

Maternal and Paternal Risk Factors for Cryptorchidism and Hypospadias: A Case–Control Study in Newborn Boys

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Little is known on environmental risk factors for cryptorchidism and hypospadias, which are among the most frequent congenital abnormalities. The aim of our study was to identify risk factors for cryptorchidism and hypospadias, with a focus on potential endocrine disruptors in parental diet and occupation. In a case–control study nested within a cohort of 8,698 male births, we compared 78 cryptorchidism cases and 56 hypospadias cases with 313 controls. The participation rate was 85% for cases and 68% for controls. Through interviews, information was collected on pregnancy aspects and personal characteristics, lifestyle, occupation, and dietary phytoestrogen intake of both parents. Occupational exposure to potential endocrine disruptors was classified based on self-reported exposure and ratings of occupational hygienists based on job descriptions. Our findings indicate that paternal pesticide exposure was associated with cryptorchidism [odds ratio (OR) = 3.8; 95% confidence interval (95% CI), 1.1–13.4]. Smoking of the father was associated with hypospadias (OR = 3.8; 95% CI, 1.8–8.2). Maternal occupational, dietary, and lifestyle exposures were not associated with either abnormality. Both abnormalities were associated with suboptimal maternal health, a lower maternal education, and a Turkish origin of the parents. Being small for gestational age was a risk factor for hypospadias, and preterm birth was a risk factor for cryptorchidism. Because paternal pesticide exposure was significantly associated with cryptorchidism and paternal smoking was associated with hypospadias in male offspring, paternal exposure should be included in further studies on cryptorchidism and hypospadias risk factors.

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Cryptorchidism and hypospadias are among the most frequent congenital abnormalities in male births. Cryptorchidism (mal descent of the testis) is observed in 1–5% of full-term male births (Toppari et al. 1996) and is a risk factor for subfertility and testicular cancer. Hypospadias (abnormal location of the orifice of the urethra) is observed in 0.3–0.7% of male births and requires surgical treatment in most cases (Pierik et al. 2002).

In the past two decades, concern has been raised over a possible increase in disorders of the male reproductive tract, including cryptorchidism, hypospadias, testicular cancer, and impaired semen quality. It has been suggested that these disorders are interrelated and share a common etiology during fetal life, described by Skakkebaek and colleagues as the testicular dysgenesis syndrome (TDS) (Sharpe and Skakkebaek 1993; Skakkebaek et al. 2001). Fetal exposure to endocrine disruptors (EDs) with estrogen-like or antiandrogen-like activity has been suggested as a cause for TDS (Sharpe 2003; Sharpe and Skakkebaek 1993). Various groups of chemicals, including pesticides and phthalate esters, have been identified as being weakly estrogenic or antiandrogenic (Sharpe 2003). These chemicals may occur in working environments, drinking water, and food (Toppari et al. 1996). Humans can also be exposed to natural phytoestrogens, through

consumption of food products derived from plants (Toppari et al. 1996).

There is only limited evidence that the suggested increase in male urogenital abnormalities in humans can be attributed to exposure to EDs (Sharpe 2003) or environmental chemicals in general. An excess of hypospadias has been reported among newborns in populations living within 2–3 km of landfill sites (Dolk et al. 1998; Elliott et al. 2001). These findings may indicate an effect of chemical wastes, but exposure classification was too crude to differentiate this exposure from confounding factors (Dolk et al. 1998; Elliott et al. 2001). In contrast, no association was observed between hypospadias and occupational exposure to EDs by the mother during pregnancy (Vrijheid et al. 2003). A maternal vegetarian diet during pregnancy has been associated with hypospadias in the offspring, suggesting a role of a higher intake of phytoestrogens (North and Golding 2000). Although several studies have demonstrated male-mediated developmental effects of environmental exposure (Davis et al. 1992; Robaire and Hales 2003), its role in the etiology of cryptorchidism and hypospadias remains unclear.

The aim of the present study was to evaluate the role of maternal and paternal occupational and dietary exposures to potential EDs in the occurrence of cryptorchidism and hypospadias.

Materials and Methods

Design and participants. We conducted a nested case–control study within a large cohort of newborn boys in the city of Rotterdam. This cohort consisted of newborns who were examined at their first visit to child health care centers (CHCs). In the Netherlands, CHCs are notified of live births within 2 days after registration in the municipal birth register. CHCs invite all parents to participate free of charge in the nationwide preventive child health care program, including growth monitoring and vaccination. From 1 October 1999 to 31 December 2001, 9,146 male births were registered, of which 8,695 boys (95%) were examined by CHC physicians at a median age of 34 days (5th and 95th percentiles, 25 and 105 days, respectively). CHC physicians ($n = 30$) were trained in a standardized genital examination by a pediatric urologist and a pediatric endocrinologist during a workshop. In addition, all CHC physicians received written instruction on the genital examination procedure. During the course of the study, new CHC physicians were instructed on the standardized examination, and every 6 months a meeting with the CHC physicians, researchers, and expert pediatricians was organized to refresh the CHC physicians on the procedures. Boys were diagnosed as cryptorchid if one or both testes were nonpalpable or if they could not be manipulated to a stable position at the bottom of the scrotum (de Muinck Keizer-Schrama 1987). Hypospadias was defined as a displacement of the urethral meatus from the tip of the glans penis to the ventral side of the phallus, scrotum, or perineum (Pierik et al. 2002). All 91 cases of cryptorchidism (1.1%) and 67 cases of hypospadias (0.8%) that were identified by CHC physicians were eligible for the case–control study, of which four cases had

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