Research Paper

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Maternal Reproductive Factors in Male Newborns with Hypospadias.

Medical Science

KEYWORDS : Hypospadias; maternal; reproductive

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ABSTRACT

Aim

Birth defects are the leading cause of infant mortality and are responsible for substantial child and adult morbidity. Hypospadias a relatively common male genital anomaly may be caused by different maternal demographic or anthropometric characteristics that are poorly defined. On the other hand there is debate about temporal trends in hypospadias prevalence. The aim of this study was to determine prevalence and impact of these risk factors of hypospadias in newborn infants of at the largest tertiary hospital located in Qatar.

Methods

We performed a population-based, case control study using linked birth-hospital discharge data from Hamad General Hospital from . All cases of hypospadias were identified on the basis of International classification of diseases, Ninth Revision. Cases were studied for possible risk factors. This study included only hypospadias cases; those subjects described as ambiguous genitalia without further description or associated with other anomalies were excluded from study.

Results

73 newborn males with a birth were included. Birth body weights were lower in patients with hypospadias compared with those for controls (3096 ± 823 vs 3283 ± 583 g). Placenta-to- fetal weight ration (0.243 ± 0.2 vs 0.211 ± 0.04) and gestational age were higher in the patients with hypospadias. There were no differences between singleton and multiple-gestation births. However, the frequency of occurrence was similar among first-born infants compared with all other infants.

Conclusion

Disparities in the prevalence of birth defects may result from different underlying genetic susceptibilities; exposure to risk factors among the subpopulations examined. Summer was the most epidemiology factor for occurring of hypospadias probably due to conception in cold season. Although the causes of male genital malformation are multifactorial, our data support the hypothesis that older maternal age, and preexisting diabetes were associated with increased risk of hypospadias among male offspring.

INTRODUCTION

Birth defects occur in approximately 3% of all live births and are a major contributing factor to infant mortality and childhood and adult disability. 1, 2 Evaluation of trends in the prevalence of birth defects and their distribution among subpopulations can help public health professionals and care providers better evaluate potential clusters, conduct etiologic and outcome research, determine health services needs, and target health care.

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. It is the second most common genital abnormality (after cryptorchidism) in male newborns with an incidence in different series ranging between 0.3%. 3 Other anomalies that may accompany hypospadias include meatal stenosis, hydrocele, cryptorchidism (in 8% to 10% of cases). When complications occur, the resultant morbidity of corrective procedures, psychologic stress, and potential loss of function can be devastating to the patient and family.

On the other hand, in the past two decades, concern has been raised over a possible increase in disorders of the male reproductive tract, including cryptorchidism, hypospadias, testicular cancer, and impaired semen quality. It has been suggested that these disorders are interrelated and share a common etiology during fetal life, described by Skakkebaek and colleagues as the testicular dysgenesis syndrome (TDS). 4

Although hypospadias are the most common congenital abnormalities, their aetiology is not yet completely understood. However, it is known that androgens, including dihydrotestosterone (DHT), play an important role for normal testicular descent and for development of external male genitalia. Mutations in the AR gene or in the gene encoding for the 5-a-reductase type II enzyme, responsible for the conversion of testosterone to DHT are associated with undescended testis(-es) and/or hypospadias. However, these mutations are extremely rare and hardly responsible for the ethnic gradient in the occurrence of TDS. No association has been found between the AR CAG repeat length and any of these congenital male genital abnormalities. In contrast, it found a difference between Swedish healthy men and ethnically matched subjects with penile hypospadias or a history of cryptorchidism with regard to the length of distribution of another trinucleotide repeat in the AR gene – the GGN repeat. 2 In a few cases maternal exposure to progestin between 8 and 14 weeks gestation has been the cause of hypospadias. 5

Studying such interactions has biological and public health related implications. It will help us to understand the background for the defects in male reproductive organs, facilitate proper design of epidemiological studies and add to identifying individuals susceptible to certain environmental and life-style related hazards.

Moreover, because of the wide distribution of hypospadias, the aim of the study was to determine frequency distribution and risk factors of hypospadias in children of the only tertiary hospital in Qatar located in Hamad Medical Corporation.

The goal of the study was to evaluate the extent to which maternal age, reproductive data, race/ethnicity, are associated with hypospadias among male offspring. We also calculated yearly prevalence rates, to determine whether the prevalence of hypospadias is increasing in Qatar.

METHODS

We conducted a nested case –control study within a large cohort of newborn boys in the city of Doha. From approximately … million discharge records in the Hospital's Medical record database 2002 – 2012, Case subjects were defined as male singleton infants with an ICD-10 code for hypospadias (752.61). Hypospadias (anterior, middle and posterior) was defined as a displacement of the urethral meatus from the tip of the glans penis to ventral side of the phallus, scrotrum.

Hypospadias (anterior, medium and posterior) was defined as a displacement of the urethral meatus from the tip of the glans penis to the ventral side of the phallus, scrotum or perineum 6-10

This study was approved by the institutional review board. We extracted information on demographics, maternal reproductive data (parity, usage of contraceptive pills, assisted reproductive techniques) and patient birth weight, family history, type of hypospadias and procedure subsequently done.

Data were summarized on the standardized questionnaire entered into an electronic database and checked for accuracy and the data extraction and entry were performed by the same investigator. We analyzed the information according to age, sex, clinical signs date of hospitalization and the diagnostic and treatment related characteristics.

This study included only hypospadias cases; those subjects described as ambiguous genitalia without further description were excluded from study. Children with recognized gene disorders or chromosomal abnormalities were also excluded.

Control subjects were randomly selected from the remaining male singleton infants, at a relative frequency of 1 control subject per case subject. We contextually selected at random 100 healthy male newborns as controls from boys without hypospadias or micropenis matched for parity (primiparous), twin birth, gestational age (+1 week) and date of birth (+7 days). Control subjects were frequency –matched to case subjects according to year of birth.

Initially, stratified analyses were conducted to obtain odds ratio (OR) estimates of the relative risk and 95% confidence intervals (95%CIs). Subsequently, logistic regression was used.

Crude yearly birth prevalence rates were determined by dividing the total number of cases that occurred during a calendar year by the total number of male singleton births during the same year.

Descriptive statistics were used to summarize the demographic characteristics of patients. Mean (+- standard deviation) are reported were appropriate.

RESULTS

The study subjects included 73 newborn males with hypospadias and 97 normal (control) male newborns. Mean body weight at birth was lower in newborns with than without hypospadias (3096 ± 823 g vs 3283 ± 583 g).

The numbers of hypospadias had remained almost stable over the last 5 years and raged between 33 cases in 2007 to 37 cases in 2011. (Fig 1)

Fig1. Numbers of hypospadias managed in our center over the last 5 years.

Almost equal percentages of boys with hypospadias were born of primiparous mothers and those of other parities (Table 1), and 4.1% were products of twin or triplet pregnancies. Infants with hypospadias were slightly more likely to be delivered at gestational age of <37 weeks, and their mothers were slightly less likely to have had prior births (Table 1). Most other characteristics were similar for case and control subjects.

The risk of hypospadias did not increase with increasing maternal age, with ORs of 1.95 (95% CI; 0.37-10.20) for infants of mothers 20 to 24 years of age to 0.46 (95% CI: 0.03-6.89) for infants of mothers >40 years of age (Table 2). However, placental weight <600 g was slightly more common (OR 1.77; 95% CI: 0.66-4.80), and placental weight 600-700 g slightly less common (OR 0.76; 95% CI: 0.35-1.65), in newborns with than without hypospadias, although the differences were not statistically significant.

Table 1 Maternal reproductive factors in comparison in between patients with hypospadias and controls.

Characteristic		Hypospadias N (%)	Control N (%)
Prior Pregnancies	1	15 (20.5%)	15 (15.5%)
	2	13 (17.8%)	20 (20.6%)
	3 or more	45 (61.8%)	62 (63.9%)
Prior births	0	17 (23.2%)	20 (20.6%)
	1	16 (21.9%)	27 (27.8%)
	2	18 (24.7%)	15 (15.5%)
	3 or more	22 (30.2%)	35 (36.1%)
Gestational Age	Less 37	15 (20.5%)	6 (6.2%)
	38 - 42	38 (52.1%)	90 (92.8%)
	More than 42	20 (27.4%)	1 (1%)

Table 2. Factors in newborn males with and without hypospadias

Characteristic Hypospadias		No (%)		OR (95% CI)
		Control		
Age of mothers, yr	Less than 20	2 (2.8%)	6 (6.3%)	1.00 (referent)
	20-40	68 (95.4%)	85 (88.5%)	1.95 (0.37-10.20)
	More than 40	2 (2.8%)	5 (5.2%)	0.46 (0.03-6.89)
Placenta weight, g	Less than 600	17 (23.9%)	13 (14.0%)	1.77 (0.66-4.80)
	600 – 700	30 (42.3%)	52 (55.9%)	0.76 (0.35-1.65)
	More than 700	24 (33.8%)	24 (30.1%)	1.00 (referent)

Table 3; hypospadias in relation to selected factors;

CHARACTERISTIC	NO %		
	Hypospadias Mean +- SD	Control Mean +- SD	P
Age	29.69+-5.68	28.60+- 5.63	0.22
BMI	31.44+-7.45	30.93+- 5.65	0.64
Gravida	3.25+-2.37	3.19+- 1.96	0.85
Parity	1.85+-2.06	1.71+-1.63	0.63
Misscarriage	0.41+-0.94	0.40+- 0.68	0.95
Fetal Weight(g)	3096.41+-822.53	3283.72+-583.14	0.09
Placental Weight(g)	656.97+-147.98	677.42+-99.162	0.29
Placental-to-fetal Weight	0.24+-0.20	0.21+-0.043	0.14
Placental weight/ Fetal age	17.62+-3.78	17.3373+-3.05	0.61
Head Circumference (cm)	34.02+-2.62	34.39+-1.62	0.27

However, different clinical parameters were compared between the two different groups (with and without hypospadias) including age, BMI and others. No significant difference in the number of current pregnancy was noticed between the two groups as well as the number of miscarriages. On the other hand, fetal weight was higher in the control group but this was also not statistically significant as well as head circumference (Table 3).

DISCUSSION

Hypospadias is the second most common genital abnormality (after cryptorchidism) in male newborns with an incidence in different series ranging between 0.3% and 0.8%. 3 Incidence of hypospadias has been increased in European and American countries so that it has been doubled from 1970 to 1993. 11

In Stokowski study (12), 7-9% of fathers with hypospadiasic son had also hypospadias. In other 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. 5

Documenting the variation in prevalence of birth defects among racial/ethnic subpopulations is critical for assessing possible variations in diagnosis, case ascrtainment, risk factors among such groups.

True racial/ethnic variation in the prevalence of birth defects may result from differential access to early and high-quality prenatal care, which may lead to differential patterns of prenatal diagnosis and pregnancy termination. Alternatively, some variation in prevalence by maternal race/ethnicity may represent different genetic or environmental risk factors. In some surveillance systems, variation by race/ethnicity may also reflect differential ascertainment and diagnosis of cases postnatally. 13

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 chromosomal abnormality. Severe hypospadias (penoscrotal or perineal) occurs with approximately a 15% risk of such problems. 3

Although the causes of male genital malformation are multifactorial, our data support the hypothesis that prenatal contamination by pesticides may be a potential risk factor for newborn male external genital malformation and it should thus be routinely investigated in all undervirilized newborn males. 14 Older maternal age, white race, and preexisting diabetes were associated with increased risk of hypospadias among male offspring. 15

We found a strong positive association between advancing maternal age and risk of hypospadias. In 2001, however, it was reported that there is a 50% higher risk of hypospadias among women 35 years of age or more compared with women 20 or less years of age. 16

It is not known why maternal age may be a risk factor for hypospadias. It is clear, however, that older women are at higher risk of having children with genetic defects.24 It is therefore plausible that the risk is mediated via underlying genetic defects associated with aging. Some authors have suggested that subfertility is a potential mechanism linking hypospadias with maternal age, because subfertile women often are older at the time of first conception.17

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 18-20, it increases with decreasing birth weight without dependency to gestational age. Gatti et al also found that hypospadiasis is 10 times more common in small for gestational age infants compared with normal infants 19. There are enquired studies in correlation between advanced maternal age and primiparity as a risk factor 21, in the present study also parity was not a significant risk factor.

Since hypospadias is an anomaly of external genitalia and in some cultures like Qatar, 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.

Our reliance on hospital discharge data might have resulted in some under reporting of hypospadias, although the use of these data allowed a longer window of observation for birth conditions and anomalies that might not be reported on birth certificates alone. Even birth defect registries might not identify milder forms of hypospadias. 12, 22 Moreover, a limitation of our study was that not all possible maternal, perinatal and environmental risk factors were included in the analysis, such as familial clustering, maternal smoking and iron supplementation. Larger studies could facilitate the identification of these risk factors and provide opportunities for additional indepth investigation of the associations found to date.

Nevertheless, the strength of this retrospective study is that it analyzed data from the only tertiary care facility in the country with complete investigations and reliable documentation. The specificity of case ascertainment is therefore likely to be high and description of clinical presentation, treatment outcomes, and epidemiology is consequently an accurate representation of hypospadias in the population in Qatar.

The present study may be of interest since it is the first Qatari case-control study nested within a large birth population from a low risk maternity ward. It thus presents a good indication of the prevalence of male genital abnormalities in the general population of Eastern Arab Peninsula. Although the causes of hypospadias are multifactorial, we have investigated the most probable maternal reproductive risk factors.

The main risk factors of hypospadias in this study were maternal age and fetal weight. We suggest that further research with larger sample size on the effect of these factors is required.

Authors' Contributions:
TA was responsible for most of the proposal writing, data analysis and manuscript writing. MA participated in manuscript structuring.

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Institutional Ethics Committee:
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