Original Article

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Prevalence and Risk Factors of Hypospadias in a Private Hospital in Northeast Iran

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Abstract

Objective: The aim of this study was to determine prevalence and risk factors of hypospadias in newborn infants of a private hospital in Mashhad city located in northeast Iran.

Methods: All live birth deliveries in maternity hospital were enrolled from Oct 2006 to Sep 2008. All hypospadias cases were compared with the next male live births for possible risk factors. This study included only solitary hypospadias cases, those associated with other anomalies were excluded. Both parents were asked to fill out the same written questionnaires seperately. Data was analyzed by using SPSS.

Findings: During two years 6149 babies were born in our hospital; 25 cases (0.4%, 4 in1000 live births) of hypospadias were identified. Hypospadias occurred in 0.76% of male deliveries. Most cases of hypospadias were born in summer and winter was the season which least number. Positive family history (P=0.04) was regarded as a potential risk factor that was present in 44% of cases in hypospadias group. Iron supplement consumption in first trimester of pregnancy in control group was significantly more than in hypospadias group (P=0.001) and also usage of folic acid in control group before and in first trimester of pregnancy was taken more by mother in control group than in hypospadias group (P=0.049 and P=0.001 respectively).

Conclusion: Prevalence in this population was intermediate (4 in 1000 live births). Summer was the most epidemiology factor for occurring of hypospadias probably due to conception in cold season. Iron and folic acid supplementation may have preventive effect in hypospadias.

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Key Words: Hypospadias; Prevalence; Risk factors; Newborn

Introduction

Hypospadias is the most common congenital anomaly of the penis. The condition is characterized by a urethral meatus that is ectopically located proximal to the normal location on the ventral aspect of the penis. In severe cases, the urethral meatus opens onto the scrotum or perineum. Hypospadias is the second most common genital abnormality (after cryptorchidism) in male newborns with an incidence in different series ranging between 0.3%

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and 0.8%[2]. It occurs less frequently (0.4%) in blacks than in whites (0.6%). Hypospadias is more common in Caucasians, least common in Hispanics and intermediate among African-Americans[1,3]. Approximately 87% of cases are glandular or coronal, 10% penile and 3% penoscrotal or perineal[2]. Other anomalies that may accompany hypospadias include meatal stenosis, hydrocele, cryptor-chidism (in 8% to 10% of cases). Eight percent of patients with hypospadias have a similarly affected brother or father, this figure reaches 16.7% for individuals with penoscrotal or perineal hypospadias[1,2]. This family tendency is thought to result from a polygenic mode of inheritance. Mild hypospadias (glandular to penile) occurs without other genital abnormalities or a dysmorphic feature is very unlikely to be associated with an identifiable endocrinopathy, intersex problem or chromo-somal abnormality. Severe hypopadias (penoscrotal or prineal) occurs with approxim-ately a 15% risk of such problems[2]. The cause of hypospadias in at least some cases is a partial deficiency in testosterone production to DHT (5-reductase deficiency) or in the function of the androgen receptor protein. In a few cases maternal exposure to progestin between 8 and 14 weeks gestation has been the cause of hypospadias. Because of wide distribution of hypospadias the aim of this study was to determine frequency distribution and risk factors of hypospadias in newborn infants of a private hospital in Mashhad city located in northeast Iran.

Subjects and Methods

The population for this descriptive study was collected from Sina Hospital, a private maternity hospital. The study protocol was approved by the research office, and the parents of subjects had giaven informed consent before the study. The study was done during October 2006 to September 2008. This study included only hypospadias cases; those subjects described as epispadias or ambiguous genitalia without further description were excluded from study. Infants with recognized single gene disorders or chromosomal abnormalities were also excluded. Parents of cases were asked to fill out the same written questionnaire seperately. The questionnaire for each parent contained questions about age, education, prenatal exposure to diethylstilbestrol (DES), medical history, life style, and occupational exposure to various agents. Information was requested for three months before conception based on last menstruation and in first the trimester of pregnancy. Additionally, mothers were questioned about oral contraceptive use, assisted reproductive techniques, and the course of pregnancy. Finally, the mothers were asked to provide information on their other children and pregnancies. Educational level was defined as low (elementary school or lower vocational education), intermediate (intermediate secondary school or intermediate vocational education), and high (higher secondary school, higher vocational education or university). In this study we compared the environmental risk factors among hypospadias babies with the next male delivery as control group. The same questionnaire was recorded for the two groups. The mothers who delivered for a second time during two years of the study were estimated as one case.

Statistical analysis: Data of the questionnaires was analyzed by using SPSS. To obtain frequency distribution we used frequencies statistics. Also, frequency of risk factors was determined by descriptive and frequencies statistics. All potential risk factors, with exception of birth weight and maternal age, were dichotomous (yes vs. no). For control of confounding variables logistic regression was used and odds ratio (OR) and confidence interval (CI) were determined for potential risk factors.

Findings

From October 2006 to September 2008 totally 6149 babies (3260 = 53% males) were born in our hospital among which 25 (0.4%) cases of hypospadias were identified. Incidence of hypospadias in this study was 4 per 1000 live births and 0.76% of males had hypospadias of which 24 cases were glandular and one case was perineal. We did not find any significant difference

Table 1: Characteristics of parents and newborns in the two groups

Variable	Case [Mean (SD)] (n=25)	Control [Mean (SD)] (n=25)	*P*-value
Birth weight (gr)	2910.63 (872)	3101.90 (0.93)	0.3
Gestational age (wk)	37.43 (3.16)	38.96 (2.25)	0.04
Maternal age (yr)	29.58 (5.38)	28.62 (5.08)	0.5
Paternal age (yr)	35.00 (6.50)	32.28 (5.73)	0.1

SD: Standard Deviation

between the two groups in birth weight (*P*=0.32), or maternal and paternal age (*P*=0.49, *P*=0.10 respectively), but there was significant difference in gestational age (*P*=0.04) (Table 1).

Forty-four percent of hypospadias cases were born of primipara mothers and 12% were products of twin or triplet pregnancies. 48% were born in summer, 24% in spring, 20% in fall and 8% in winter. Twelve of 879 (1.37%) of males were born in summer, 6 of 801 (0.75%) in spring, 0.65% and 0.25% in fall and winter respectively. In 44% of hypospadias cases it was associated with positive family history (*P*=0.04) as a potential risk factor (Table 2). Low birth weight also was a risk factor (*P*=0.001).

There was no significant difference between the two groups in other potential risk factors. Iron supplementation in the first trimester of pregnancy in control group was significantly more than in hypospadias group (*P*=0.001) and consumption of folic acid in control group before and in the first trimester of pregnancy also was more than in hypospadias group (*P*=0.049 and *P*=0.001 respectively) (Table 3). Results show that among all variables consumption of iron with 95% CI: 0.01 to 0.91 and folic acid with 95% CI: 0 to 0.18 in first trimester of pregnancy was preventive factor of occurrence for hypospadias. Odds ratio for iron was 0.1 and for folic acid 0.003.

None of parents were smoker. In hypospadias group one father had contact with pesticide and the other one was leather maker.

Discussion

The incidence of hypospadias has been reported from 0.4 to 8.2 in 1000 live births [1]. There is geographical variation in the birth prevalence of hypospadias. It occurs from as low as 1 in 4000 to as high as 1 in 250 boys [3,4]. The milder forms of hypospadias which are not clinically significant might be missed and affect the incidence statistics but in this study we determined its prevalence at

Table 2: Association between hypospadias and potential risk factors

		Case (n=25) No (%)	Control (n=25) No (%)	*P*-value
Low birth weight (<2500 grams)		5 (20)	3 (9.7)	0.001
Gravida [Mean (SD)]		2.04 (1.35)	1.56 (0.65)	0.1
Primipara		11 (44)	13 (52)	0.8
Maternal age at time of delivery ≥35 years		3 (12)	4 (16.7)	0.5
Paternal age at time of delivery ≥35 years		11 (44)	12 (48)	0.8
Education level of mother	**Low**	1 (7.1)	2 (22.2)	
	Intermediate	9 (64.3)	4 (44.4)	0.8
	High	4 (28.6)	3 (33.3)	
Education level of father	**Low**	2 (14.3)	1 (11.1)	
	Intermediate	9 (64.3)	4 (44.4)	0.7
	High	8 (57.1)	4 (44.4)	
Positive relativity in parents		9 (36)	6 (18.8)	0.1
Positive family history		11 (44)	5 (15.6)	0.04
Hypospadias in father		3 (11)	0	0.1

Table 3: Medication in mothers

Risk factor	Case (n=25) No (%)	Control (n=25) No (%)	*P*-value
Fertility treatments	1 (4)	4 (12.5)	0.3
Mother used iron supplements			
Before pregnancy	5 (20)	11 (34.4)	0.2
In the first trimester of pregnancy	8 (32)	24 (75)	0.001
Mother used folic acid			
Before pregnancy	3 (12)	11 (34.4)	0.049
In the first trimester of pregnancy	13 (52)	31 (96.9)	0.0001
Mother used LD*(%)	2 (6.3)	0	0.3

*LD: low dose contraceptive

birth so that no cases could be missed.

Incidence of hypospadias in this study was 4 in 1000 live births. It occurred in 0.76% of male deliveries, so distribution is intermediate and similar to that in African-Americans [1]. Incidence of hypospadias has been increased in European and American countries so that it has been doubled from 1970 to 1993[1]. It has been explained by increase in the preterm or low birth weight deliveries and fetal contact with progesterone or estrogen, medical care, improved recognition or better reporting.

Although hypospadias happens with unknown or multifactorial reasons but in 31 to 36% the reason is known and some risk factors can be associated with its incidence [1-6]. Drugs such as diethylstilbestrol, progesterone or estrogen, herbal diet, hematenic use before or in the first trimester of pregnancy, anticonvulsant drugs or contact with chemical agents during pregnancy increase the risk of hypospedias [7-10]. Inheritance gene is a main feature for hypospedias, as studies indicated there are family positive backgrounds in 20% of neonates. There is also about a 7% family risk of recurrence [1]. Indeed it has been measured that offspring of hypospadias cases has an increased chance of 14% to be affected by hypospadias. Asklund study showed that fathers of boys with hypospadias have increased frequency of hypospadias [11]. In Stokowski study [12] 7-9% of fathers with hypospadiasic son had also hypospadias. In present study 11% of fathers had hypospadias too. We also found that positive family history of hypospadias was significant in affected babies, as 44% of neonates had positive background in family. Since hypospadias is an anomaly of external genitalia and in some cultures like Iran, the issue often remains hidden, so the answer to this question, namely family history of anomaly in affected persons, may affect the accuracy of family history. Therefore family history may be regarded as a factor of limitation in our study. In spite of this cultural characteristic, reported positive family occurrence of 44% is noticeable in this study.

Seasonal pattern of occurrence as an environmental factor in this study was that about half of the affected babies were born in summer and least figure of occurrence was recorded in winter. This is the first report on seasonal pattern of hypospadias occurrence. The conception age and first trimester of pregnancy in these births were in winter and must be attributed to cold environment as a cause of hypospadias.

Medication of folic acid before and after the first trimester was seen more in control group. Therefore, like in other congenital anomalies, folic acid may have preventive effect in this congenital anomaly too. Iron supplementation in the first trimester was also higher in the control group. Iron supplementation immediately prior to conception or during the first trimester of pregnancy was found to increase the risk of hypospadias [1]. In this study iron supplementation was not only no risk factor for hypospadias but also appears as if it had a preventive effect, probably as a result of treatment of anemia in these mothers. Although this is the first finding in our experience, further studies with more sample size are needed to document the effect of iron. On the other hand, as we extracted this finding retrospectively from our questionnaires, its result must be interpreted with caution.

Exposure to estrogen during urethral development may also be a risk factor. Exposure can result when the mother ingests pesticides on

fruits and vegetables or milk from pregnant cows. But in this study there was no history of these factors in mothers in the first trimester, except in cow's milk which is impossible to detect, because the pregnant women often drink it.

In the present study 20% of hypospadias cases were low birth weight. It has been established that there is an association between intrauterine growth retardation and hypospadias [13-15], it increases with decreasing birth weight without dependency to gestational age [15]. Gatti et al also found that hypospadiasis is 10 times more common in small for gestational age infants compared with normal infants [14]. The incidence of low birth weight in the normal population is 7 percent, in our hospitals it is 9%, and 20 % of newborns with hypospadias were low birth weight. Therefore, occurrence of one hypospadias in five low birth weight neonates is a significant result. There are enquired studies in correlation between advanced maternal age and primiparity as a risk factor [1], in the present study also first parity was no significant risk factor.

Conclusion

The main risk factors of hypospadias in this study were season of conception, family background and preventive effect of medications in the first trimester of pregnancy. As far as we know, this is the first report that hypospadias has seasonal pattern. Folic acid and iron can be used for prevention. We suggest that further research with more sample size on preventive effect of iron and folic acid are required.

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Conflict of Interest: None

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