Original Article

Maternal and Fetal Risk Factors Associated with Hypospadias in a Sample of Iraqi Boys

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Abstract

Background: Hypospadias is one of the most common congenital anomalies among boys. The exact causes of this anomaly are not clearly defined yet. However, many of the risk factors have been identified in different ethnic groups. **Objective:** The objectives of this study are to evaluate the maternal- and fetal-related risk factors for hypospadias in a sample of Iraqi patients. **Materials and Methods:** This case–control study included 42 boys with hypospadias cases and other 42 age-matched boys free from any genital anomalies as a control group. Maternal data, including age, parity, body mass index, hypertension, diabetes mellitus (DM), the use of assisted reproduction techniques (ART), level of education, consanguinity, and residence; and infant-related factors. Logistic regression analysis was used to predict the risk of each variable through the calculation of odds ratio (OR) and its corresponding 95% of confidence interval (CI). **Results:** Three maternal factors were found to be associated significantly with increased risk of hypospadias. These were maternal age >33 years (OR = 3.08, 95% CI = 1.02–9.26, $P = 0.045$), consanguineous marriage (OR = 3.0, 95% CI = 1.02–8.8, $P = 0.045$), and rural residence (OR = 2.64, 95% CI = 1.04–6.73, $P = 0.041$). Hypertension, DM, and using ART were more frequent among mothers of cases than controls; however, the differences were not significant. For fetal-related factors, infants with low-birth weight (LBW) were more frequent among cases than controls (40.48% vs. 19.05%), with a statistically significant difference (OR = 2.89, 95% CI = 1.08–7.75, $P = 0.035$). Of note, twins were more frequent among cases than controls; however, this difference was not statistically significant ($P = 0.074$). **Conclusions:** These results highly suggest the critical role of advanced maternal age, consanguinity, rural residence, and infant LBW, as predisposing factors for the occurrence of hypospadias among Iraqi boys.

Keywords: Fetal risk factors, hypospadias, maternal risk factors

Introduction

Hypospadias is a congenital malformation in which the urethral opening occurs on the ventral side of the penis, as a result of abnormal urethral closure at approximately 8–14 weeks gestation. It is the second-most common congenital anomaly in boys,[1] affecting about 30–40 children in each 10,000 life birth.[2] However, the incidence of this anomaly varies widely among different ethnic populations.[3] Although most cases of hypospadias can be surgically corrected, a wide range of medical, social, and sexual problems may persist after surgery.[4]

Hypospadias is often classified into anterior hypospadias: where the urethral opening is slightly displaced but still in the glandular or subcoronal region; middle hypospadias: where the urethra opens into the ventral surface of the penis; and posterior hypospadias: where the urethral opening is located in the penoscrotal junction, scrotum, or perineum.[5]

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The etiology of hypospadias is largely unknown. Some hypospadias cases are monogenetic in origin, but the vast majority of cases seem to be multifactorial with many genetic and environmental factors playing a role. Insufficient testosterone, dihydrotestosterone, and/or human chorionic gonadotropin (HCG) or androgen receptor defect may be responsible for hypospadias in some cases.[6] Several environmental exposures and maternal factors have been outlined. Of these, infant low-birth weight (LBW), maternal hypertension, preeclampsia, and maternal intrauterine diethylstilbestrol exposure were consistently found to have a significant association.[7]

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To the best of our knowledge, there are no previous studies in Iraq, which addressed the risk factors for hypospadias. Thus, this study aimed to investigate some maternal and fetal risk factors that predispose for hypospadias among Iraqi boys.

Materials and Methods

This case–control study was conducted during the period from April 2017 to August 2018 at Al-Imamain Al-Kadhemain Medical City/tertiary center in Baghdad, Iraq. The eligible cases were 42 boys aged 2–7 years with hypospadias as confirmed by an urologist without other genital malformations.

Those boys were admitted to the urosurgery ward at the medical city for surgical repair. Other 42 age-matched boys without hypospadias or other genital anomalies were selected from those who were hospitalized in the pediatric department of the same hospital for other reasons.

Mothers of participants were invited to participate in this study. A detailed questionnaire was prepared to collect data from the mother of cases and controls. However, some data were collected from hospital records or extracted through simple calculation of time periods for same data. Maternal data refer to boys' mother at the time of delivery of the affected or control boys. These data included maternal age, parity, maternal body mass index (BMI), blood pressure, diabetes mellitus (DM), level of education, consanguineous marriage, residence, and the usage of assisted reproduction techniques (ART) for that pregnancy. Data related to boys included infant weight at birth, gestational age, and outcome of the delivery (singleton or twin).

Statistical analysis

The statistical calculations were performed using the Statistical Package for the Social Sciences software version 20 (SPSS, IBM Company, Chicago, USA). Bivariate logistic regression analysis was used to calculate the predicted effect of each variable on the incidence of hypospadias. Odds ratios (OR) with 95% of confidence interval (CI) were calculated. The statistical tests were two sided, and a value of $P \leq 0.05$ was considered as statistically significant.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patient s verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee.

Results

Table 1 shows maternal-related risk factors for hypospadias. Of the eight studied factors, only three were found to be significantly associated with the incidence of hypospadias. The first factor of these was increased mother age. There were 15 (35.71%) mothers whose age ≥33 among cases compared to 7 (16.67%) among controls. Logistic regression test revealed a statistically significant difference between the two groups (OR = 3.08, 95% CI = 1.02–9.26, $P = 0.045$). The second factor was consanguinity. One-third of women among cases (33.33%) have consanguineous marriage, compared to only 14.29% among controls (OR = 3.0, 95% CI = 1.02–8.8, $P = 0.045$). Finally, the rural dwelling of boys' mother significantly increased the risk of hypospadias. The rural residence in cases and controls was 19 (45.24%) and 10 (23.81%), respectively (OR = 2.64, 95% CI = 1.04–6.73, $P = 0.041$).

Factors such as hypertension, DM, and ART were more frequent among mothers of cases than controls; however, the differences did not reach significant levels. On the other hand, BMI, parity, and educational level seem to have no influence on hypospadias.

Table 2 summarizes fetal-related factors of hypospadias which included in this study. Among the three factors, only infant weight at birth was significantly associated with the incidence of hypospadias. Infants with LBW were more frequent among cases than controls (40.48% vs. 19.05%), with a statistically significant difference (OR = 2.89, 95% CI = 1.08–7.75, $P = 0.035$). Of note, the frequency of twin among cases was >2-fold than that among controls; however, this difference was not statistically significant ($P = 0.074$).

Discussion

The current study aimed to determine some of the maternal- and fetal-related factors that may associate with the hypospadias. Advanced maternal age was the most important maternal factors that had a significant association with increased this anomaly in the current study (OR = 3.08, 95% CI = 1.02–9.26, $P = 0.045$). This implies that offspring from the mother of >33 years old will have about three-fold increase risk of hypospadias compared with those born from younger mothers. In agreement with this result is a large population-based case–control study including 2155 American boys with hypospadias and 10,775 controls. The risk of hypospadias in this study increased with increasing age, ranging from OR = 1.12 for infants from the mother of 20–24 years old to 1.7 for those from the mother of >40 years compared with infants from the mother of <20 years old as reference.[8] More recently, Jorg *et al*.[9] studied the effect of maternal age on the incidence of hypospadias among 128 boys in Puerto Rico. The authors reported that mothers of 40 years or older will have a 3.89-fold greater risk to have a child with hypospadias as compared with the younger mother.

It is generally accepted that children from older women are at high risk of genetic defects such as esophageal defects, cardiac malformations, urethral abnormalities, and hypospadias.[10] Accordingly, the significant association between advanced age and hypospadias may be explained through the underlying genetic defects that associate with aging. Another explanation could be maternal subfertility because it is usually accompanied by some hormonal disturbance.[11] Subfertile women have

Table 1: Maternal-related risk factors for hypospadias

Variables	Cases (*n*=42), *n* (%)	Controls (*n*=42), *n* (%)	*P*	OR (95% CI)
Age (years)				
≤18-24	16 (38.1)	23 (54.76)	0.132	1.0 reference
26-32	11 (26.19)	12 (28.57)	0.602	1.32 (0.47-3.72)
≥33	15 (35.71)	7 (16.67)	0.045	3.08 (1.02-9.26)
Parity				
1-2	27 (64.29)	24 (57.14)	0.503	1.0 reference
≥3	15 (35.71)	18 (42.86)		0.741 (0.31-1.78)
BMI (kg/m^2)				
≤19-24	14 (33.33)	11 (26.19)	0.475	1.0 reference
≥26	28 (66.67)	31 (73.81)		0.71 (0.28-1.82)
Hypertension				
No	22 (52.38)	29 (69.05)	0.12	1.0 reference
Yes	20 (47.62)	13 (30.95)		2.03 (0.83-4.95)
DM				
No	35 (83.33)	37 (88.1)	0.535	1.0 reference
Yes	7 (16.67)	5 (11.9)		1.48 (0.43-5.1)
Using ART				
No	38 (90.48)	41 (97.62)	0.20	1.0 reference
Yes	4 (9.52)	1 (2.38)		4.32 (0.46-40.35)
Education (years)				
≤6	16 (38.1)	13 (30.95)	0.544	1.0 reference
7-12	19 (45.24)	24 (57.14)	0.361	0.64 (0.25-1.66)
≥13	7 (16.67)	5 (11.9)	0.853	1.14 (0.29-4.44)
Consanguinity				
No	28 (66.67)	36 (85.71)	0.045	1.0 reference
Yes	14 (33.33)	6 (14.29)		3.0 (1.02-8.8)
Residence				
Rural	23 (54.76)	32 (76.19)	0.041	1.0 reference
Urban	19 (45.24)	10 (23.81)		2.64 (1.04-6.73)

BMI: Body mass index, ART: Assisted reproduction technique, OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus

Table 2: Fetal-related risk factors for hypospadias

Variables	Cases (*n*=42), *n* (%)	Controls (*n*=42), *n* (%)	*P*	OR (95% CI)
Weight at birth (g)				
≥2500	25 (59.52)	34 (80.95)	0.035	1.0 reference
<2500	17 (40.48)	8 (19.05)		2.89 (1.08-7.75)
Gestational age (weeks)				
≥37	27 (64.29)	33 (78.57)	0.151	1.0 reference
<37	15 (35.71)	9 (21.43)		2.04 (0.77-5.38)
Delivery outcome				
Singleton	33 (78.57)	39 (92.86)	0.074	1.0 reference
Twin	9 (21.43)	3 (71.43)		3.55 (0.87-14.18)

OR: Odds ratio, CI: Confidence interval

been identified to be associated with a delay in their first pregnancy (older ages). Thus, subfertility may be the underlying risk factor of hypospadias in infants from mother with advanced age.

One of the most interesting results in the current study was the significant effect consanguinity on hypospadias. Boys from mothers having this type of marriage are at three-fold greater risk to develop hypospadias than the off-springs of mothers with distant marriage. There are no available studies which directly addressed this risk factor. Two recent Indian studies in this regard reported zero number of consanguineous marriage in both affected and healthy control boys.[12,13] However, this risk factor can be viewed from the familial clustering point. According to the Danish health registers, Schnack *et al*.[14] identified 5380 boys with hypospadias during the period from 1973 to 2005. Using binomial log-linear regression, the authors estimated recurrence risk ratios of hypospadias for the first, second, and third-degree relatives of hypospadias case to be 11.6, 3.27, and 1.33, respectively. This linear relationship

between the degree of kinship between the mother and the father and the risk of hypospadias implies the presence of genetic loci that characterize certain families and are associated with a high risk of hypospadias and/or other congenital abnormalities.

The other maternal-related factors which were significantly associated with increased hypospadias are the rural residency. In a recent case–control study involving 440 Chinese boys, Huang *et al*.[15] reported rural residence as a main risk factor predisposing for hypospadias. The most plausible explanation for these finding lies in the fact that mothers in the rural areas are usually engaged in agricultural work which associates with increased exposure to pesticides. Occupational pesticide exposure was significantly associated with hypospadias in a hospital-based case–control study in China.[16] Although there is no convenience cause-effect between pesticide exposure and hypospadias, it was reported that maternal exposure during early gestation could alter the normal fetal environment and disrupt embryogenesis.[17]

BMI, parity, hypertension, DM, and using of ART were reported in different previous studies to have a significant association with the incidence of hypospadias.[3,18-21] Similarly, in the current study, all these risk factors were more frequent among cases' mothers than controls; however, the differences were not significant may due to the relatively small number of cases in the current study or due to ethnic variation.

LBW of the infant was the most obvious fetal-related risk factor for hypospadias in the current study. Infants whose weight >2500 g at birth will be at 2.89-fold more risk of hypospadias compared with those of normal weight. In agreement with current results is a recent study in Denmark which investigated 223 cases of infants with hypospadias. The study revealed three times higher occurrence of this anomaly in very LBW infants compared with those of normal weight.[22] This association is mainly attributed to hormonal reasons. LBW and preterm birth are found to be associated with disturbance in placental function in early pregnancy. As placenta is the main source of hormones (especially HCG) during this period, abnormalities in these hormone negatively affect the fetal differentiation and development.[23] For example, HCG was reported to stimulate the growing of fetal testis before the fetus's own pituitary gland axis is established.[24] Thus, reduced levels of HCG may cause improper closure of urethra with eventual hypospadias.

Although twin delivery did not significantly associated with hypospadias in the current study, it really had such association in many other studies.[25,26] This variation in the results is mainly attributed to the small number of cases in the current study compared with over 300 cases employed in these studies. It is believed that the presence of more than one fetus in the uterus will restrict the fetal growth which results in arrested development of the urethra and urethral surface of the penis. Accordingly, the urethral opening is displaced to occur in anywhere along the shaft, within the scrotum, or in the perineum.[13]

Conclusion

These data indicate the importance of advanced maternal age, consanguineous marriage, rural residence, and LBW of the infants as risks factors for hypospadias. More study with larger cases and including other risk factors are needed to fully clarify the causes of hypospadias.

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Conflicts of interest

There are no conflicts of interest.

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