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Maternal and fetal risk factors for bladder exstrophy: A nationwide Swedish case-control study

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Summary

Introduction
Bladder exstrophy is a rare, congenital, complex malformation where the underlying cause is largely unknown. Both environmental and genetic mechanisms are thought to be involved.

There are divergent results concerning the prevalence, birth descriptive data, and potential maternal risk factors for bladder exstrophy. Few previous studies have reflected nationwide populations, population registers, or spanned a longer period of time.

Objective
To describe and assess bladder exstrophy and the potential maternal risk factors, for a time period of four decades, by conducting a nationwide register study of bladder exstrophy in Sweden.

Methods
A matched-design, case-control, linkage-analysis study nested within the entire pool of live births in Sweden between 1973 and 2011 was performed. Cases with bladder exstrophy were identified using nationwide population-based birth and health registers. Inclusion criteria were people born in Sweden with the classification of bladder exstrophy according to the ICD coding system. Cases were matched with five controls per patient, based on birth year and sex.

Prevalence was assessed and birth descriptive data were compiled. Potential maternal risk factors were obtained from medical birth registers of cases and assessed using conditional and multivariate logistic regression models to obtain odds ratios as a measure of the relative risk.

Classification of the diagnosis in the registers constituted a possible limitation for determining the correct study population, which demanded strict validation and inclusion criteria. All data were collected prospectively, thereby avoiding potential recall bias.

Results
The prevalence was calculated to be approximately 3 per 100,000 live births, with a male-to-female ratio of 1.14:1. In 92.5% of the cases, bladder exstrophy was an isolated malformation without associated major malformations. However, 41% had had surgery for congenital inguinal hernia and 11% of the male subjects had been operated on for cryptorchidism. A significantly higher proportion of cases had a birth weight <1500 g compared with controls, but other characteristics were comparable with controls. High maternal age was the only significant potential associated maternal risk factor.

Conclusions
One hundred and twenty children born with bladder exstrophy in Sweden during the last four decades were identified; this resulted in prevalence in Sweden of 3 per 100,000. The prevalence was stable over time and the sex ratio was equal. Birth characteristics were comparable to controls, and bladder exstrophy generally occurred as an isolated malformation without major associated malformations. Advanced maternal age was the only significant potential maternal risk factor.

Summary table A. Birth descriptive data on infants born with bladder exstrophy and B. Multivariate logistic regression model of potential maternal risk factors.

A.	Cases	Controls	
	N = 120	*N* = 600	
	n (%)	*n* (%)	
Infant, sex			
Male	64 (53.3)	320 (53.3)	
Female	56 (46.7)	280 (46.7)	
Birth weight (grams), mean ± SD	3405 ± 617	3499 ± 563	
<1500	5 (4.2)	4 (0.7)	
	N = 120	Male	Female
		N = 64	*N* = 54
Associated major malformations	9 (7.5%)	3 (4.7%)	6 (10.7%)
Inguinal hernia	49 (41.0%)	40 (62.5%)	9 (16.1%)
Cryptorchidism		7 (11%)	
B.	Odds ratio (95% CI)[a]		
BMI (obesity vs normal)	1.44 (0.57–3.63)		
Age (≥35 years vs 25–29.9 years)	3.60 (1.62–7.99)		
Smoking, at any time	0.98 (0.47–2.05		

[a] Models adjusted for maternal age >35 years, smoking (at any time during pregnancy), and obesity.

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Introduction

Bladder exstrophy (BE) is a rare congenital malformation in which the child presents with a defect of the lower abdominal wall, which exposes an open bladder. The malformation also involves the bony pelvis, the urethra and genitalia. A disrupted closure of the abdominal wall and the pelvic rings leads to a malformation of the pelvic bone with widening of the pubic bone. Boys present with epispadias, and girls with cleft clitoris and shortened vagina. BE is the most common condition of the spectrum of genitourinary malformations ranging in severity from epispadias, affecting only the urethra and genitalia, to cloacal exstrophy, also involving the intestines. BE is commonly considered to be an isolated malformation, but associated major malformations, such as cleft lip-palate, spina bifida, and orthopedic and gastrointestinal anomalies, have also been described [1—4].

The prevalence of BE has been reported to range between 1.6 and 4.0 per 100,000 live births. Male-to-female ratios have varied between 1.0 and 2.8:1 in previously published studies from different regions [1—3,5—11]. In Sweden, the prevalence was 3 per 100,000 live births, with a male-to-female ratio of 1.5:1 between 1970 and 1989 [12].

The etiology of BE is not completely understood, but it is considered to be a complex disease involving both environmental and genetic mechanisms [13]. Variations in the prevalence between different ethnic groups, an increased risk among relatives, and several chromosomal aberrations, particularly 22q11 duplication, have been described, and indicate genetic involvement in the pathogenesis [13—18]. Assisted reproductive technology (ART) [19,20] and seasonal variation [9] have been associated with an increased risk, whereas the results concerning maternal age [2,5,8] and smoking [8] as potential risk factors are inconclusive.

There are no data, to date, on the contemporary prevalence or the prevalence over time of BE in Sweden, and studies on associated malformations and potential risk factors are sparse and contradictive. Therefore, the objectives of this study were to: (a) assess the prevalence of BE in Sweden during the last four decades; (b) describe associated malformations; and (c) investigate potential risk factors for BE, in a nationwide register-based cohort study.

Materials and methods

Study design

A case-control study nested within the entire pool of live births in Sweden between 1973 and 2011 was performed.

Setting

The Swedish healthcare system is publicly funded, and patients with congenital malformations, such as BE, are treated at one of four pediatric surgery clinics. A unique personal identification number (PIN) is assigned to all residents and can be used for linkage of national registers.

The Karolinska Institutet Ethics Committee approved the study.

Data sources

Several sources were used to identify the study subjects, outcomes, and exposures:

(a) The Medical Birth Register (MBR) contains data on approximately 99% of all antenatal care and deliveries, as well as data from the first medical examination of each newborn since 1973. The MBR was used to retrieve data on exposures and covariates.
(b) The Register of Congenital Malformations has been part of the MBR since 1973 and contains data as of 1964. It is based on chromosomal abnormalities and congenital malformations reported from maternity wards, pediatric wards, and cytogenetic laboratories.
(c) The National Patient Register (NPR) holds information on discharge diagnoses (primary and contributory) coded according to the ICD system for in-hospital and out-patient care, with nationwide in-hospital care coverage since 1987.
(d) The Cause of Death Register contains data on all deaths of Swedish residents since 1952, coded according to the ICD system.

The Swedish National Board of Health and Welfare (SNBHW) maintains all registers.

Study subjects

Cases and controls were identified within the population of total live births in Sweden between 1973 and 2011. Cases were subjects with a diagnostic code for BE: 753.50 [ICD-8], 753F [ICD-9] and Q64.1 [ICD-10], from the registers (a—d). Altogether, 213 patients were registered with an ICD code for BE. Three of the authors (GRE, MF, AN) independently validated all data for each individual case in order to ensure a correct classification of the diagnosis. After validation, 120 cases were identified as true BE cases (Appendix A). Cases were randomly matched with five controls per patient, based on birth year and sex, from the MBR. The match was performed by the SNBHW.

Exposures and covariates

Birth descriptive data (i.e. sex, delivery mode, Apgar score, multiple births, gestational age, birth weight, small for gestational age/large for gestational age (SGA/LGA), perinatal and neonatal mortality, and time to first discharge from hospital) were obtained from the MBR. Information on associated malformations (ICD-coded) and syndromes, as well as surgical procedures, including surgery for congenital inguinal hernia, and cryptorchidism, were assembled by individual registry entries. Information on maternal exposures (i.e. ART, parity, age, origin of birth, body mass index (BMI), smoking, and maternal comorbidities) was collected from the MBR. Maternal age (mean) was reported and categorized. Origin of birth was categorized into Nordic (Sweden, Norway, Finland, Denmark, and Iceland) or Non-nordic. Maternal weight and height at 10—12 weeks of pregnancy were used for BMI calculations, and categorized into four groups. Maternal smoking was categorized into smoker or