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“Can We Prevent Hypospadias?”

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Hypospadias is one of the most common birth defects (1). The etiology remains unknown, except for in a small number of cases where it can be attributed to specific defects in either androgen metabolism or the androgen receptor (2,3). The incidence is approximately 1 in 250 newborn males, and according to studies from the Center for Disease Control, the number of newborn males born with hypospadias has doubled over the last three decades (4). Hypospadias can be defined as an anatomical defect in the formation of the urethra on the ventral aspect of the penis, an arrest in the development of the normal circumferential prepuce, and varying degrees of penile curvature. Hypospadias can be quite mild with the urethral opening on the proximal aspect of the glans, quite severe, where there is penile scrotal transposition and the urethra exits within the scrotum or the perineum or gradations of severity between these two extremes.

A working hypothesis to explain the etiology of hypospadias as well as the increase in hypospadias is maternal environmental exposure or endocrine disruptors. A myriad of epidemiologic papers have been published on the incidence of hypospadias related to environmental exposure. An extensive review published in 2001 in *Environmental Health Perspectives* summarizes these findings (5). To study the effects of endocrine disruptors on the developing urethra, an animal model has been validated using CD1 mice (6). The critical time for urethral development is between embryonic days 12 and 17, out of a total gestation of 21 days in these animals. Exposing pregnant dames to physiologic doses of endocrine disruptors and analyzing the urethral anatomy via histology, three dimensional computer reconstruction, and plastic resin cast has shown the utility of this technique. It has now been confirmed that estrogens such as 17 β estradiol, pesticides such as vinclozolin, pharmaceutical products such as the antihistamine loratadine, and the flame retardant, benzophenone-2, can all cause hypospadias in this animal model at physiologic doses (7-9).

Further work in humans has analyzed genetic markers using microarray analysis of excess skin procured at the time of surgery for correction of hypospadias compared to skin from age matched children undergoing elective circumcision. A number of genes have been shown to be associated with an increased risk of hypospadias based on the array analysis with confirmation using both protein expression within the skin and mRNA expression. These include activating transcription factor 3, zinc finger protein 36, connective tissue growth factor, and CYR 61 (10,11).

Presently, our working hypothesis to explain both the baseline incidence of hypospadias and the increase that has been noted in industrialized nations is a **genetic susceptibility combined with environmental exposure** during the critical time of embryonic urethral development. To

prevent hypospadias, we plan to identify patients with a genetic susceptibility to hypospadias. This group especially should take ever precaution to avoid exposure to endocrine disruptors that cause hypospadias via maternal exposure in the first trimester of pregnancy.

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