

# Evaluation of Risk Factors in Children with Hypospadias

## Hipospadiaslı Çocuklarda Risk Faktörlerinin Değerlendirilmesi

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### Abstract

**Objective:** Hypospadias is one of the most common congenital defects in boys. Multifactorial factors such as genetic predisposition and environmental factors play a role in the etiology of hypospadias. In this study, we investigated the risk factors of patients diagnosed with hypospadias.

**Materials and Methods:** Thirty-six patients who applied to the pediatric endocrinology and urology outpatient clinics with the diagnosis of hypospadias were evaluated retrospectively. Risk factors were evaluated by recording the parental ages, exposure to environmental factors, the maternal BMI, history of pregnancy, drug use, and the father's fertility status.

**Results:** The mean age of the patients was 3.5 ± 2 years. The patients had anterior (n:27 : 75%), middle (midshaft) (n:8 ; 22.2%), and posterior (n:1 ; 2.8%) hypospadias. The mean body mass index (BMI) of the mothers was 24 ± 4.1 kg/m<sup>2</sup>. Eight (22.2%) mothers were overweight and six (16.6%) mothers were obese. There was a history of hypospadias in the family of 4 (11%) patients.

**Conclusion:** Although combinations of environmental and genetic factors play a role in the etiology of hypospadias, many unexplained factors are responsible for this disease.

**Keywords:** hypospadias, risk factors, etiology, family history

### Öz

**Amaç:** Hipospadias, erkek çocuklarda en sık görülen doğumsal kusurlardan biridir. Genetik yatkınlık ve çevresel etkenler gibi multifaktöriyel etkenler hipospadias etyolojisinde rol oynamaktadır. Biz bu çalışmada hipospadias tanısı konulan hastaların risk faktörlerini araştırdık.

**Gereçler ve Yöntemler:** Çocuk endokrinoloji ve üroloji polikliniğine hipospadias tanısı ile başvuran 36 hasta retrospektif olarak değerlendirildi. Ebeveyn yaşları, çevresel etkenlere maruz kalma, annenin vücut kitle endeksi (VKİ), gebelik öyküsü, ilaç kullanımı, babanın fertilitate durumu kayıt altına alınarak risk faktörleri değerlendirildi.

**Bulgular:** Hastaların ortalama yaşı 3,5 ± 2 yıl idi. 27 (%75) hastanın anterior, 8 (%22,2) hastanın orta, 1 (%2,8) hastanın ise posterior hipospadiası mevcuttu. Annelerin ortalama VKİ 24± 4,1 olup, 8 (%22,2)'i fazla kilolu, 6 (%16,6)'sı obez idi. Hastaların 4 (%11)'ünün ailesinde hipospadias öyküsü mevcuttu.

**Sonuç:** Hipospadias etyolojisinde çevresel ve genetik etkenlerin kombinasyonları rol oynamakla birlikte henüz açıklanamamış birçok faktör de bu hastalıktan sorumludur.

**Anahtar kelimeler:** hipospadias, risk faktörleri, etiyoloji, aile öyküsü

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## Introduction

Hypospadias is a congenital anomaly due to inadequate virilization of the genital tubercle, characterized by insufficient tissue formation in the ventral aspect of the penis and urethra, and in which the urethral meatus opens more proximally than it should be in the ventral aspect of the penis [1]. It is a common disease affecting one in every 200 to 300 newborn males [2]. The total prevalence of hypospadias in Europe is 18.6 new cases per 10,000 births [3]. The most commonly used classification is formulated as anterior or distal hypospadias, midshaft, middle or penile hypospadias, and posterior or proximal hypospadias, depending on the position of the external meatus [4]. It has been suggested that genetic factors, maternal-placental factors, insufficient hormonal stimulation and environmental factors are involved in the etiology of hypospadias. Therefore, hypospadias etiology is thought to be multifactorial [5–7]. Studies conducted to evaluate the etiology of hypospadias have focused on different components with resultant lots of confusing information [8]. The aim of our study is to contribute to the etiology of hypospadias and to evaluate the risk factors associated with it.

## Materials and Methods

Thirty-six patients who applied to pediatric endocrinology and urology outpatient clinics due to hypospadias were included in our study. Children diagnosed with hypospadias were classified according to the location of the external meatus. Birth weights, presence of hypospadias in other siblings and father, obesity status of the mother, medications used before and during pregnancy, occupational exposure to various agents, use of assisted reproductive techniques, the course of pregnancy and the father’s spermatogenesis status were recorded and evaluated retrospectively. Patients with additional congenital anomalies were excluded from the study. Written consent was obtained from the parents of the patients for the publication of the study data. Ethics committee approval was not obtained due to the retrospective nature of the study.

## Results

The mean age of 36 patients with hypospadias included in the study was  $3.5 \pm 2$  years. The patients had anterior (n:27; 75%), middle (n: 8 ; 22.2%), and posterior hypospadias (n:1 ; 2.8%). The mean maternal, and paternal ages of the patients were  $23.9 \pm 3.6$ , and  $25.7 \pm 4.1$  years, respectively. The mean BMI of the mothers was  $24 \pm 4.1$  kg/m<sup>2</sup>. Eight (22.2%) mothers were overweight and six (16.6%) mothers were obese. There was a history of hypospadias in the family of 4 (11%) patients including 3 patients with anterior and 1 with middle hypospadias. Two (5.5%) patients had been delivered as low birth weight newborn. Oligospermia was present in the father’s spermogram of 3 children. None of the parents had a history of occupational exposure. The data of the patients and their parents are given in **Table 1**.

## Discussion

Although hypospadias has a multifactorial etiology, there are many studies showing that heredity is an important factor in the etiology [9,10]. It has been shown that 7% of the children with hypospadias have a history of hypospadias in their relatives [10]. The chance that a brother of an affected boy will also have hypospadias is 9–17% [9,11]. Anterior and middle forms are more common in children with family history of hypospadias than posterior forms [10,12]. In our study, family history of hypospadias was reported for 4 (11%) children with hypospadias including 3 cases with anterior, and one patient with middle hypospadias. It has been proven by histochemical studies that androgen and estrogen receptors are intensely expressed on the urethral plate during normal fetal development [13]. Male sexual differentiation is generally dependent on testosterone, its metabolite dihydrotestosterone, and the expression of androgen receptors by target cells and the balance between androgens and estrogens. Disruption of this balance by endogenous or exogenous factors may cause hypospadias [14]. The use of oral contraceptives after conception has increased the risk of hypospadias (especially middle and posterior hypospadias). However, the use of oral

**Table 1.** Risk factors for hypospadias associated with the patient and his parents

| Parameters   | N                     |
|--|-----------------------|
| Number of patients                                   | 36                    |
| Patient’s age (years)(mean .± SD)                    | 3.5 ± 2               |
| Paternal age (years)(mean .± SD)                     | 25.7 ± 4.1            |
| Maternal age (years)(mean .± SD)                     | 23.9 ± 3.6            |
| Maternal BMI kg/m <sup>2</sup> (mean .± SD)          | 24 ± 4.1              |
| Obese mothers, n (%)                                 | 6 (16.6 %) 8 (22.2 %) |
| Overweight mothers, n (%)                            |                       |
| Family history n (%)                                 | 4 (11%)               |
| Oral contraceptive use after conception n (%)        | 1 (2.7%)              |
| Low birth weight (n) (%)                             | 2 (5.5%)              |
| Parents using assisted reproductive techniques n (%) | 3 (8.3%)              |
| Number (%) of subfebrile fathers                     | 3 (8.3%)              |

contraceptives before pregnancy has not been found to be associated with hypospadias [12,15,16]. The mother of one of the patients in our study used oral contraceptives for 2 months after conception. This patient had posterior hypospadias.

Assisted reproductive technologies are widely used for couples who apply to health institutions for infertility. Hormonal treatment is often applied during these methods. Many studies have shown that the use of assisted reproductive techniques increases the risk of hypospadias [8,17]. The risk is increased frequently after the intracytoplasmic sperm injection (ICSI) method [18,19]. In our study, assisted reproduction techniques with ICSI method were applied to the parents of 3 (8.3%) patients diagnosed with hypospadias.

It is known that some maternal factors are effective in the development of hypospadias. It has been shown that the presence of obesity in the mother is associated with hypospadias [20]. Endogenous levels of free estradiol increase with increasing BMI which may play a role in the development of hypospadias [21]. Many studies have shown that the risk of hypospadias increases in children of overweight or obese mothers [22,23]. However, Rankin et al. showed that obesity was not associated with hypospadias [24]. In our study, the mothers of 8 (22.2%) patients were overweight, and the mothers of 6 (16.6%) patients were obese.

It has been found that the risk of hypospadias is higher in children with low birth weight [12,15]. It is known that human chorionic gonadotropin (hCG) secreted from the placenta in the fetus stimulates fetal testicular steroidogenesis. Placental insufficiency may result in inadequate provision of fetal hCG and fetal nutrients, possibly explaining the association between hypospadias and low birth weight [25]. In addition, several studies have shown that preterm birth may be associated with late placental dysfunction and cause hypospadias [26,27]. In 2 (5.5%) of the patients in our study, history of low birth weight was elicited, and none of the mothers of the patients had a history of premature delivery.

Lower sperm count, sperm motility and higher abnormal sperm morphology were found in fathers of children with hypospadias [28]. It is stated in the testicular dysgenesis syndrome (TDS) hypothesis that hypospadias and male subfertility may share the same genetic and environmental factors [29]. In this way, subfertile fathers may transmit a certain predisposition to their children. Oligospermia was present in the fathers of our 3 (8.3%) patients.

When occupational exposures are evaluated, although there are conflicting results in terms of the relationship between exposure to pesticides and hypospadias, it has been shown that fathers exposed to pesticides are more likely to have children with hypospadias [30,31]. There was no occupational pesticide exposure in the parents of any of our patients.

Our study has some limitations. Since it is a retrospective study, we could not obtain data about some etiologic factors responsible for the development of hypospadias.

## Conclusion

As a result, there is no single factor responsible for the development of hypospadias. The combination of both genetic and environmental factors play a role in etiology. However, since

the development of the disease is multifactorial, there are many factors that have not yet been revealed. Avoiding proven risk factors can reduce the incidence of the disease. We think that prospective studies with greater number of patients may help to find the factors responsible for the development of the disease.

**Ethics Committee Approval:** Ethics committee approval was not obtained due to the retrospective nature of the study. Informed consent forms were obtained.

**Informed Consent:** An informed consent was obtained from the parents of all patients.

**Publication:** The results of the study were not published in full or in part in form of abstracts.

**Peer-review:** Externally peer-reviewed.

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

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