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MATERNAL RISK FACTORS ASSOCIATED WITH HYPOSPADIAS

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Abstract

Introduction: Epidemiological studies have elucidated maternal and fetal factors that are associated with an increased risk of hypospadias .This study examined the association of hypospadias risk with several maternal reproductive and demographic characteristics: age, parity, body mass index (BMI), nausea and vomiting of pregnancy, fertility treatments , education and diet .

Materials and Methods: Mothers of children with hypospadias were invited to participate in this case control study. Participating mothers completed a self administered questionnaire or a social worker administered/assisted questionnaire. Mothers of age matched children without hypospadias acted as controls and they too similarly completed the same questionnaire.

Results: The risk factors associated with hypospadias were maternal age, primiparity , previous fertility treatment and nausea and vomiting of pregnancy .

Conclusions: Increased maternal age, primiparity and previous fertility treatments in mothers are associated with an increased risk of hypospadias in male offsprings.

Keywords: Hypospadias, Maternal age, Parity, Fertility, Maternal education, Nausea and vomiting

Introduction

A detailed report by Sorensen[1] and more recent reviews by Sweet and colleagues[2] and Baskin[3] suggest a multifactorial etiology of hypospadias, fitting a polygenic model. Responsible etiologic factors may include one or more of an environmental or other endocrine disruptor; an endocrinopathy, enzymatic or local tissue abnormality; and/or a manifestation of arrested development. The characteristic defects of hypospadias may result from one or more of the following: (1) abnormal androgen production by the foetal testis, (2) limited androgen sensitivity in the target tissues of the developing external genitalia, or (3) premature cessation of androgenic stimulation secondary to premature involution of Leydig cells of the foetal testis[4]. Other possible causes include insufficient testosterone and/or dihydrotestosterone synthesis (presumably defective or deficient 5α-reductase enzyme activity) and/or defective androgen receptor quality and/or quantity. Several entities in the spectrum of androgen resistance (androgen insensitivity syndromes) have been elucidated at the clinical and molecular level[5,6].

Epidemiological studies have elucidated maternal and fetal factors that are associated with an increased risk of hypospadias. Maternal factors are advanced maternal age, primiparity, obesity, and fertility treatments[7-9]. There is less information on maternal and fetal factors associated with the severity of hypospadias, rather than their effect on the overall incidence of the condition.

This study uses data from case-control study to examine the association of hypospadias risk with several maternal reproductive and demographic characteristics: age, parity, body mass index (BMI), nausea and vomiting of pregnancy, multiple pregnancy, fertility treatments and procedures and education. These factors were selected because they may be associated with maternal endocrine function and/or with other endocrine-related outcomes.

Materials and Methods

The data for this study was collected as a part of a case control study of hypospadias. A detailed questionnaire was used to collect exposure information from the mothers of cases and controls. The study complied with all applicable regulations and was approved by the institutional ethical committee and the subjects gave informed consent before the study.

Recruitment of hypospadias cases and controls

Children with hypospadias without concomitant malformations or chromosomal abnormalities admitted to the Paediatric Urology wards for repair, formed the study group. Mothers of these children were invited to participate in this case control study. Participating

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mothers completed either a self administered questionnaire or a social worker administered/assisted questionnaire. A study coordinator was available at that time to answer any questions the mothers had about the questionnaire, but was otherwise uninvolved in its administration. For each hypospadias case, two children of similar age without hypospadias or known malformations were randomly selected from the paediatric ward. The mothers of these children also completed the same questionnaire.

Similarly mothers admitted for delivery in the maternity wards and gave birth to male neonates with hypospadias without concomitant malformations, identified by the Paediatric Urologist formed the second group of the study. The mothers were examined so as to calculate the BMI. The mothers were similarly administered the questionnaire. For each neonate with hypospadias, two other neonates of similar age and birth weight without hypospadias or known malformations were randomly selected from the maternity/neonatal ward. The mothers of these neonates also completed the same questionnaire.

Collection of exposure data

Each mother completed a questionnaire that included questions about her gynaecologic and reproductive history, her health and diet before and during the index pregnancy, and parental demographic, physical and social characteristics and characteristics of the case/control child . For most questions, the questionnaire provided two or more choices of response. We assessed contraceptive use at conception by listing seven types of contraception: combined oral contraceptives, minipills, injections, implants, intrauterine device (IUD), and other methods such as condom and natural methods. We ascertained history of complications such as high blood pressure with yes/no questions. In the question, regarding nausea during pregnancy, we asked those who stated that they had been nauseous to specify the trimester of nausea, and permitted them to specify more than one trimester. We assessed meat and fish consumption by asking whether meat/fish had been consumed at least once a week.

Statistical analyses

We performed analyses using descriptive statistics and Student's t-test to compare risk factors.

Results

During the study period Aug 2008 to Dec 2009, 7 children were born with hypospadias in our hospital, an incidence of 0.33% of all male live births. The maternal reproductive and demographic risk factors are as shown in Table 1. The risk factors associated with hypospadias were maternal age, primiparity, previous fertility treatment and nausea and vomiting of pregnancy.

Table 1

	Hypospadias (n=7)	Controls (n=14)
Maternal age (yrs)	27.14±3.20 *	23.4±3.15
BMI	26.24±1.159	25.87±0.07
Primiparity	6 (85.7%) *	4 (28.5%)
Fertility Treatment	0.57±0.53 *	0.0
PIH (Pregnancy induced hypertension)	0.0	0.0
NVP (Nausea , vomiting of pregnancy)	0.71±0.48 *	0.0
Education	-	-
Consanguineous marriage	0.0	0.0

During the same period 23 children with hypospadias underwent repair. The maternal reproductive and demographic risk factors during the index pregnancy were as shown in Table 2.

Table 2

	Hypospadias (n=23)	Controls (n=46) P
Maternal age during Index Pregnancy	29.75±3.6*	24.21±2.46
Primiparity during Index pregnancy	12 (52.17%) *	11 (23.91)
Fertility Treatment	0.43±0.50 *	0.17±0.38
PIH	0.0	0.0
NVP	0.65±0.48*	0.30±0.46
Education	-	-
Consanguineous marriage	0.0	0.0

The risk factors in this group were the same i.e. maternal age at the time of index pregnancy, primiparity during index pregnancy, fertility treatment during index pregnancy and NVP of pregnancy. Maternal education was not a relevant risk factor as the mothers in both the group were educated atleast upto high school level and were well versed in reading and writing. None the mothers in both the groups had consanguineous marriage and none experienced or reported pregnancy induced hypertension .There was no relevant data in relation to use of contraceptive pills in any group of mothers. Similarly there was no difference in meat/fish consumption in the mothers of both the groups. The number of mothers consuming only vegetarian diet and non vegetarian diet were similar in both the groups.

Discussion

Hypospadias occurs as a result of abnormal urethral closure from 8 to 14 weeks after conception and is one of the most common birth defects with a prevalence of 3 – 5 per 1000 births[10]. Conversion of testosterone to dihydrotestosterone and proper androgen receptor signalling are critical to normal urethral closure. One factor that is known to interfere with this process is oestrogen [11]. Thus it has been hypothesized that increased maternal oestrogen levels may be associated with increased hypospadias risk [12,13].

Maternal primiparity, age 35 years or older and BMI > 26 are factors known to be associated with increased risk of hypospadias among offspring, especially when present in combination. Two studies[14,15] have examined the combination of maternal age and parity , and both these studies have shown twofold to threefold higher risks of hypospadias among older primiparous women , as compared to younger, multiparous women. Carmichael et al [8] have suggested that BMI may further modify the increased risk. Carlson et al[16] have reported that advanced maternal age was associated with increased severity of hypospadias in their population. Several explanations have been postulated for the finding of increased incidence and severity of hypospadias with increasing maternal age. Older mothers would potentially have longer exposure to endocrine disruptors than younger mothers and thus a greater risk of hypospadias[17]. A population based study has noted an increase in organochlorine pesticide concentration in adipose tissue that correlated to increasing age. The main exposure source for these environmental toxins was suggested to be dietary, particularly fish and other animal products[18]. Organochlorine pesticides have well documented estrogenic effects[19]. A case control study has demonstrated an increase in cytogenetic damage that correlates with increasing age in women with occupational exposure to pesticides [20]. Our study too revealed that the age of the mothers of children with hypospadias was significantly more than mothers of children without hypospadias.

The specific association of maternal age, parity and BMI either individually or in combination, with maternal hormone levels seems to be somewhat unclear. One study which has utilised samples from the collaborative perinatal study , found that free oestradiol levels during early pregnancy were higher in women's first pregnancies than during their second pregnancies [21] .Results stratified by pre-pregnancy weight indicated that levels were particularly high among women who were experiencing their first pregnancy and had pre-pregnancy weight >125 lbs.

Maternal sub-fertility has been proposed to contribute to higher risks of hypospadias observed among older and primiparous women[22]. Multiple births and fertility treatments, specifically intracytoplasmic sperm injection, are associated with increased risk of hypospadias [23] .Several studies [8,24] have shown association of multiple birth with increased risk in univariable analyses , but with reduced risk in subjects with birth weight ≥ 2500 g. This finding supports the hypothesis that the association of hypospadias with multiple birth stems from its association with growth retardation [25]. Multiple gestation is associated with elevated oestradiol during early pregnancy, but also with elevated levels of other hormones such as testosterone, progesterone and HCG [26].

Nausea in early pregnancy is believed to be caused by the early surge of pregnancy hormones, particularly HCG; the onset and peak of nausea and vomiting in early pregnancy parallel the HCG curve[27]. First trimester nausea is considered to be a sign of a healthy pregnancy, because it is associated with lower risks of miscarriage and premature birth[28,29]. In contrast, the absence of nausea may reflect potential problems with the pregnancy and is associated with low HCG levels[27,29]. Akre et al [30] showed absence of nausea during early pregnancy was associated with increased risk of hypospadias, which lends support to the hypothesis that abnormally low HCG levels resulting from placental insufficiency in early pregnancy may be involved in the etiology of hypospadias[8]. Carmichael et al [8] reported a similar negative association between early nausea and hypospadias.

Several studies have found associations between hypospadias risk and preterm birth and low birth weight[25,31]. Disturbance of placental function early in pregnancy is a key mechanism underlying both preterm birth/low birth weight and the improper closure of the urethra, because the placenta is the main product of pregnancy hormones in early pregnancy and is thus instrumental in the differentiation and

development of the fetal organs [31-33]. Hypospadias risk is associated with gestational hypertension , which in turn is associated with preeclampsia and placental dysfunction[32] .This provides further support for the notion that placental dysfunction is involved in the etiology of hypospadias .

Our study does have its limitations in that the collected data is based on self report in the questionnaire. Our data on previous fertility treatments, NVP and PIH lacked several details to make a meaningful conclusion. Most Indian women are vegetarians and even among the mothers having nonvegetarian diet, the amount of meat/fish consumption is variable and does not give adequate statistical information. We also lacked several factors that might play a role in the etiology of hypospadias such as genetic susceptibility; paternal semen quality and exposure to environmental toxins .We have also not made a comparison of severity of hypospadias and risk factors.

Conclusions

The results of our study show that increased maternal age, primiparity, NVP and previous fertility treatment were associated with increased risk of hypospadias on univariate analysis.

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