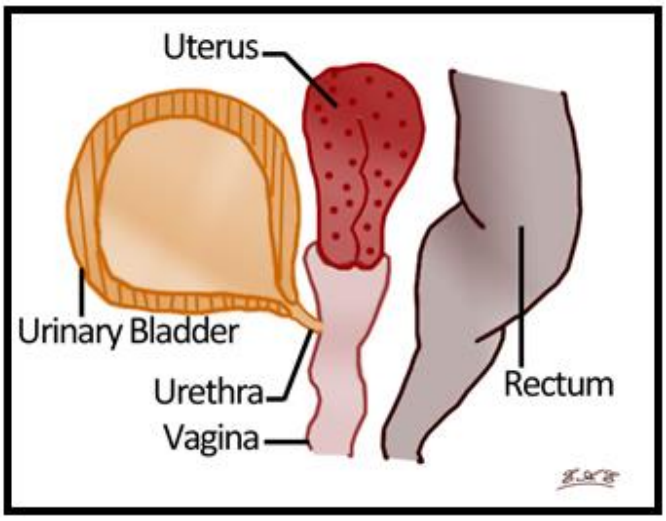



**Fig 10. Female Proximal Hypospadias.**

The second presentation of the Female Hypospadias is when the Urethral Meatus opens to the distal part of the anterior wall of the Vaginal Canal nearby the Urogenital

Vestibule [18]. This is called a Female Distal Hypospadias and it is believed to be resulted from a defect in the differentiation of the Pelvic part of the Definitive Urogenital Sinus [18] which gives rise to the distal or lower portion of the Vagina [19]. Such deformity is considered a less severe or a mild type of Female Hypospadias (Fig-11) [18].

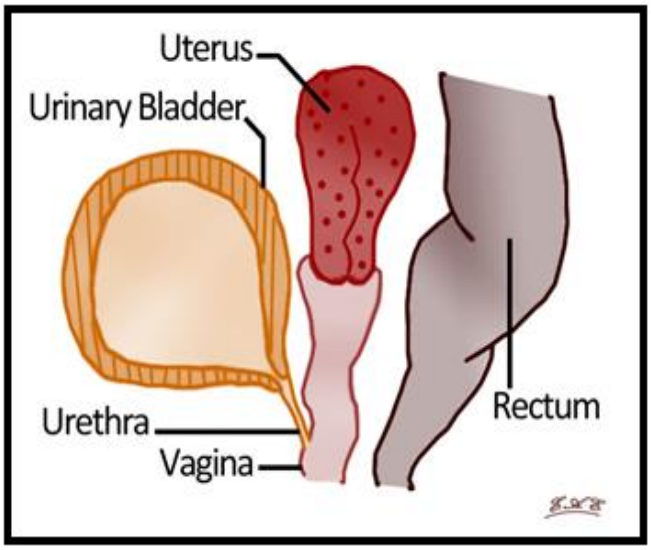



**Fig 11. Female Distal Hypospadias.**

In both types of Female Hypospadias, Proximal Hypospadias and Distal Hypospadias, the length of the tube that becomes the Urethra is insufficient which leads the Urethral Canal to open in an abnormal position as a result [5]. This abnormal deformation involves a complete or a partial agenesis of the Urethrovaginal Septum, resulting in the urinary excretion draining into the female genital tract – the Vaginal Canal [3].

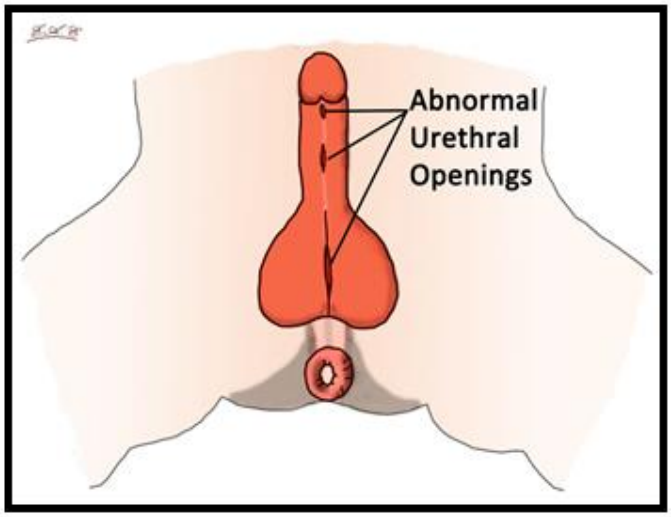
Male Hypospadias is a congenital deformity that arises from several degrees of ontogenetic failures during the male embryo development that affects the tube of the Penile Urethra (Fig-12).

The first degree is related to the failure of the canalization of the Ectodermal Cord of the Glans Penis, this results in the External Urethral Meatus to open in a ventral Glanular or a Coronal-Subcoronal position [20].

A second degree of the teratogenicity of the Urethral Canal results during the fusion of the Urethral Folds. This process may cease too early or prematurely at any level of the tube, leading the External Urethral Meatus to open in a Distal, Mid or Proximal position within the shaft of the penis [21].

A third degree of Male Hypospadias emerges from the incomplete or total failure of the fusion of the Urethral Folds leading to the Meatus presented in a Penoscrotal, a Scrotal or even a Perineal positioning [22]. Such severe type is usually demonstrated with an Ambiguous Genitalia [23] where the Scrotal Folds are non-fused and the External Urethral Orifice is located between the two separate folds of the cleft Scrotum [20]. The Phallus or the Penile Shaft is mostly curved ventrally in the second and third degree of Hypospadias deformity because of the existence of the fibrous tissue of the non-fused Urethral Plate that extends from the Urethral Orifice till the tip of the Penis [24].

The factors leading to the failure of the proper fusion of the Urethral Folds of the Spongy (Penile) Urethra or the canalization of the Ectodermal Cord of the Glans Penis during embryological development are to be illustrated in the following discussion.




**Discussion**

Hypospadias is a congenital anomaly that in some cases is presented in isolation (in males more than females) [5] but in many other cases it is associated with a group of developmental anomalies and/or symptoms. An Association is defined as the appearance of a couple or more of some specific congenital anomalies non-randomly; those anomalies occur together more frequently than alone by chance and their cause have not been determined indefinitely. An example of an Association that may exhibit Hypospadias as a part of a Renal Anomaly is the VACTERL Association (Vertebral Anomalies, Anal Atresia, Cardiac Defects, Tracheoesophageal Fistula, Esophageal Atresia, Renal Anomalies and Limb Defects) [25]. Many factors are contributing to the manifestation of the Hypospadias anomaly in the process of embryogenesis, especially those interrupting the Urogenital Tract development during the first 6 to 8 weeks of gestation [22]. Those factors are either Genetic, Hormonal or Environmental Factors that affect the developing embryo in utero.

Genetic factors that contribute to the deformity of the Urogenital Tract including Hypospadias are basically related to a specific cluster of HOX (Homeobox) genes, a group of genes that control the body plan of an embryo in higher vertebrates, this cluster of genes is HOXA which is located in chromosome 7 at p15.2-p14.3. An entire deletion of the HOXA causes a clinically recognizable syndrome that includes Urogenital Malformations among others [26]. A specific deletion involving the HOXA13 gene is found to be related to Hand-Foot-Genital Syndrome characterized by small short digits, divided uterus and hypospadias [26, 27]. These genital defects are due to the fact that H0XA13 gene plays a magnificent role in the development of the cloaca into the Urogenital Sinus and the Anal Canal in both sexes [27]. Other gene mutations are carried on the X chromosome that lead the male embryo to show less development of male features and make his body tissues insensitive to the Testosterone hormone due to inadequate receptor sites for it on those tissue cells, in a condition known as Androgen Insensitivity [20, 22]. These genetic mutations may become hereditary passing through a family relative [21].

Hormonal factors that contribute to the deformity of the Urogenital Tract including Hypospadias are related to the failure or insufficient production of Androgens and Testosterone hormones by the embryo testes and other endocrine organs leading to a disturbance of the molecular signals that direct the process of the complete folding and fusion of the Urethral Tube [6, 20].

Environmental factors leading to Hypospadias became evident and they are noticed to be involved in the congenital malformations in humans [6, 28]. Those factors are exogenous agents known as Endocrine Disrupters that mimic the action of the Estrogen hormone through its receptors to cause developmental abnormalities of the Urogenital Tract [6, 10, 22]; or by preventing Testosterone hormone from acting effectively on the cells of the male embryo tissues [10, 20], a situation that can be manifested with a congenital case known as Male Pseudohermaphroditism, when the male individual is a genetic and gonadal male but with feminized characteristic that includes a Perineal Hypospadias and a Scrotum devoid of Testes [23, 29]. An Undescended Testis or Cryptorchidism is presented in around 8-10% of the Male Hypospadias cases and Inguinal Hernia is detected in around 9-15 % of those cases [8, 30]. The Environmental Estrogenic Compounds of many chemicals, pollutants, additives or food-derived hormones are becoming a big concern as they interfere in the normal development of the embryo Urogenital System and lead to many teratogenic effects that include Hypospadias among other malformations [6, 10, 22]. Such chemicals may be pharmaceutical drugs such as Valproic Acid and Phenytoin (Diphenylhydantoin), some anticonvulsants that cause many defects to the embryo in utero; also the Progesterone hormonal therapy that is given to mothers as a part of the IVF (In Vitro Fertilization) treatment; or the DES (Diethylstilbestrol) which is used to prevent abortion [10, 21]. Other chemicals may be of an environmental pollution origin such as pesticides, fungicides and industrial pollutants that are suspected to cause Hypospadias among other birth defects [21].

A study reported in The Journal of Urology in March, 2001 indicated that older women appeared to exhibit a greater risk of delivering male infants with severe hypospadias. These findings showed that pregnant women at 35 years old and above had a 20% higher risk chance of delivering a baby with a Severe Hypospadias [31].

Female Hypospadias is resulted from either a partial or total agenesis of the Urethrovaginal Septum. It is rarely detected as an isolated defect as it is usually associated with other Urogenital Tract or Spinal anomalies in female embryos. [3, 5]

**Conclusion**

Male Hypospadias is represented within an incomplete development of the Penis [5], It includes various types namely the Glanular, the Coronal, the Penoscrotal and the Perineal types [24]. The first two types (Glanular and Coronal) constitute the Male Distal Hypospadias and are considered a mild degree of defect. It is found in 80% of Hypospadias cases. The severe degree of Male Hypospadias is consisted of the third and the last types (Penoscrotal and Perineal) and is considered as the Male Proximal Hypospadias. This severe degree of Hypospadias is found in 20% of cases. [8]

A male with hypospadias may suffer from other symptoms including an abnormal spraying of urine, having to sit down to urinate, an erectile dysfunction because of the downward curving of the Penis and sometimes an inability to fertilize the female partner because of the inability to deliver the semen into her vagina during the sexual intercourse [6, 22, 32]. As a result a sexual and psychological dysfunction may result because of the sense of shame and/or anxiety that emerges from such symptoms. [21, 22]

The Female Hypospadias is diagnosed more lately than Male Hypospadias due to the fact of the difficulty in visualizing the infant vagina, on the other side, an external male genitalia examination done at birth may be able to detect a Hypospadias deformity immediately; unless the Male Hypospadias type is either a Glanular or a Subcoronal one with a (fish mouth) meatus which may not be diagnosed if the circumcision has not been performed yet [5, 30].

The relevance of this study clinically is to draw a set of factors to alert surgeons and anesthetists in the knowledge of to the surgical treatment of Male Hypospadias [33, 34]. It requires that the circumcision to be avoided because the Prepuce or the Foreskin of the Penis is used in the repair of most cases. The ideal age of the surgical intervention to repair the Male Hypospadias is in between 6 to 12 months of age [30-64]. It involves tubularization of the urethral plate distal to the urethral meatus and a covering by a vascularized flap from the foreskin, in a surgical reparative operation called Meatoplasty. The more distal is the Hypospadias condition the more successful is its reparative surgical prognosis and the less of surgery sessions is needed to accomplish the final result [30].

Female Hypospadias is differentiated into a Distal and a Proximal Type as mentioned before. In the less severe distal type of Female Hypospadias the urethra is more likely to have a normal diameter with no stenosis; therefore it can be asymptomatic or cause symptoms like recurrent Urinary Tract Infection and Post-micturition Incontinence with pain and urgency during Micturition. The more severe condition of Female Hypospadias is the proximal type and often expresses a narrowing or stenosis of the female Urethra with a urinary outflow obstruction and it is associated with Female Pseudohermaphroditism [18]. The surgical treatment of Female Hypospadias is more complicated than that one of the Male Hypospadias but can be completely executed within a short interval of time [5].

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