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Is Hypospadias Associated with Prenatal Exposure to Endocrine Disruptors? A French Collaborative Controlled Study of a Cohort of 300 Consecutive Children Without Genetic Defect

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Abstract

Background: Numerous studies have focused on the association between endocrine-disrupting chemicals (EDCs) and hypospadias. Phenotype variability, the absence of representative comparison groups and concomitant genetic testing prevent any definitive conclusions.
Objective: To identify the role of occupational and environmental exposures to EDCs in nongenetic isolated hypospadias.
Design, setting, and participants: A total of 408 consecutive children with isolated hypospadias and 302 normal boys were prospectively included (2009–2014) in a multi-institutional study in the south of France, the area of the country with the highest prevalence of hypospadias surgery.
Outcome measurements and statistical analysis: In patients without *AR*, *SRD5A2*, and *MAMLD1* mutations, parental occupational and professional exposures to EDCs were evaluated based on European questionnaire QLK4-1999-01422 and a validated job-exposure matrix for EDCs. Environmental exposure was estimated using the zip code, the type of surrounding hazards, and distance from these hazards. Multivariate analysis was performed.
Results: Fetal exposure to EDCs around the window of genital differentiation was more frequent in the case of hypospadias (40.00% vs 17.55%, odds ratio 3.13, 95% confidence interval 2.11–4.65). The substances were paints/solvents/adhesives (16.0%), detergents

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(11.0%), pesticides (9.0%), cosmetics (5.6%), and industrial chemicals (4.0%). Jobs with exposure were more frequent in mothers of hypospadiac boys (19.73% vs 10.26%, $p = 0.0019$), especially cleaners, hairdressers, beauticians, and laboratory workers. Paternal job exposure was more frequent in the cases of hypospadias (40.13% vs 27.48%, $p = 0.02$). Industrial areas, incinerators, and waste areas were more frequent within a 3-km radius for mothers of hypospadiac boys (13.29% vs. 6.64%, $p < 0.00005$). Association of occupational and environmental exposures increases this risk.

Conclusions: This multicenter prospective controlled study with a homogeneous cohort of hypospadiac boys without genetic defects strongly suggests that EDCs are a risk factor for hypospadias through occupational and environmental exposure during fetal life. The association of various types of exposures may increase this risk.

Patient summary: Our multi-institutional study showed that parental professional, occupational, and environmental exposures to chemical products increase the risk of hypospadias in children.

1. Introduction

Hypospadias is the second most common malformation of the male genitalia. It consists of congenital hypoplasia of the ventral face of the penis, with displacement of the urethral opening, disjunction of the corpus spongiosum, a dorsal hooded foreskin, and, in some cases, ventral chordee. A multifactorial pathophysiology has been proposed, including genetic and environmental causes [1,2], to explain this undermasculinization of the fetus. Mutations of the many genes implicated in male sex development have been described, regardless of phenotype severity [3–5]. However, the majority of hypospadias cases do not exhibit genetic variants with functional consequences, and large studies have called into question the impact of these variants [6].

The increasing incidence of hypospadias in certain regions or time periods [7,8] has led to the suspicion that environmental chemicals may be detrimental to male genital development during fetal life, even though the findings are not generalizable [9]. According to the theory of testicular dysgenesis syndrome [10], fetal exposure to xenoestrogens suppresses testosterone production and action and/or androgen receptor (AR) expression [11], thereby causing neonatal genital malformation and long-term effects, including decreased spermatogenesis. Wildlife observations [12], experimental exposure to diethylstilbestrol (DES), which is a xenoestrogen model in mammals, and experimental in vitro data have suggested that manmade chemicals may interfere with androgen-dependent sex differentiation of the male fetus [13]. Some 8% of all known chemicals exhibit antiandrogen activity [14] and their widespread use has prompted the suspicion that endocrine-disrupting chemicals (EDCs) are a potential cause of hypospadias. Whether results from in vitro and animal experiments can be transposed to human pathology is questionable, and the key issue to be resolved is whether the real level of EDC exposure is sufficient to induce hypospadias in boys [15].

Recent studies by our group reported an association between genital disorders and environmental exposure to EDCs. For example, it was found that the prevalence of micropenis was higher in French regions with intensive pesticide use [16] and that male disorders of sexual development were more frequent in boys born to parents with occupational exposure to pesticides [17]. Increased serum estrogenic bioactivity may be a marker of exposure to pollutants [18], with clinical repercussions for both genital development [19] and puberty [20]. Exposure to medications with estrogenic activity such as DES can also lead to genital malformation [21].

Discrepancies among epidemiologic studies should nevertheless be noted [22,23]. For example, studies of occupations that expose workers to pesticides—one of the EDC classes most investigated in hypospadias—show contradictory results. Some authors have shown that farmers have a higher risk of giving birth to a boy with hypospadias [24], whereas others show no association with maternal exposure to pesticides [25]. Measurement of pesticide concentrations in maternal serum [26] and investigation of residential proximity to pesticide applications [27] have not helped to resolve these discrepancies. Many studies have focused on other professions, including the leather, automotive, and metal industries, as well as hairdressing, and have shown potential confounding factors at best or even completely contradictory results. The surrounding home environment has been also evaluated [28]. The prevalence of hypospadias seems to be higher in areas with intensive agriculture [29], but the increasing level of potential contaminants in maternal serum has not reached significance [30,31]. These results may be explained by the complexity of the mechanisms of action of xenoestrogens, the highly effective metabolites of EDCs, or the cocktail effects of hundreds of EDCs.

Most studies have also been retrospective and based on data banks with limited clinical details and sometimes wide variability in phenotypes and nonhomogeneous cohorts. Ethnic pair-based comparison groups that are representative of the population from which cases are derived are often missing, as is concomitant genetic testing to rule out genetic causes, making it difficult to draw conclusions. To address these issues, this multicenter prospective phenotype-specific study was performed in an area of France with the highest national rate of hypospadias surgery [32]. The study focused on patients with strictly isolated hypospadias after excluding the most frequent genetic defects.