Research Paper

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Is Hypospadias A Result From Early Gestational Placental Insufficiency or Still an Unexplained Malformation?

Medical Science

KEYWORDS : Placenta, hypospadias, genital birth defects, birth weight

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ABSTRACT

Aim

Hypospadias a relatively common male genital anomaly may be caused by different maternal hormone levels, blood glucose levels or nutritional deficiencies that are poorly defined. The association of growth retardation and hypospadias is well established. Fetal testosterone secretion is under the influence of placental human chorionic gonadotropin during first 14 weeks of gestation. We hypothesized that placental insufficiency may disrupt the supply of nutrients and human chorionic gonadotropinto the fetus leading to both growth retardation and hypospadias. To validate this hypothesis, we analyzed placental and birth weight indices in infants with and without hypospadias.

Methods

We performed a population-based, case control study using linked birth-hospital discharge data from Hamad General Hospital from January 2007 to December 2012. A retrospective cohort analysis of these infants was performed. Infants' growth parameters at birth (weight, head circumference) were analyzed along with maternal risk factors known to be associated with changes in fetal growth, including maternal age, diagnosis of preeclampsia, gestational diabetes as well as placental weight.

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

The significant association between the occurrence of hypospadias and early growth retardation with higher placenta-to-fetal ration and placental abnormalities suggest that placental dysfunction in early gestation may play an important role in the development of hypospadias. The increasing frequency of hypospadias and its association with poor intrauterine growth originating in early gestation suggest that common environmental factors that have an impact on both conditions may be involved. Careful evaluation of the genitalia is advised when early-onset placentally mediated IUGR is encountered.

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 is one of the most common congenital abnormalities, their aetiology is not yet completely understood. The male urethra forms by fusion of the genital folds under the influence of testosterone synthesize in the fetal testis between 8 and 14 weeks of gestation. 5 HCG, produced by the placenta, controls fetal Leydig cell growth and stimulates fetal testicular steroidogenesis, the generation of steroids from cholesterol 6. The enzymatic steps of steroidogenesis, mainly taking place in the Leydig cell, are well documented, and the expression of key genes in this pathway is dependent on the expression of SF1 7. Testosterone leaves the Leydig cell and is converted into dihydrotestosterone (DHT) by steroid-5-alpha-reductase (SRD5A). Testosterone promotes the formation of the internal reproductive structures from the Wolffian ducts, whereas DHT induces the development of the external genitalia 8, both through their effect on the androgen receptor (AR).

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.

At least three potential mechanisms may relate maternal obesity to risk of hypospadias. Levels of circulating hormones, including androgens differ between obese and normal-weight mothers. 9, 10, 11, 12, 13, 14 Lower overall diet quality and blood concentrations of micronutients have also been observed in obese women and may relate to risk of birth defects like hypospadias although data are incoistent.15, 16, 17, 18. Finally, impaired fasting glucose and glucose tolerance before and during pregnancy are associated with obesity 19, 20 and uncontrolled glucose levels have been associated with birth defects 15.

There was a trend to lower placental and fetal weight in SGA infants with hypospadias than in the controls. This finding merits further evaluation using a larger population database and suggests that factors resulting in SGA infants occur at a critical point early in development, affecting both somatic and urethral development. 21

We aim to study the relationship between hypospadias and perinatal anthropometrical measurements at birth (as a marker of intrauterine growth) between boys with hypospadias and healthy ones.

METHODS

This study was approved by the institutional review board. 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, 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. 22- 26

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. The infant data included information on gestational age, birth weight, and wether it was a single or multiple births. The maternal data included information on age, parity, the presence of maternal diabetes, hypertension or preeclampsia. Maternal age was defined as the mother's age at delivery. Parity was defined as the number of pregnancies including the present one. Gestational age was calculated primarily from the date of the last menstrual period. Children with recognized gene disorders or chromosomal abnormalities were also excluded. Maternal diabetes, hypertension, and preeclampsia were diagnosed by the attending obstetrician.

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. We performed statistical analysis to determine the associations between hypospadias and potential risk factors. We also computed crude odds ratio (ORs) and 95% confidence intervals (95% CIs) of all potential risk factors.

RESULTS

73 newborn males with hypospadias and 97 normal (control) deliveries were included. Birth body weights were lower in patients with hypospadias compared with those for controls (3096 ± 823 vs 3283 ± 583 g).

Almost equal percentages of hypospadias cases were born of primipara and other mothers (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 examined were similar for case and control subjects. The risk of hypospadias did not increase with increasing maternal age, ranging from an OR of 1.95 (95% CI; 0.37-10.20) for infants of mothers 20 to 24 years of age to an OR of 0.46 (95% CI: 0.03-6.89) for infants of mothers _40 years of age (Table 2). However, the placental weight was slightly higher in patients with hypospadias less than 600 gm but not statistically significant with an OR of 1.77 (0.66-4.80) in comparison to control group individuals with placental weight between 600-700 gm an OR of 0.76 (0.35-1.65).

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 Different characteristics compared between hypospadias patients and controls

Characteristic Hypospadias		No (%) Control		OR(95%CIs)
Age of mothers	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	Less than 600 gm	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)

Mothers' ages were not different between patients with hypospadias and control group. On the other hand, placental weight was lowe in hypospadias patients 656.97+-147.98 gm in comparison to control group 3283.72+-583.14 gm but still statistically not significant (P value 0.09). Other variables were not different between the two groups including Placental-to-fetal Weight and Placental weight/Fetal age and head circumference. (Table 3).

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
Fetal Weight(g):	3096.41+-822.53	3283.72+-583.14	0.09
Placental Weight(g)	656.97+-147.98	677.42+-99.16	0.29
Placental-to-fetal Weight	0.24+-0.20	0.21+-0.04	0.14
Placental weight/ Fetal age	17.62+-3.78	17.34+-3.04	0.60
Head Circumference (cm)	34.02+-2.62	34.39+-1.62	0.27

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. 27

In Stokowski study (28) 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.29

Documenting the variation in prevalence of birth defects among racial/ethnic subpopulations is critical for assessing possible

variations in diagnosis, case ascertainment, risk factors among such groups.

A wide spectrum of potential risk factors in the development of isolated hypospadias has been reported.Genetic predisposition, placental insufficiency, endocrinologic problems, and more recently, environmental factors have been implicated; however, the exact cause of this condition is still largely unknown 30- 32

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. 33 Older maternal age, white race, and preexisting diabetes were associated with increased risk of hypospadias among male offspring. 34

The most severe forms of placenta-mediated IUGR originate in the early part of thefirst trimester, around weeks 7–8, when the male external genitalia are forming. This has been supported by studies showing that low maternal circulating levels of PAPP-A at 8–14 weeks of gestation are significantly predictive of IUGR, and more so when measured prior to 13 weeks. However, the underlyingmechanism of the association between hypospadias and placental insufficiency is unclear.35

Placental hCG stimulates fetal testicular steroidogenesis before the fetus's own pituitary–gonadal axis is established. Placental insufficiency may result in inadequate fetal hCG provision and IUGR, possibly explaining the association between hypospadias and low birthweight or being small for gestational age (SGA) that was consistently reported, although not always statistically significant. Nausea in early pregnancy may be caused by the early surge of hCG, suggesting that placental insufficiency may cause absence of nausea. Indeed, vomiting and nausea during early pregnancy were shown to decrease hypospadias risk 36

SGA newborns are certainly a group whose nature is very heterogeneous, including some absolutely normal babies, "smaller" than the rest of the population for constitutional reasons, and newborns affected by different kinds of disease. Typically, "symmetric" SGA newborns, if pathological, are considered to be affected mainly by genetic, chromosomal and infectious diseases or any other condition affecting the growth of the fetus in the early stages of gestation, while "asymmetric" SGAs are often explained by placental pathologies in late pregnancy. 37 The association between growth retardation and hypospadias is well established. It was reported that the incidence of hypospadias in SGA infants admitted to the NICU was _10 times greater than that reported for the general population.21

The causes for intrauterine growth retardation resulting in SGA

infants include malnutrition, chronic maternal systemic disease (eg, diabetes, toxemia, renal failure), placental or fetal infection, isoimmunization, maternal age extremes (_18 or _35 years), recurrent premature labor, chromosomal abnormalities, idiopathic causes, and abnormalities of the placenta. These factors resulting in SGA infants occur at a critical point early in the development, affecting both somatic and urethral development.11

We found a strong positive association between advancing maternal age and risk of hypospadias. In 2001, however, Fisch et al 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. 38 Our results are consistent with those findings. However, we were also able to demonstrate a linear relationship between maternal age and hypospadias risk, with risk nearly doubling by the time women were _40 years of age.

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. 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.39

Maternal hypertension during pregnancy and pre-eclampsia were consistently associated with hypospadias, and both factors may be associated with placental dysfunction, possibly by compromising uteroplacental perfusion 40.

It is well known that maternal diabetes is associated with increased perinatal morbidity and mortality (increased incidence of congenital anomalies, macrosomia and intra-uterine foetal death). The placenta shows several histological abnormalities of the placenta like immaturity and hydropic changes of the chorionic villi, increased fibrinoid necrosis and chorangiosis. Despite good glycemic control these abnormalities can still be found (41). The immaturity of the villi and decreased formation of terminal villi also results in a less decreased diffusion distance with similar detrimental effects as described for the other two above mentioned disorders. These placenta abnormalities however, are not specific and recently it was demonstrated that similar histological features could be found in placentas from large-for-gestational age infants from non-diabetic mothers. 42

In patients with hypospadias, the intrauterine growth parameters that we measured, that is, weight and head circumference at birth, demonstrated a proportionate decrease in either somatic or brain growth. These findings are highly suggestive of an effect on growth occurring early in gestation.

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. Is spite of this, reported positive family history of % is noticeable in this 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. 28, 43

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. We suggest that further research with larger sample sizeis 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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