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Platinum Priority – Editorial and Reply from Authors

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Prevalence of Hypospadias in European Countries: Is It Increasing?

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Hypospadias is one of the most common congenital anomalies, the treatment of which is both appealing and challenging for any experienced paediatric urologist. The hypospadiac malformation can be defined as a consequence of a misdevelopment of the urethral spongiosum tissue, with a defect of the ventral aspect of the prepuce and the skin of the distal shaft. Usually, an arrest in the normal embryologic correction of penile curvature is associated, although in a range of different degrees [1,2].

Many anatomic variants are present on a continuum of severity. The minor forms are characterised by an ectopic urethral meatus on the glans penis or on the coronal sulcus as well as on the subcoronal aspect of the penis; the most severe variants present a proximal urethra opening on the penoscrotal junction, scrotum, or perineum. Undescended testicles and penile–scrotal skin transposition with bifid scrotum may be frequently associated (15%), especially in the more severe anatomic degrees [2].

Hypospadias has been evaluated as occurring in approximately 1 out of 200–300 live male births in the US population [1], with small variations between Caucasian children and those of other ethnicities or races. In European countries the prevalence of the hypospadiac malformation has been assessed at up to 3 per 1000 live male births. A Dutch study published in 2002 suggested a higher hypospadias rate, up to 3.8 per 1000 live male births [3].

The recent epidemiologic survey on prevalence of hypospadias in Danish boys, carried out in a longitudinal study from 1977 to 2005 by Lund et al [4], confirmed the prevalence rate of 3.8 per 1000 male newborns. The authors conducted a survey of the incidence of hypospadias over almost 3 decades through the National Patients Registry, covering all Danish hospitals. All boys diagnosed with hypospadias in Denmark were identified, and information on maternal age and on the total number of live-born boys per year from 1977 to 2005 were recorded from the Danish Birth Registry. Among >920 000 boys born alive in the considered period of time, a total of 3490 boys with hypospadias were identified. The strength of the study results from the large examined population and from the long time interval of the observation. Interestingly, this longitudinal study covering 28 yr showed a significant increase in hypospadias prevalence, from 0.24% in 1977 to 0.52% in 2005, corresponding with an annual increase in prevalence of 2.40%. The recorded increase was documented as 2-fold during the considered period of time.

No significant difference in hypospadias prevalence was observed based on maternal age, and this datum was clearly demonstrated by the authors [4]. As criticism, no information was given about the severity or grading of the observed hypospadiac malformation in the study or about any associated urogenital abnormalities, such as cryptorchidism.

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Other recent reports suggest increasing occurrence of hypospadias in male newborns [5]. Genetic syndromes or defects involving the androgen receptors may be associated with severe hypospadias. Increases in the use of assisted reproductive techniques during the last 3 decades, such as in vitro fertilization or widespread use of progesterone/oestrogen treatments to facilitate pregnancy, have also been associated with an increased risk of hypospadias in male offspring [5]. The aetiologic factors determining the onset of hypospadias in a male foetus, however, remain unknown, and familial cases support the role of a genetic component for a significant percentage of hypospadias cases.

According to Baskin and Ebbers [2], development of the external male genitalia is a complex process during the embryonic life, involving genetic programming, cell differentiation, hormonal signalling, enzymatic activity, and tissue remodelling. Recently, attention has been paid to the role of environmental contamination as a possible explanation for the worldwide increase in the prevalence of the hypospadiac malformation as well as of other maldevelopment of male genitalia features [1,6,7]. Several chemicals such as organochlorine pesticides and phyto-oextrogens acting as endocrine disruptors may flush out and drain into fresh water and seawater all over the world and may be accumulated in the adipose tissue of large fish, birds, mammals, and eventually humans. It could be argued that environmental endocrine disruptors act at the genetic level to disrupt activating transcription factors, thus resulting in higher risk of hypospadic malformation onset [8].

Evidence shows that the prevalence of hypospadias has increased from the 1970 s up to the present in Europe [3,4] and probably in the United States [1]. We should consider that any reported rising trend may not reflect a real increase in prevalence but rather a more frequent or early diagnosis of the more distal forms of hypospadias, such as glandular or subapical forms, over time. Moreover, the increase could result from an increasing tendency to report *any* case of hypospadic defect to congenital malformations registers, including mild or minor cases that were previously neglected or disregarded. In this respect, it is probable that we will never be able to pinpoint retrospectively the true changes in prevalence of hypospadias in any Western country. The increasing prevalence of hypospadias and of other urogenital male defects over time seems to be confirmed by several prevalence studies using different data collection methods in several regions and countries [1,3]. The recent survey of the Danish group very efficiently demonstrates the upward trend [4].

Regarding possible aetiological factors of hypospadias, we should consider the concomitant increases in related abnormalities of the male genital tract, such as undescended testes, and testicular cancer as well as a demonstrated decrease in male fertility in the last few decades. These problems could be interpreted as the consequence of a single aetiologic disorder affecting the embrional development and functionality of the male reproductive system. In this respect, the effect of endocrine-disrupting chemicals and hormonal aetiological factors has recently been emphasised [1,2].

The increasing exposure to endocrine-disrupting chemicals, including xeno-oestrogens and other exogenous substances, could adversely affect health in modern society through interference with the human endocrine system and by different action modalities including mimicking agonists hormones, binding to receptor sites without activation, antagonising endogenous hormones, interfering with the synthesis of hormones, or interacting with the physiologic hormonal complement. Endocrine-disrupting chemicals that act as an antiandrogens include dioxins and furans, organochlorine pesticides, and dietary phyto-oestrogens consumed by pregnant women [7]. Vegetarian diets, high soy intake, and pesticide intake may be related to risk of hypospadias onset during the embryonal life, since the development of the male genital tract is under hormonal influence. A recent meta-analysis indicates that the risk of hypospadias resulting from parental exposure to pesticides is modestly increased [9]. Genomic variants of *ATF3*, an oestrogen-responsive gene expressed during genital development, could be implicated in the aetiology of hypospadias and has recently been reported as present in 10% of hypospadias cases [10]. Moreover, maternal age has been demonstrated clearly by Lund and co-authors [6] as not significantly increasing the risk for hypospadias onset in the newborn.

In conclusion, the biochemical, hormonal, and genetic bases of hypospadiac malformation during foetal life remains controversial and not well understood. The role of endocrine disruptors in modern societies should be better defined by epidemiologic studies in a wide range of populations. New research studies could contribute to the knowledge of the embryogenesis of this frequent urogenital malformation that has a significant impact on the clinical and scientific activities of urologists and paediatric urologists.

Conflicts of interest: The author has nothing to disclose.

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Reply from Authors re: Paolo Caione. Prevalence of Hypospadias in European Countries: Is It Increasing? Eur Urol 2009;55:1027–9

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In the editorial on our article [1], Paulo Caione considers that the reported rising trend in prevalence of hypospadias may not reflect a real increase in prevalence but rather a more frequent or early diagnosis of the more distal forms of hypospadias over time. Since our study [2] does not have information on type of hypospadias, we are not able to examine changes in prevalence of the distal forms of hypospadias over time. Speaking against increased surveillance as an explanation for the increase in incidence are findings from the US Centers for Disease Control and Prevention that the prevalence of severe cases of hypospadias has been increasing while the prevalence of mild cases has remained constant [3].

This leads to the possible explanations for an increasing trend. From an ecological point of view, as Caione highlights, the increase in prevalence of hypospadias has occurred concomitantly with an increase in the prevalence of related abnormalities in the male genital tract and a decrease in male fertility. The prevalence of asthma [4], the incidence of breast cancer [5], and the use of in vitro fertilization (IVF) [6] have also been increasing in the same time period. Some of these diseases or syndromes may also be markers of increased exposure to corticosteroids, to high levels of estrogens, or to endocrine-disrupting chemicals. Our study showed no association between maternal age and increasing hypospadias prevalence. In another study from Denmark, the overall association between use of asthma drugs during pregnancy and risk of hypospadias in the offspring was null, and the use of inhaled or systemic corticosteroids was associated with an odds ratio (OR) of 1.1 (95% CI: 0.4–2.7). That study reported an association between preeclampsia and hypospadias (OR: 2.6; 95% CI: 1.5–4.3) [7] and concluded that the etiologies of the two conditions are partly shared.

Clinically, *hypospadias* refers to a urethral meatus proximal to the normal place at the tip of the glans. Extending distally from this opening is the tissue that should have been tubularized to complete the urethral development referred as the urethral plate. The most used classification of hypospadias is based on the location of the meatus (glandular 50%, middle 30%, and posterior/scrotal 20%). Often the ventral part of the foreskin is deficient, resulting in the typical *hood* appearance that is found during the examination after birth [8]. In approximately 15% of the distal cases, a ventral curvature of the penis (chordee) is present, which also has to be addressed during surgical repair. The incidence is greater within affected families; however, most cases appear sporadically. As pointed out in the present editorial [1], other recent reports suggest an increasing incidence of hypospadias in male newborns [8]. Genetic syndromes or defects

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