AN UPDATED REVIEW OF ETIOLOGY OF HYPOSPADIAS

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Introduction

Hypospadias is a developmental anomaly, resulting from abnormal development of male external genitalia resulting in the abnormal position of external meatus on the ventral side of penis instead of tip and ventrally deficient prepuce with hooded skin on the dorsal surface of glans. Its most common male external genitalia defect following cryptorchidism.[1] Unfinished or incomplete virilization of male external genitalia produces hypospadias. Anatomically, the external meatus is present on the ventral side and there is hood like skin projecting from the dorsal side covering the place of normal external meatus opening. The part of the urethra present distal to the ectopic meatus is transformed into dysgenetic urethra, which is a structure with ventrally curved structure called chordee. This ventral curvature, which means that the penis is curved ventrally producing urinary as well as sexual problem for patient, was thought to be of fibrous origin but after analyses of the resected specimens it was found out to be a vascularized structure without any signs of fibrosis so the term is not used around anymore. A few children presented with normal placed meatus but with deficient prepuce on the ventral side of the penis, which is called "chordee without hypospadias".

The prevalence and incidence of hypospadias in many countries around the world is increasing in a constant manner.[2] Various parts of the globe has a little difference in the rate though. In some Scandinavian countries it's almost constant. While in USA and Canada, its incidence is increasing. Hypospadias is one of the most common congenital anomalies in the United States, occurring in approximately 1 in 250 newborns or roughly 1 in 125 live male births. In developing countries like India, Pakistan and other Southeast Asian countries as well as many African countries, due to lack of data no precise statement about its incidence and prevalence may be given but due to increasing risk factors and awareness, its reporting is increasing.[3]

Hypospadias are classified according to the anatomical difference.

1. Glanular Hypospadias

In glanular hypospadias, the external meatus is present on the ventral surface of the glans penis. Usually it is not considered clinically significant. There is also slit like groove on the ventral surface of penis.

2. Coronal Hypospadias:

In this condition, the external meatus in not on the glans but just below the glans. The coronal and sub coronal which are relatively more common are included in it.

3. Penile Hypospadias:

Penile hypospadias, as the name indicates is present on the ventral aspect of penis. It can be proximal, distal or in the mid-shaft of penis.

4. Scrotal/penoscrotal Hypospadias:

The external meatus is either present near the scrotum or in the scrotum. It can also be at the junction of penis and scrotum.

5. Perineal Hypospadias:

In this type of hypospadias, the external meatus is present in the perineum. It can be anywhere in the perineum but common site is just below scrotum. It's the difficult and worrisome type for both the patient and the surgeon to deal with.

Proximal hypospadias has a higher incidence of association with diseases of sexual development (DSD`s) as well as various other syndromes described elsewhere in the article, and are usually considered severe types while distal are considered milder types.

Cryptorchidism is one of most common anomaly associated with hypospadias for which parents seek help of pediatric urologist.

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Etiology

A lot has been done to find out the etiology of hypospadias around the world. There is solid evidence still lacking as what to blame precisely for the incomplete development of male external genitalia, which leads to the ventral positioning of external meatus rather than on the tip of glans penis. A lot of associated conditions and diseases have been proved to be related to the development of hypospadias in a male child. Endocrinopathies and maternal use of various chemical substances including cosmetics use as well as occupational hazard of working and living in industrialized areas are usually pointed out to be associated with this anomaly. In this article we will review all the etiological factors that so far has been discussed in various researches to keep clinicians as well as a concerned parents up to date.

a. Endocrinopathies (EDC):

Various studies looking into the effects of endocrinological pathologies onto the development of hypospadias and other urogenital disorders of development were done. One of which emphasized the testicular carcinoma and sperm quality to adversely affect the outcome of urogenital development.[3] Another study showed that endogenous or exogenous estrogen may act like endocrine-disrupter chemicals which may halt the progression of development and the evidence was solidified by the relationship of EDC`s with testicular dysgenesis syndrome. Combined OCPs contain a large quantity of estrogen, still evidence is lacking as to whether it acts as disrupter or not. In a few researches the use of plants which contain plant estrogens (phytoestrogens) was linked positively to act as risk factors for hypospadias.[3]

Placenta produces Human Chorionic Gonadotropin (hCG) which helps fetus produce various hormones acting as substitute for pituitary at the time, as the fetal pituitary isn`t developed by that time. Placental insufficiency results in producing various insults to the fetal growth leading to deficiency of hCG as well as harboring many morbidities for mother including preeclapmsia and intrauterine restriction of growth for the fetus. Placental insufficiency also increases the risk of various stunted developmental anomalies of the fetus including hypospadias. hCG in early pregnancy have a surge which causes not only nausea but also ensures safe gestation as early pregnancy nausea is found to be associated with low risk of abortion or miscarriage. Deprivation of a woman`s gestation with early pregnancy nausea is associated with decreased surge or pulse of hCG which was found to be associated with hypospadias in the child. In a study done on Di-ethylstillbestrol (DES)2,3 out of 573 mothers who were exposed to DES, 18 gave birth to children with hypospadias indicating some connection of DES with hypospadias. In another study done in Dutch boys,[3] DES was indicated to be associated very firmly with hypospadias indicating its role somehow with the development of hypospadias in the boys of whom mothers were previously exposed to DES in utero. Paternal exposure to DES did not increase the risk.

b. Genetic:

Various genes are involved for the normal embryological development of urogenital system of the fetus. These genes produce their effect via multiple pathways. Producing hormonal variations during the critical time period for the gonadal genesis, is an important milestone for the proper development of the genitalia. Any defect caused by a mutation or any germ cell`s incapability may lead to a sequence of events which halts the normal progression of the external genitalia. It could be a hormonal pathology or delayed signaling and various other aspects of genetic aberration. Hypospadias is present in 7 % of affected individual`s first, second and third degree relatives indicating its familial aggregation.[4]

ATF3: Activating transforming factor 3, is a gene responsible for male urethral development as evidenced by its presence in the foreskin both the hypospadiac and healthy child. Three single nucleotide polymorphism (SNP`s) were found to be associated with hypospadias. All three SNP`s were found to have no link with other yet they proved additive effect on each other. With all three SNP`s presence proved to be most significant.[4] ATF3 probably balances the estrogens and androgens in the pulsations and provision as to which hormone will exceed in quantity to produce its effects. GnRH also was found to produce its effects via the ATF3 production of various proteins found on immunohistochemistry analysis of foreskin of normal and hypospadiac child. GnRH induces the production of LH and FSH, which in various

mammalian studies were found to be associated with ATF3.[4,5]

Androgen Genes: The gene for androgen and androgen receptor (AR) is responsible for the normal production of androgens and their conversion to functional mature forms is disrupted at some point in the patients of hypospadias during development in the fetal life rendering them vulnerable to various other male external genitalia anomalies as well. Mutations in the genes responsible for 5-alpha-reductase and 17-hydroxydehydrogenase which converts testosterone to its active metabolite is also mutated in a large number of cases of hypospadias.[5]

Estrogen receptors: Estrogen may not have a direct effect on development of external male genitalia but it affects androgen in more than one pathway including its synthesis and mechanism. Various estrogen receptors like ESR1 and ESR2 work with androgens and testosterone to produce an equilibrium state during the developmental period which turns indifferent pattern of sexual organ formation towards male phenotype. Estrogen and androgens collectively produced this effect. Any variation in the rhythm and rate of any of the hormone may result into anomalies of male external genitalia. Any increase in the exogenous or endogenous estrogen by any source whether its internal increase of estrogens due to any hormonal response of the body mediated by genetic mutation/SNP or external influence on estrogen up regulation by various organopollutants and pesticides, can increase the up regulation and modulation of estrogen receptors in the maternal body leading to disequilibrium between androgens and estrogens leading to maldevelopment of male external genitalia.[5,6]

3, HSD-2: Hydroxy-steroid-dehydrogenase-2-beta-3 is a gene linked to the normal genesis of estrogen and androgens and their delicate balance, in a study mutation was found in the gene for more than 70 percent of patients.[6]

17, HSD-3: Another gene responsible for equilibrium and conversion of testosterone to DHT is type 3-hydroxysteroiddehydrogenase-17, mutation of which produces hypospadias irrespective of the type and severity.[6]

c. Environmental& behavioral:

Various pesticides and synthetic chemicals used in agriculture and industry may induce hypospadias. In a study estrogenic compounds were found to have a role to induce hypospadias in boys of mothers exposed to estrogenic compounds in plants and other products like dairy milk etc. Study was done on more than 1000 women showed a mild association of consumption of soya products associated with hypospadias.[6,7]

While Oral Combined contraceptive pills have been shown to be very safe, various other drugs and medicines which include biologic synthetic compounds mimicking actions of testosterone and progesterone were shown to have a role for hypospadias. These compounds are used as pregnancy protectors.[7]

In a study authors found a significant relationship between maternal diet during pregnancy and male external genitalia developmental problem especially hypospadias and cryptorchidism. They proved the link between diet lacking in animal meat and fish played some role for hypospadias. Role of soya bean was also mentioned to be of some significance because of presence of phytoestrogens in these which acts both as estrogenic and anti-estrogenic actions. Meat and fish probably contain essential amino acids as well as essential fatty acids.[8]

Energy drinks disrupt the normal estrogenic hormone in the female body, this disruption if done during pregnancy may expose the fetus to increased maternal estrogen hormone level which was linked positively with hypospadias.

In a study, *polychlorinated biphenyls* (PCBs)[8] were investigated due to their some association with estrogenic like compounds. They were considered to have a role in hypospadias and cryptorchidism but their association wasn`t proved. A large population was studied considered to be using PCBs inadvertently but no correlation was confirmed. Many studies have proved various environmental toxins and heavy metals as well as organic sprays including pesticides and insecticides to have a firm association with the development of hypospadias in the male offspring of mothers exposed to these material.[9] But isolated exposure to these toxins and pesticides isn`t enough alone to produce hypospadias in the children of mothers exposed, these toxins and pesticides are supposed to work by either disrupting

the endocrinal mechanism or genetic influence. These chemicals which shift the equilibrium to one side of the balance in the endocrinal pathways of hormones especially the balance between estrogens and androgens. Androgens are known to affect the fetus during critical period 8-11 weeks of external genitalia development leading to differentiation into male phenotype, any disturbance in this mechanism leads to various problem of male external genitalia including hypospadias and cryptorchidism as well. Another author pointed out in a study that many other organopollutants like Hexachlorbenzene and p, p-DDE affect the maternal health leading to hypospadias and other birth defects as well like cryptorchidism.[8,9]

In another study done on *cocoa* consumption and testicular cancer and hypospadias risk, it was pointed out that increasing cocoa dose was associated with testicular cancer and hypospadias particularly.[10] A western diet contain desserts and sweeteners which increase the production of insulin; insulin acts to reduce the SHBG in women.[11] The male children of these women were found to be at greater risk of developing hypospadias. Theo bromine an ingredient of the cocoa was linked to various types of testicular cancers and to hypospadias as well in the male child.[12] Theobromine was also found to be the part of ochratoxin A which have well defined role in various cancer induction in the body. In the study, Theobromine given to the rats for a few weeks induced testicular cancer in them and in the male rats produced various semen and sperm problems like oligospermia and azoospermia. Theobromine was also secreting through the milk of breast feeding women to their children, thus increasing the risk further for the children of cocoa consuming mothers.[13]

d. Gestational:

While studies have found no association of maternal smoking on the development of hypospadias, some authors found evidence of hypospadias related to increasing maternal age as well as small age on prim parity.[14] Various gestational problems e.g. intrauterine growth retardation (IUGR) and others abnormalities like pre-eclapmsia and eclapmsia are considered to be a strong risk factors for hypospadias.[15] Higher maternal age, low birth weight of the child, preterm birth leading to asphyxia may lead to hypospadias.[16] Twin pregnancy is linked with hypospadias especially in monochorionic twins in which both the fetuses were male, the chances of one or both twin developing hypospadias were as high as 8.5 %, probably something to do with decreased supply of endocrine hormones like hCG which substitutes pituitary hormone during early gestation. The deficiency of which is thought to result in hypospadias.[17]

Pre-gestational as compared to gestational diabetes mellitus is associated more with various anatomical and endocrinological anomalies later in the child of affected mother. Neural tube defects (NTD`s) with its many manifestations like Spina bifida and Meningocele are linked clearly with diabetes mellitus. Many authors believed hypospadias to be caused by higher glycemic level during pregnancy and this was linked positively by many researches. Hypertension and other systemic diseases like systemic lupus erythmatosis (SLE) did seem to have an indirect role via interrupting during critical period of genitalia development by maternal morbidity.[18] *Increased maternal age and weight* renders a child vulnerable to various developmental anomalies and diseases later in life like down`s syndrome.[19] Women who were obese before starting their pregnancy and BMI`s greater than 25 were found to be at greater risk of developing pre-ecclapmsia and later placental insufficiency.[20] This was linked with plasminogen activator inhibitor-2 (PAI-2), which was decreased in the overweight women, the deficiency of which was a risk factor for the development of hypospadias in the male offspring of these mothers. Women who were underweight are also at increased risk of having hypospadias in their male children.[21]

e. Drugs:

Anti-epileptic drugs especially valproic acid was associated with a greater chance of developing hypospadias in the boys of mothers exposed.[22] Maternal use of various drugs like antibiotics, paroxetine, loratidine[13,23] and many other drugs were found to have no association with the development of hypospadias. But evidence for the development of hypospadias by maternal use of anti-epileptics was convincing. Assisted conception procedures like IVF and ICSI are also associated with hypospadias,

probably the risk of twin or higher multiple gestation working as a risk factor in these procedures making placental problems more likely to occur. A study done in Denmark, the authors checked the role of loratidine compared to other anti-allergic in mothers inducing hypospadias in their male child. The evidence proved that loratidine did have no role in the induction of hypospadias or any other significant disorder of sexual development.[24]

f. Parental:

Fathers of boys with hypospadias were investigated in one study and a large proportion was found to be having various germ cell abnormalities e.g. abnormal morphology of sperms, dysmotility syndromes as well as decreased semen quantity. Parental age seemed to have no effect on the developmental delay leading to hypospadias, but dysfunctional sperms with abnormal morphology were linked with hypospadias in more than one study probably alluding to the role of genes. Semen analysis done by various studies indicated that fathers of many hypospadiac children had sperm level lower than normal as well as they had abnormal morphology of sperms.[24,25]

Many surgeons prefer to go for complete evaluation including karyotyping, familial history and ruling out the possibility of many other syndromes like urinary tract abnormalities when hypospadias is diagnosed. The distal and shaft hypospadias were found to be largely exclusive while proximal types were associated more with other abnormalities of renal tract and hormonal origin. In majority of cases in which the etiology was found were proximal types and milder types were exclusive.

CONCLUSION

Hypospadias is a worldwide male external genitalia developmental problem. Any external synthetic analogue of estrogen or various environmental toxins, pollutants, pesticides, insecticides and many other agricultural and industrial chemicals may act to disrupt the endocrinological balance leading to hypospadias. Many genes have been identified but these all act additively and no single gene was found responsible for hypospadias. All factors which affect maternal health negatively are also associated with hypospadias. Balanced diet, avoidance of any agricultural and industrial chemicals and unnecessary hormonal supplement may reduce the risk of hypospadias in many women. Well managed care of twin pregnancy and higher multiple gestation, reducing the risk of placental insufficiency and its various manifestations by medical maneuvers, pre-conception folate and multivitamin supplementation and avoidance of any estrogenic food like soya and a strict vegetarian diet which may contain exogenous estrogen may reduce the likelihood of hypospadias in boys of these women. Avoidance of nuts, oilseeds, soya, cereals, processed foods and bread which contain phytoestrogens may also reduce the risk. Cruciferous vegetables like cabbage and citrus fruits decrease the level of estrogen in the body by clearing it from liver and kidney, and so should be taken. In fact, hypospadias is a multifactorial environmental and genetic developmental anomaly, which may be prevented by above mentioned ways and in a large proportion of cases is sporadic.

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