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Testicular Dysgenesis Syndrome and Phthalates: Where do we Stand?

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Introduction

In the last two decades, several researchers from different parts of the world have been investigating the effects of endocrine disruption on male reproductive system. There are serious reports and epidemiological studies showing the decline in male fertility as well as the incline in congenital reproductive tract anomalies (cryptorchidism and hypospadias) and late-life testicular cancers.

The "testicular dysgenesis syndrome (TDS) hypothesis" proposes that a proportion of the male reproductive disorders–cryptorchidism, hypospadias, decline infertility (or loss of fertility) and testicular cancer–may be symptoms of one underlying developmental disease, TDS, which is most likely a result of disturbed gonadal development in the embryo. Endocrine disrupting chemicals (EDCs) are suggested to play role in the perceived decline of male fertility as well as the increase in the number of cases with TDS. There is very good evidence that lifestyle factors (e.g. smoking and/or alcohol consumption, drug abuse, physiological stress, eating disorders) can have an impact on fertility [1]. However, the increased TDS prevalence seems not to depend on life style solely. Geographical regions and higher exposure to chemicals in metropolis seem to be effective in the higher outcome of TDS. An interesting example comes from two Nordic countries, Denmark and Finland. The lowest testicular cancer incidences in Europe are observed in Finland whereas Denmark has had a lead for many years. Finnish men have a higher sperm concentration compared to Danish men, and the prevalence of cryptorchidism and hypospadias in Finnish newborn boys is considerably lower than Danish boys [2,3]. However, there are indications that the good reproductive health in Finland is also following a downward tendency. The testis cancer incidence is increasing, while sperm concentrations may be decreasing in Finland due to higher EDC exposure compared to recent decades [4]. In Finnish boys and men, the lower rates of testicular cancer and TDS seem to be dependent on good genetic background; however the increasing rates seem to be dependent on the higher exposure to EDCs. Interestingly, Finnish men, who migrated to Sweden in their 20s follow the Finnish incidence of testis cancer, whereas their sons, who were conceived and born in Sweden, follow the Swedish incidence rate [5]. This phenomenon provides further evidence for the hypothesis that high EDC exposure during fetal development may play an important role in the etiology of TDS.

By far, phthalates are most suspected chemicals for being the underlying factors of TDS [6]. These chemicals are plasticizers used in a variety of consumer products. They are shown to induce cryptorchidism, hypospadias and decreased anogenital distance in male rodents after *in utero* exposure [7]. Moreover, in our previous reports, we have shown that di(2-ethylhexyl)phthalate (DEHP) caused decrease in sperm count and progressive sperm motility and induced abnormal sperm morphology in pubertal rats [8]. We have also observed these chemicals caused germ cell apoptosis, disturbance of testicular vimentin structure and alterations in sex hormones [9].Their effects seem to be anti-androgenic rather than estrogenic [8]. Other than endocrine disruption, one of the most suspected mechanisms underlying their toxicity is oxidative stress, which is evident by the increase in lipid per oxidation, decrease in reduced glutathione (GSH) levels and alterations in the activities of antioxidant enzymes [10]. There are also human studies suggesting the decrease in anogenital distance as well as hypospadias, cryptorchidism and decrease fertility are associated with high exposure to phthalates [11-13].

It should be expressed that TDS may not be the cause of poor semen quality, cryptorchidism and hypospadias in all the cases, although the rapid increase in male fertility problems may not be explained by genetics or other disorders alone. A clear genetic background (rare complex syndromes, Y-chromosome base deletions, other genetic disorders including Klinefelter's syndrome, cystic fibrosis, celiac disease, Kallmann's syndrome, Kartagener syndrome) is present in the big proportion of male infertility which may not manifest until adulthood. In addition, poor semen quality can also be caused by obstruction, ejaculation issues (due to diabetes, spinal cord injuries, bladder/prostate surgery), medications (steroids particularly anabolic steroid use, chemotherapy, cimetidine), infections in puberty (mumps orchitis), genital infections (prostatitis) and occupational hazards (exposure to heat, X-rays, heavy metals, other EDCs in workplace) [14]. However, in most cases testicular cancer is a probable result of TDS as in 1940s the incidence for testicular cancer was 1-2/100,000 whereas in 2000, it was 16/100,000. In Turkey, during 15-24 years, the most common cancer among males is testicular cancer (23% of all cases in 15-24 years of age), whereas in 24-49 years of age, testicular cancer is at fourth place (6,2%) after lung, colorectal and stomach cancer. Its incidence seems to be very low after 50 years of age [15]. However, testicular cancer risk has been also increasing in our country along with increases in hypospadias, cryptorchidism and significant decreases in male fertility. We may attribute these disorders to wide usage of plastic material in kitchen and wide exposure to plasticizers (through cosmetics, food packages, drugs, cloths etc) as by our studies among Turkish pubertal girls and boys, we observed that they are abundantly exposed to phthalates [16,17].

In modern clinical practice, the clinical signs of TDS should be evaluated and treated by clinicians in different specialties consequently. In earlier life, a pediatric endocrinologist should examine and analyze the malformations and treat the patients accordingly, whereas in later life, andrologist/urologist and perhaps an oncologist should evaluate the patients. The doctors should work in concordance in these patients and should share their points of view with each other. If the semen quality of the patient is low, then these doctors should share their ideas with the gynecologist and they should agree on a fertility therapy or IVF if the patient wants to be a father. Therefore, toxicologists, epidemiologists as well as doctors from different specialties should be aware of TDS and should work in a harmony to prevent exposure or else to treat the symptoms.

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