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Pesticides Exposure and Risk of Hypospadias

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1. Introduction

Hypospadias is a common congenital anomaly, the cause of which is still unknown. The term hypospadias is derived from the Greek prefix “hypo” meaning below and the term “spadon”, meaning rent or defect (Dorland’s Medical History, 1981).

The defect is readily observed, and hence it has been recognised since ancient times (Aristotle. Generation of animals, 1943). In both males and females the urethra is a perfect canal, but in the congenital anomaly of hypospadias, the canal becomes a gutter. This phenomenon is easily seen in males but not in females. In females anomalies of the urethral meatus are considered anomalies of the urogenital sinus (J.E. Skandalakis & S.W.Gray, 1994). The term “hypospadias” refers to an opening on the ventral side of the penis, while “epispadias” is an opening on the dorsal side. Hypospadias denotes a condition in which the urethra has failed to completely form and is often associated with a ventral curvature of the penis (chordee). Hypospadias is classified according to severity. The first degree is the mildest form, and the urethra opens on the anterior portion of the penis (glandular and subcoronal). The second degree is more severe and involves openings on the midshaft of the penis. The third degree is the most severe and involves posterior penile, penoscrotal, scrotal, and perineal openings. First-degree hypospadias accounts for approximately 50% of cases, second-degree for 30%, and third-degree for 20% (Duckett et al, 1996; Levitt SB & Reda, 1988).

2. Embryology of hypospadias

The development and elongation of the phallus occurs between weeks 8 and 14 of prenatal life under the influence of the androgens testosterone (T) and 5 α dihydrotestosterone (DHT), which are synthesized in response to a surge of luteinizing hormone (LH) from the fetal pituitary (Moore KL, 1988; Bingol N & Wasserman, 1990).

Testosterone is a key hormonal agent that influences the undifferentiated fetal sex organs, including internal and external genitalia, to develop into the male phenotype. The placenta regulates the production of fetal testosterone by the stimulatory effect of human chorionic gonadotropin-(hCG)- on Leydig cells at an early stage of gestational age, including the critical 8th–12th weeks for male genitalia development (Winter *et al.*,1977).

The fetal pituitary begins to regulate the production of testosterone at midgestation by the secretion of luteinizing hormone (LH). The growth and development of the testis and accessory sex structures in the human, are unequivocally dependent upon the continuous support of the hypothalamo-hypophyseal-testicular axis (Grumbach, M.M., 1980; Claude Desjardins 1981).

At the end of the third month, the urethral folds close over the urethral plate to form the penile urethra. The distal part of the glanular urethra, develops by one of the following mechanisms (Gunha GR & Baskin LS., 2004). The classic theory states that the distal portion of the urethra develops as an in growth from the tip of the penis until it joins the proximal tubular urethra (Moore KL et al., 2003; Kurzrock EA et al. 1999) Recent evidence, however, suggests that the entire urethra from base to tip, is formed by continuous extension and fusion of the endodermal urethral groove (Hynes PJ & Fraher JP, 2004; Belman AB., 2002). The penile urethra forms as a result of the medial edges of the endodermal urethral folds fusing to form the median raphe (Baskin LS., 2000).

Undescended testes (cryptorchidism) and inguinal hernias are urogenital anomalies that are most commonly associated with hypospadias. In one series, 9.3% of hypospadias patients had undescended testes (Khuri FJ et al., 1981). There was a 5% incidence of undescended testes with first-degree, 6% with second-degree, and 32% with third-degree hypospadias. The overall occurrence of inguinal hernia associated with hypospadias is estimated to be 9%, but with third degree hypospadias the occurrence can be as high as 17% (Khuri FJ et al., 1981). Congenital anomalies not involving the urogenital tract have been found in 6.7% of all patients with hypospadias, and primarily involve the craniofacial, cardiothoracic, and gastrointestinal systems and the extremities. With increasing severity of hypospadias, the occurrence of associated non-urogenital anomalies can reach 12.7% (Latifoglu et al., 1998).

3. Epidemiology

Recent evidence shows an increase in the prevalence of hypospadias in Europe and US without certain aetiology (Paulozzi LJ et al., 1997; Paulozzi LJ, 1999). Classical textbooks of embryology and Paediatric Surgery report that the incidence of hypospadias is ranging from 1-8.2 per 1000 live male births (J.E. Skandalakis & S.W.Gray, 1994; Ashcraft Murphy, 2000; O'Neil, J, et al, 2006). Hypospadias is a relatively common congenital anomaly, with a birth prevalence ranging from 0.3% to 0.8% of Caucasian male live births in the United States, and 0.05% to 0.4% for other racial groups (Bingol N & Wasserman, 1990). A greater frequency of hypospadias has been found in Caucasians than in other races (Chavez GF et al., 1988; Gallentine ML et al., 2001). In the 1970s and 1980s, birth defect surveillance systems reported transient 1.5- to 2-fold increases in the prevalence of hypospadias in Norway, (Bjerkedal T & Bakketeig LS., 1975) Sweden, (Kallen B & Winberg J., 1982) Denmark, (Kallen B et al., 1986) England, (Matlai P & Beral V, 1985) and Hungary (Czeizel A., 1985).

An international study of hypospadias from seven birth defect surveillance programs (Denmark, Hungary, Italy, Mexico, South America, Spain and Sweden) included data from over 7,400 cases of nonsyndromic hypospadias (Kallen B et al., 1986). Differences in prevalence rates between countries were found that could not be explained completely by variations in case definition or different levels of ascertainment. The inclusion of less severe forms of hypospadias did not explain the higher rates in some programs compared to others. In some countries there was a 5–21% level of over estimation due to misdiagnosis of

normal infants. Counteracting this was a 30–64% under estimation among cases severe enough to require surgery. However, geographic variability in prevalence rates could not be explained solely on the basis of ascertainment problems.

Rates based on Swedish registry data from 1973–1974 (incomplete ascertainment) were 40% higher than rates from 1965–1968 based on hospital records and registry data (more complete ascertainment) (Kallen B & Winberg J., 1982). Consequently, hypospadias is difficult to assess in studies utilizing data from geographically diverse surveillance programs (Kallen B et al., 1986).

A Centers for Disease Control (CDC) study evaluated the birth prevalence of hypospadias in the United States from two birth defects surveillance systems: the Metropolitan Atlanta Congenital Defects Program (MACDP) and the Birth Defects Monitoring Program (BDMP) (Paulozzi LJ et al., 1999). The MACDP is a hospital-based registry that was initiated in 1968 and is based on case ascertainment in 22 hospitals and clinics in the Atlanta, Georgia area. The BDMP is a population-based registry that was initiated in 1970, in which diagnoses from newborn discharge summaries are collected from a nationwide sample of hospitals (Paulozzi LJ et al., 1999). The total hypospadias rate (mild and severe) doubled in the MACDP between 1968 and 1993 from approximately 1.5 to 3.0/1000 births, and the overall trend was statistically significant. The annual rate of increase was 2.9%, and the overall increase occurred at a rate of 1.4% per year among Caucasians and 5.7% per year among non-Caucasians. For severe hypospadias, the rate increased three- to five-fold (0.11–0.55/1000 births) from 1968 to 1993, and this trend was also statistically significant. Overall, however, approximately 60% of cases could not be classified by severity. In the BDMP, the total hypospadias rate also doubled (2.02 to 3.97/1000 births) from 1970 to 1993, and this trend was also statistically significant. The increase occurred nationwide, and was highest in the Southeast and lowest in the West (Paulozzi LJ et al., 1999).

The prevalence of hypospadias was assessed in The Netherlands by prospective examination of newborns in Rotterdam over a 2-year period. A total of 7292 consecutive male births were examined for the presence of hypospadias (excluding glandular cases), and rates were increased four-fold compared to earlier time periods studied (Pierik FH et al., 2002).

Consequently, comparable rates of increases in the birth prevalence of hypospadias have been seen in both the United States as well as in The Netherlands in studies utilizing population-based as well as hospital-based epidemiologic approaches (Paulozzi LJ et al., 1999). A recent study from Denmark reports a rate of hypospadias of about 1% in a population of 1072 boys studied at birth which increased to almost 5% when followed for 3 years (K.A.Boisen, et al, 2005).

On the other hand studies reporting prevalence rates of hypospadias in Washington State and California do not support the idea of increased prevalence during the periods of 1987–2002 and 1989–1997 respectively (Susan L. Carmichael et al., 2003; Michael P. Porter et al, 2005).

Reviewing the international literature on the epidemiology of hypospadias one cannot stress enough the difficulties that arise when comparing different studies with variations in inclusion criteria and even definition of the different forms of the disease. The differences in ascertainment and in the descriptive epidemiology of hypospadias pose a question as to whether the reported increase in prevalence by some authors is true. However increasing trends are being reported by recent careful studies concerning some populations (Michael Michalakakis, et al. 2008; A.M.Tsatsakis et al., 2008).

4. Etiology

Reports of increasing prevalence of hypospadias have raised questions concerning aetiology, treatment, and prevention. To date, there is no comprehensive understanding of the aetiology of hypospadias that can inform primary prevention efforts and improve therapeutics. The aetiology of many hypospadias is often assumed to be multifactorial, implicating some combination of genes and environment in the development of the anomaly. Efforts to define a clear aetiology have been unsuccessful (Baskin LS et al., 2001). In a report, 33 patients with severe (scrotal or penoscrotal) hypospadias were evaluated with a range of diagnostic techniques including clinical assessment, ultrasonography, karyotyping, endocrine evaluation, and molecular genetic analysis of the androgen receptor (AR) and 5 α -reductase genes to classify and determine the cause of the hypospadias (Albers N, 1997). In 12 patients, diagnoses were determined. The remaining 64% of patients were classified as hypospadias of unknown aetiology.

5. Genetic predisposition for hypospadias

There is a well recognized familial clustering of hypospadias, and male relatives of boys with hypospadias are more likely to have this condition than would be expected by chance. In a study by Sorenson, (Sorenson HR., 1953) male relatives of 103 index cases with nonsyndromic hypospadias were evaluated. It was found that 28% had at least one other family member with hypospadias. The more severe the hypospadias in the index case, the higher the incidence of hypospadias in first-degree relatives. With the mildest form of hypospadias, 3.5% of relatives were affected; with second-degree, 9.1%; and with third-degree, 16.7%. The overall risk for a brother of an affected infant to also have hypospadias was 9.6%. Chen and Woolley (Chen YC, 1971) identified a similar figure of 9.7%. The risk of hypospadias in sibs of affected infants was found to be 4.2% in the international study, with a range of 0–11.3% (Kallen B et al, 1986). These sib occurrence risks are compatible with a multifactorial mode of inheritance for hypospadias. An increased risk for hypospadias among twins has been described. The prevalence of hypospadias is higher among members of male–male pairs and lower among males in male–female pairs. Concordance among twins of the same sex was 18% for both mild and severe forms, with increased risk evident in both monozygotic and dizygotic twins (Kallen B et al, 1986). When monozygotic twins discordant for hypospadias were evaluated, the twin with the lowest birth weight had hypospadias in 16 out of 18 pairs, suggesting a gene–environment interaction (Fredell L et al., 1988).

6. Genetic impairment

Theoretically, genetic alterations in any of the genes involved in development of the male urogenital system could result in hypospadias. However, currently only a small percentage of hypospadias has been linked to genetic or chromosomal damage (Bentvelsen FM et al., 1995; Aaronson IA et al., 1997; Alléra A. et al., 1995).

One in nine patients with severe hypospadias had a single amino acid replacement of the Androgen receptor gene (AR) (Alléra A. et al., 1995). Single-strand conformational polymorphism analysis revealed a missense mutation of exon 2 of the AR gene in 1 of 40 patients with distal hypospadias (Sutherland RW et al., 1996). Several other authors

concluded that mutations in the AR gene are rarely associated with hypospadias, (Wilson JD et al., 1981; McPhaul MJ et al., 1993; McPhaul MJ et al., 1993;– Hiort O et al., 1994) implying that other factors are responsible.

6.1 Homeobox (HOX) genes

Homeobox (*HOX*) genes are transcription factors that play a role in embryonic organization and patterning. Genes of the *Hoxa* and *Hoxd* clusters are expressed in regionalized domains along the axis of the urogenital tract.

Transgenic mice with loss of function of single *Hoxa* or *Hoxd* genes exhibit homeotic transformations and impaired morphogenesis of the urogenital tract (Dollé P et al., 1991; Benson GV et al., 1996; Hsieh-Li HM et al., 1995; Podlasek CA et al., 1997). Human males with hand-foot-genital syndrome, an autosomal dominant disorder characterized by mutations in *HOXA13*, exhibit hypospadias of variable severity, suggesting that *HOXA13* may be important in normal patterning of the penis (Mortlock DP & Innis JW, 1997; Donnenfeld AE et al., 1991; Fryns JP et al., 1993).

6.2 Fibroblast growth factor (FGF) genes

Fibroblast growth factor (*FGF*) genes have been demonstrated to play a role in genital tubercle development. As with *Hoxa-13*, *Fgf-10* and insulin-like growth factor receptor (*Igfr*) knockout mice have been shown to develop hypospadias. More specifically, the condition of the external genitalia *Fgf-10* knockout mice suggests impairment in the development of the glans penis (Haraguchi R et al., 2000).

6.3 The Sonic hedgehog (Shh) gene

Genetic mutations might also interfere with epithelial-mesenchymal interactions necessary for normal embryogenesis (Kurzrock EA et al., 1999). The Sonic hedgehog (*Shh*) gene is expressed in the epithelium of the male urogenital sinus and is not regulated by testosterone. *Shh* has also been shown to be critical for prostate development; however, it has not been studied in relation to hypospadias (Podlasek CA et al., 1999). Genetic impairment of *Shh* during development may be involved in hypospadias and is consistent with the well-established role of *Shh* in limb development (Cohn MJ & Bright PE, 1999). Genetic mutations could theoretically interfere indirectly with fetal testis and adrenal testosterone production and with the adequate virilization of the urogenital sinus and external genitalia during embryogenesis if the conversion of testosterone to DHT by 5 α -reductase is interrupted. In addition, any errors in the activity of enzymes involved in converting cholesterol to testosterone could indirectly affect urogenital virilization. Aaronson et al. determined the incidence of defects in three major enzymes in the biosynthetic pathway leading to the production of testosterone (3 β -hydroxysteroid dehydrogenase, 17 α -hydroxylase, and 17,20-lyase) in 30 boys with fully descended testes but with penoscrotal or proximal shaft hypospadias. One-half of the boys had evidence of impaired function of one or more of these enzymes, suggesting that there was an underlying defect in the biosynthesis of testosterone (Aaronson IA et al., 1997).

6.4 Steroid 5-alpha reductase type 2 (SRD5A2)

The differentiation of the male external genitalia (penis, scrotum and urethra) depends upon conversion of testosterone (T) to dihydrotestosterone (DHT) via the enzyme steroid 5 alpha-

reductase (SRD5A) located in the urogenital tubercle. DHT also initiates differentiation of the urogenital sinus into the prostate while it inhibits the development of the vesico-vaginal septum. T and DHT bind to the same intracellular androgen receptor and interact with a cognate DNA response element to regulate gene expression. Even though T and DHT are active via the same androgen receptor, these hormones produce distinct biological responses. The reasons for this are not clear at the molecular level; however, DHT binds to the androgen receptor more avidly than T, and the DHT-receptor complex is more efficiently transformed to the DNA-binding state than is the T-receptor complex (Siiteri P & Wilson J., 1974; Russell DW & Wilson JD., 1994; Zhu Y-S et al., 1998).

The role of T and DHT in formation of the male genital tract is vividly illustrated in men with congenital SRD5A enzyme deficiency, who are known as male pseudohermaphrodites (Zhu Y-S et al., 1998; Griffin J, & Wilson J., 1989; Imperato-McGinley J et al., 1987). They have a normal XY karyotype but ambiguous external genitalia, and thus are reared as females in many cases. T and estrogen (E) levels are normal to elevated, but DHT levels are reduced. These individuals lack Mullerian duct derivatives, while T-dependent Wolffian duct derivatives (the epididymides, seminal vesicles, vas deferens) are present. The DHT-dependent external genitalia are abnormal, however, and a small phallus, bifid scrotum, blind vaginal pouch, and varying degrees of hypospadias are present. Two different isozymes of SRD5A have been identified in humans: one is located in genital tissue and the prostate, with an optimum pH of 5.5 (type 2; SRD5A2), and the other is found in nongenital skin and the liver, with an optimal pH of 6–9 (type 1; SRD5A1) (Moore R, & Wilson J, 1976). Male pseudohermaphrodites have deficiencies only in the SRD5A2 enzyme, the gene for which is located on the short arm of chromosome 2 (2p23). The gene for SRD5A1 is located on the short arm of chromosome 5 (5p15), and is normal in male pseudohermaphrodites (Andersson S et al., 1991; Thigpen A et al., 1992). In children, SRD5A1 expression is localized to the sebaceous gland in nongenital skin and is markedly elevated at puberty (Thigpen A et al., 1993). The virilization of male pseudohermaphrodites at puberty may be influenced by synthesis of DHT in nongenital skin via SRD5A1 activity. As a means of diagnosing SRD5A2 deficiency in children, T/DHT ratios have been measured in serum after hCG stimulation. Excretion of 5 α /5 β steroid metabolites, and enzyme activity in cultured fibroblasts from genital skin have also been examined (Peterson R et al., 1985). These parameters are highly variable and difficult to interpret in prepubertal children, and T/DHT ratios are increased only in the most severely affected patients (Hiort O et al., 1996; Sinnecker GH et al., 1996). More recently, direct evaluation of allelic variants in the SRD5A2 gene has been used to diagnose SRD5A2 deficiency (Hiort O et al., 1996).

6.5 Androgen receptor gene

The AR gene plays a critical role in male sexual differentiation by mediating the biological effects of gonadal androgens. There are more than 150 mutations described in the AR gene that give rise to androgen insensitivity syndrome (MacLean HE et al., 1995). Most reports of AR gene mutations in individuals with hypospadias have included patients with additional genitourinary malformations, and the disorder analyzed was partial androgen insensitivity syndrome rather than nonsyndromic hypospadias. Mutations of the androgen receptor coding sequence are infrequent in patients with isolated hypospadias (Allera A et al., 1995; Klocker H et al., 1995; Sutherland RW et al., 1996).

In a study of 63 cases of severe hypospadias obtained from a single centre, cases were evaluated for a spectrum of known risk factors, including patient history, physical

examination, karyotyping, hormonal evaluation, and assay of genes involved in androgen action and metabolism. In 31% of cases, the underlying aetiology was identified. Of these, 17% were due to complex genetic syndromes, such as Smith-Lemli-Opitz and Opitz-Frias. Sex chromosomal anomalies, such as XY mosaicisms, accounted for 9.5% of cases. Isolated causes in one case each were the androgen insensitivity syndrome and 5 α -reductase type 2 deficiency. Also, in patients with elevated T to DHT ratios, no mutations were found in the SRD5A2 gene. These findings indicate that gene mutations in the SRD5A2, and AR genes may not be common in patients drawn from the general population with nonsyndromic hypospadias (Boehmer AL et al., 1999). Until larger studies are undertaken, however, the role of genetic factors in genes controlling androgen action and metabolism will not be clearly understood. Evaluations of genotype, as well as exposure to endocrine disrupting chemicals, are likely to be important in explaining the majority of cases of nonsyndromic hypospadias.

7. Risk factors for hypospadias

Several studies have found that male infants with hypospadias have lower birth weight, shorter length of gestation and/or evidence of growth retardation in utero (Sweet RA et al., 1974; Akre O et al., 1999; Hussain N et al., 2002).

The recent study by Hussain et al contains a systematic evaluation of all these risk factors. A retrospective cohort study of 6,746 male infants admitted to neonatal intensive care units (NICU) at the University of Connecticut from 1987–2000 was conducted. Overall, 1.66% of male infants had a diagnosis of nonsyndromic hypospadias, and there was a 10-fold increase in the birth prevalence over the 13-year period of the study. Hypospadias was significantly more common in infants who had poor intrauterine growth (10th percentile) as measured by birth weight, length, and head circumference. The proportionate decrease in all of these growth parameters suggests that the primary insult occurred early, during the first trimester of pregnancy (Hussain N et al. 2002). There were no differences between singletons and multiple-gestation births, but the frequency was significantly higher among firstborn infants (1.9%) compared to all other infants (0.9%). There was a higher occurrence (35%) of the more severe forms of hypospadias (second- and third-degree) in this study compared with other studies, (Avellan L, 1975) indicating that both the incidence and severity were increasing over time (Hussain N et al. 2002). Common environmental factors that had an impact on intrauterine growth and morphogenesis of the genital tract were considered to be the cause. Exposure to EDC (Endocrine Disrupting Chemicals) was implicated, as significant levels were found in aquatic life in proximity to the study site in Connecticut (Hussain N et al. 2002). While these findings are notable, and diagnostic criteria for hypospadias were rigorously controlled, the prevalence of hypospadias among infants in an NICU environment cannot be extrapolated to the general population. An additional risk factor for hypospadias is parental subfertility, which has been identified as delayed childbearing in several studies (Fisch H et al., 2001; Fritz G, & Czeizel AE, 1996). A 50% increase in severe cases has been demonstrated in children of mothers 35 years old compared to mothers 20 years old (Fisch H et al., 2001; Michael P. Porter et al., 2005). A correlation between paternal subfertility and increased risk of hypospadias has also been found (Fisch H et al., 2001). Abnormalities of the scrotum or testes (e.g., cryptorchidism, varicocele, hydrocele, and atrophic testes) were found in 34% of index fathers whose sons had hypospadias, compared to 3% of control fathers in a study conducted by Fritz and

Czeizel (Sweet RA, 1974; Fritz G, & Czeizel AE, 1996). They also found that 24% of fathers with affected sons had signs of subfertility (such as decreases in sperm density, motility, and morphology) that required medical treatment, compared to 6% of controls (Fritz G, & Czeizel AE, 1996). Subfertile males are now reproducing at a higher rate due to improvements in assisted-reproduction techniques, and this may be contributing to the increased occurrence of hypospadias (Czeizel A, 1985; Fritz G, & Czeizel AE, 1996).

Additional evidence that paternal subfertility is a risk factor for hypospadias has come from studies of birth outcome following *in vitro* fertilization (IVF) procedures. A five-fold increased risk for hypospadias has been found in infants conceived by IVF procedures in the Greater Baltimore Medical Center as compared to state-wide incidence figures in Maryland (Silver RI, 1999). These findings have been confirmed in subsequent studies using the Swedish Medical Birth Registry (Wennerholm UB et al., 2000; Ericson A & Kallen B, 2001). No increased risk for hypospadias was found after standard IVF in Sweden; however, there was an approximately three-fold increased risk (95% CI, 1.4 -5.4) after intracytoplasmic sperm injection (ICSI), a specific IVF procedure that is undertaken when sperm quality is poor (Wennerholm UB et al., 2000; Ericson A & Kallen B, 2001). Women undergoing IVF procedures typically receive treatment with progesterone in the first trimester to support the pregnancy after embryo transfer postulated that this treatment is the cause of increased risk for hypospadias following IVF procedures (Silver RI, 1999). Experimental studies have shown that progestins administered to laboratory animals during pregnancy can cause hypospadias (Goldman AS et al., 1967; Dean HJ, 1984). The epidemiologic evidence, however, does not support an association between increased risk for hypospadias and first trimester exposure to progestins found in oral contraceptives, hormones for pregnancy support, and/or hormone-based pregnancy tests (Sweet RA et al., 1974; Aarskog D, 1979; Czeizel A, 1979; Mau G 1981; Monteleone NR et al., 1981; Calzolari E, 1989; Kallen B et al., 1991). A meta-analysis of human studies also did not find an association between progestin exposures and external genital anomalies in male infants (summary OR, 1.09; 95% CI, 0.90 - 1.32) (Raman-Wilms L et al., 1995). In addition, Wennerholm et al. (Wennerholm UB, 2000) and Ericson and Kallen (Ericson A & Kallen B, 2001) found in the Swedish Medical Birth Registry that an increased risk for hypospadias was specific for ICSI, and not for all the other IVF procedures in which progestin support was administered. These investigators concluded that confounding by paternal subfertility explained the association between ICSI and increased risk for hypospadias. The transfer of genes involving androgen action and metabolism from fathers with poor sperm quality to their sons was considered the most likely cause (Fritz G & Czeizel AE, 1996).

In other reports white race, and pre-existing diabetes were also found to be associated with hypospadias in male offspring (Michael P.Porter et al.,2005). Reports concerning use of maternal drugs during early pregnancy, strongly associate the use of valproic acid with infant hypospadias, amongst other abnormalities (Carla Arpino et al., 2000).

8. Testicular dysgenesis syndrome (TDS) and related male reproductive disorders

Several investigators have reported adverse trends in male reproductive health, including increasing incidence of testicular cancer, cryptorchidism ie undescended testis, hypospadias and low semen quality (Adami et al., 1994; Forman & Moller, 1994; Carlsen et al. 1992; Swan et al., 1997; Andersen et al., 2000; Toppari et al., 1996; Paulozzi et al., 1997). It has been

proposed that all these disorders have common origin in fetal life and thus they all represent different symptoms of the same underlying entity called testicular dysgenesis syndrome (TDS) (Skakkebaek et al., 2001; Sharpe, 2003; Asklund et al., 2004). The observation that the occurrence of one disorder increases the risk of the occurrence of another disorder gives epidemiological evidence for the existence of TDS (Skakkebaek et al., 2001). Additionally the disorders of the male reproductive health share common risk factors. Small for gestational age infants have increased risk of developing undescended testis, hypospadias and testicular cancer (Moller and Weidner, 1999; English et al., 2003). The rapid increase of reproductive disorders and the geographical clustering of these disorders, point to environmental, life style and occupational trends rather than the accumulation of genomic defects, as the most likely cause of TDS (Virtanen HE. Et al., 2005). Animal studies have shown that several chemicals including pesticides, such as vinclozolin, procymidone, DDE, can cause TDS linked disorders (Skakkebaek et al., 2001; Damgaard et al., 2002; Fischer, 2004)

9. Endocrine disrupting chemicals

The familial clustering of hypospadias among first degree relatives has traditionally been perceived as evidence of a genetic component in the aetiology of this anomaly. However, exposure to environmental contaminants is now being considered in familial clusters because of the high probability of shared exposures among first degree relatives (Baskin LS et al., 2001).

As mentioned earlier the risk of developing hypospadias amongst relatives can be as high as 10%. This shows that the cause of hypospadias is mainly genetic for these individuals. The hypothesis of shared exposure on endocrine disrupting chemicals cannot alone justify the high incidence rate of hypospadias in familial clusters. The same hypothesis on the other hand cannot be overlooked since these agents have been shown to interfere with male sexual differentiation.

Several environmental antiandrogens have been identified in rodent models that interfere with male sexual differentiation at environmentally relevant doses (William R. Kelce et al., 1997; Gray LE et al., 1999; Tamura H et al., 2001; Gray LE et al., 2000 Gray LE et al., 2001). At relatively low in utero doses, antiandrogens reduce anogenital distance and induce transient nipple development in the neonatal rat. At mid-doses, hypospadias, agenesis of the sex accessory tissues, and retained nipples occur, while at the highest doses undescended testes and epididymal agenesis are seen. Fetal tissue concentrations of 10–20 ppm of the DDT metabolite, p,p'-DDE, an AR antagonist, are sufficient to produce these antiandrogenic effects in the rat fetus (William R. Kelce et al., 1997). These concentrations are similar to those measured in first-trimester human fetal tissues in the late 1960s. The pesticides vinclozolin, procymidone, linuron, and fenitrothion are also AR antagonists that produce dose-response effects on the developing male reproductive system (Gray LE et al., 1999; Tamura H et al., 2001).

Phthalate esters (PE) inhibit testosterone synthesis during fetal life, and produce dose-related abnormalities of the male reproductive tract similar to those caused by the AR antagonists (Gray LE et al., 2000). The PE have effects at extremely low in utero doses, and no-effect levels could not be found for the most sensitive endpoint, reduction in anogenital distance in male neonates (Gray LE et al., 2000). Prenatal administration of a single low dose of dioxin (50 –1,000 ng TCDD/kg) alters differentiation of androgen-dependent tissues; however, the mechanism of action involves interaction with the hormone-like receptor,

AhR, rather than the AR (Gray LE et al., 2001). Attempts to extrapolate findings from these rodent models to humans have been problematic. It can be difficult to determine whether effects obtained at doses employed in rodent models are relevant to human environmental exposures (Gray LE et al., 2001). An even greater problem is the difficulty of accurately measuring in utero human exposure to environmental agents for comparison. A number of epidemiology studies have been conducted concerning pesticide exposures of fathers employed as gardeners, agricultural pilots, or aerial sprayers (Roan CC et al., 1984; Rupa DS et al., 1991; Smith AH et al., 1982; Garcia AM, 1988). These studies have provided evidence, (some authors claim this evidence as very weak if any), that these types of occupational exposures result in adverse pregnancy outcomes (Roan CC et al., 1984; Rupa DS et al., 1991; Smith AH et al., 1982). A review of epidemiology studies published in 1980–1996 on the effects of agricultural occupation (and presumably pesticide exposure) on congenital malformations has been conducted. Of 34 published studies, few resulted in significant associations between birth defects and pesticide exposure (Garcia AM, 1988). Problems inherent in most of the studies were the use of occupational title or residence as a surrogate for pesticide exposure, the assessment of outcome through parental interview rather than medical records, and small study size. Recommendations from this and other reviews are that exposure to specific active ingredients or at least chemical classes must be quantitatively evaluated before assessment of effects on reproductive function can be accurately determined (Nurimen T, 1995). Regardless of these methodological issues, however, enough positive associations have been reported to warrant further investigation of pesticide effects on human reproduction.

10. Conclusion

There is substantial evidence for increases in the birth prevalence of hypospadias in the United States and in Europe. Several clinical risk factors have been identified, including intrauterine growth reduction and paternal subfertility, particularly when accompanied by assisted-reproduction procedures. Familial clustering has been well documented, and may involve both genetic and environmental risk factors. A number of candidate genes that control androgen action and metabolism are logical choices for genomic evaluation in population-based studies, including the SRD5A2, HSD17B3, and the AR genes.

The role of EDC exposure in the aetiology of hypospadias in human populations is far from clear (C. M. Rochelau, 2009). Major improvements in methodologies to measure environmental exposures are needed to determine the role of environmental exposures in the increased rates of hypospadias. The need of a prospective study that will accurately determine the exposure to EDC and quantitatively measure this exposure in a large sample of the population is needed.

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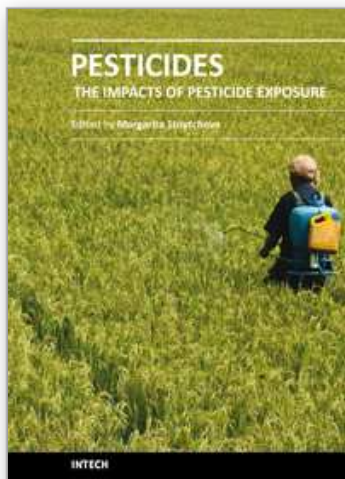
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Pesticides are supposed to complete their intended function without “any unreasonable risk to man or the environment”. Pesticides approval and registration are performed “taking into account the economic, social and environmental costs and benefits of the use of any pesticide”. The present book documents the various adverse impacts of pesticides usage: pollution, dietary intake and health effects such as birth defects, neurological disorders, cancer and hormone disruption. Risk assessment methods and the involvement of molecular modeling to the knowledge of pesticides are highlighted, too. The volume summarizes the expertise of leading specialists from all over the world.

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