

ORIGINAL ARTICLE

Trends in the incidence of cryptorchidism and hypospadias of registry-based data in Korea: a comparison between industrialized areas of petrochemical estates and a non-industrialized area

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This study aimed to represent the recent trends in the nationwide incidence of cryptorchidism and hypospadias in Korea, and to determine whether there is evidence of spatial heterogeneity in the incidence. The incidence was calculated as the number of newly diagnosed patients (males) during the first 4 years after a live birth in a population, nationally and regionally (a non-industrialized area (Chuncheon) and petrochemical estates (Yeocheon and Ulsan)), between 2000 and 2005. The data (numerator) for new patients were acquired from the National Health Insurance Review Agency, and the data (denominator) for the resident registration population were from the National Statistical Office. Between 2000 and 2005, the national incidence of cryptorchidism and hypospadias had an increased tendency from 5.01 to 17.43 per 10 000 persons and from 1.40 to 3.28 per 10 000 persons, respectively. The incidence of cryptorchidism was significantly higher in Yeocheon (throughout the study period) and in Ulsan (2001, 2002, 2004 and 2005) than the national incidence, whereas the incidence in Chuncheon was significantly lower in 2001 and 2002. It was difficult to compare the rates of hypospadias yearly and regionally because of the small number of cases. In conclusion, the incidence of cryptorchidism has recently increased in Korea. The petrochemical estates, Yeocheon and Ulsan, had a significantly higher incidence of cyptorchidism than the national incidence, which suggests that further study is needed to obtain a more precise estimation of the trends in the incidence of the anomalies and to confirm the association between petrochemicals and the anomalies.

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INTRODUCTION

Cryptorchism is the most common male genital anomaly identified at birth, affecting 2–4% of full-term male births.¹ One-half of such testicles descend in the first month after birth, hence the prevalence of true cryptorchism at 1 year of age is 1–2%.² Hypospadias is the most common congenital anomaly of the penis and has historically been identified in 0.3% of newborn boys.³ An overall increase in hypospadias in developed industrial countries of Europe and North America has been noted.⁴ Cryptorchidism can occur as an isolated disorder or may be associated with other congenital anomalies. Approximately 8–10% of boys with hypospadias have associated cryptorchidism.⁵

The etiology of cryptorchidism remains for the most parts unknown, and a large amount of research has focused on the possible genetic contribution to human cryptorchidism and on environmental factors acting as endocrine disruptors of testicular descent that might also contribute to the increased incidence of cryptorchidism in the recent decades.² Cryptorchidism has been strongly and consistently related to the risk of testicular cancer, with more than a dozen studies reporting relative risks ranging from 2.1 to 17.6.⁶ The increase in the

prevalence of hypospadias, cryptorchidism, male infertility and testicular cancer observed in Western countries suggests a possible influence of environmental factors acting as endocrine disruptors.^{2,7} Cryptorchidism and hypospadias may be caused by antiandrogenic substances, such as phthalates, which are one of the main petrochemical products in the environment.⁸

There are no data on the nationwide incidence and/or prevalence of cryptorchidism and hypospadias in Korea. We represented the recent trends of the nationwide incidence of cryptorchidism and hypospadias compared with the industrialized areas of a petrochemical complex.

MATERIALS AND METHODS

The incidence of cryptorchidism and hypospadias was defined as the number of newly diagnosed patients (males) during the first 4 years after a live birth in a population. The number of newly diagnosed patients with cryptorchidism and hypospadias (the numerator) was acquired from the National Health Insurance Review Agency (NHIRA) of South Korea, nationally and regionally (non-industrialized area and industrialized areas with petrochemical complexes),

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Table 1 Population and frequency of CO and HS in males aged 0–4 years, nationally and regionally (Yeochon, Ulsan and Chuncheon), from 2000 to 2005^a

Year	National			Yeochon			Ulsan			Chuncheon		
	Population	CO	HS	Population	CO	HS	Population	CO	HS	Population	CO	HS
2000	1 689 517	846	236	876	4	1	44 370	27	1	8558	3	0
2001	1 621 395	1821	420	844	5	0	42 056	80	5	8221	1	0
2002	1 530 531	1694	293	675	13	0	38 993	70	15	7902	0	0
2003	1 450 715	2265	434	632	13	1	36 118	67	8	7471	9	2
2004	1 372 979	2206	344	611	12	1	33 627	78	4	6993	5	0
2005	1 263 896	2156	406	707	14	1	30 770	75	9	6380	7	0

Abbreviations: CO, cryptorchidism; HS, hypospadias.

^a Yeochon and Ulsan are two industrialized cities, while Chuncheon is a non-industrialized area.

from 2000 to 2005. The data for the real population, which is the denominator, were acquired from the resident registration of the National Statistical Office of South Korea released by five age units every year. To avoid double counting, the resident registration number of new patients and addresses were compared. Table 1 shows the population and frequency of cryptorchidism and hypospadias, between the ages of 0 and 4 years, nationally and regionally. The incidence of cryptorchidism and hypospadias was measured on a scale of per 10 000 people.

The survey was conducted nationwide and in three regions, which included two industrialized areas of petrochemical estates and one non-industrialized area. The non-industrialized area, Chuncheon City (CC), is a rural area in a central mountainous region of Korea, where a few administrative and educational centers are located. The two industrialized cities were Ulsan (UL) and Yeochon (YC). UL is an industrial center and is located on the southeast coast of the Korean peninsula; the industries of UL include automobile manufacturing, ship construction and petrochemical facilities. The other industrial center, YC, is located on the southwest coast and contains oil refineries and other petrochemical facilities. The atmospheric concentrations of NO₂, total suspended particulates, PM₁₀ and volatile organic compounds increased nationwide in South Korea between 2000 and 2005.⁹ The air in YC and UL area was highly polluted with NO₂, SO₂, total suspended particulates, PM₁₀, HCHO and Volatile Organic Compounds (VOC) such as benzene, toluene, xylene, styrene, etc., including styrene and several hazardous aromatic and aliphatic species, whereas CC was one of the least polluted areas in South Korea.

The instruments used to manage health care security in South Korea comprise the Health Insurance System (HIS), which is funded by mandatory social insurance contributions and the Medical Aid Program (MAP) financed by the central government to provide medical service to the poor. The health care security system covers the

whole population: ~97% of the population is covered by HIS and the remaining 3% by MAP. When physicians request payment for a medical service to the Korean Health Insurance Corporation, they use International Classification of Disease codes for diagnosis and treatment. NHIRA then assesses all such requests for payment. We believe that this institutionalized standardized system probably increases the reliability of the data used.

The diagnosis of cryptorchidism and hypospadias was carried out by a four-rate assortment search in the International Classification of Disease 10. The diagnosis assortment code for cryptorchidism-unilateral is Q531, cryptorchidism-bilateral is Q532 and cryptorchidism-unspecified is Q539. The diagnosis assortment code for hypospadias-balanic is Q540, hypospadias-penile is Q541, hypospadias-penosrotal is Q542, hypospadias-perineal is Q543, other hypospadias is Q548 and hypospadias-unspecified is Q549. Table 2 shows frequency of the cryptorchidism and hypospadias according to four-character subcategories of the International Classification of Disease 10 in YC, UL and CC.

Statistical analysis was performed using Stata 10.0 (Stata Corp., College Station, TX, USA). The incidence rates between regions have been compared using exact Poisson 95% confidence interval (CI).

RESULTS

Cryptorchidism (cases per 10 000 persons)

The incidence rates of cryptorchidism and 95% Poisson CI at ages of 0–4 years during 2000–2005 are recorded in Table 3. The national rate of the total newly diagnosed cases of cryptorchidism has significantly increased in 2001 and 2003, and continued to increase in 2004 and 2005. The rate in YC sharply increased in 2002 and further increased in 2003 and 2005. The rate in UL also sharply increased in 2001 and further increased in 2005. The rate of CC was lower than those of national, YC and UL throughout the study period. Throughout the

Table 2 Frequency of cryptorchidism and hypospadias using four-character subcategories of the International Classification of Disease 10 in Yeochon/Ulsan/Chuncheon, respectively

Year	Cryptorchidism ^a				Hypospadias ^b						
	Q531	Q532	Q539	Total	Q540	Q541	Q542	Q543	Q548	Q549	Total
2000	2/14/1	0/4/2	2/9/0	4/27/3	0/0/0	1/1/0	0/0/0	0/0/0	0/0/0	0/0/0	1/1/0
2001	2/36/1	1/10/0	2/34/0	5/80/1	0/0/0	0/1/0	0/2/0	0/0/0	0/1/0	0/1/0	0/5/0
2002	4/26/0	1/6/0	8/38/0	13/70/0	0/1/0	0/3/0	0/4/0	0/0/0	0/0/0	0/7/0	0/1/0
2003	2/23/4	0/2/1	11/42/4	13/67/9	0/2/1	0/1/0	1/0/0	0/0/0	0/0/0	0/5/1	1/8/2
2004	1/32/2	1/13/0	10/33/3	12/78/5	0/0/0	0/1/0	1/1/0	0/0/0	0/0/0	0/2/0	1/4/0
2005	3/41/5	4/11/0	7/23/2	14/75/7	0/1/0	0/1/0	0/2/0	0/0/0	0/0/0	1/5/0	1/9/0

^a Cryptorchidism: Q531, unilateral; Q532, bilateral; Q539, unspecified.

^b Hypospadias: Q540, coronal; Q541, penile; Q542, penosrotal; Q543, perineal; Q548, other; Q549, unspecified.

Table 3 Newly diagnosed incidence rate (per 10 000 persons) of cryptorchidism and exact Poisson 95% CI between 0 and 4 years of age in 2000–2005^a

Year	Incidence (95% CI)			
	National	Yeocheon	Ulsan	Chuncheon
2000	5.01	45.66 (12.44–116.9)	6.09 (4.01–8.85)	3.51 (0.72–10.2)
2001	11.23	59.24 (19.24–138.3)	19.02 (15.08–23.68)	1.21 (0.03–6.78)
2002	11.07	192.6 (102.6–329.3)	17.95 (13.99–22.68)	0 (0–4.67)
2003	15.61	205.7 (109.5–351.8)	18.55 (14.38–23.56)	12.05 (5.51–22.9)
2004	16.07	196.1 (101.3–342.5)	23.20 (18.34–28.95)	7.15 (2.32–16.9)
2005	17.43	198.0 (108.3–332.2)	24.37 (19.17–30.55)	11.0 (4.41–22.6)

Abbreviation: CI, confidence interval.

^a Yeocheon and Ulsan are two industrialized cities, while Chuncheon is a non-industrialized area.

survey period, the incidence of cryptorchidism in YC, compared with the national, UL and CC rates, was significantly higher. UL also showed significantly higher rates than national rates throughout the study period besides in 2000 and 2003. CC had the lowest rate compared with other regions.

Hypospadias (cases per 10 000 persons)

Table 4 shows the incidence rates of hypospadias and 95% Poisson CI at the ages of 0–4 years, during 2000–2005. The national rate of the total newly diagnosed patients with hypospadias has significantly increased in 2001 (1.4) and 2003. The rate slightly dropped in 2004 and increased again in 2005 (3.8). YC had only four new cases throughout the whole study period (Table 1). Compared with the national rates, however, YC had higher incidences from 2003 to 2005, especially in 2004 (Table 4). The incidence in UL was slightly lower than the national level during the study period, except in 2002. There was no newly diagnosed case in CC throughout the study period besides 2003. However, the number of new cases was too small to compare yearly and regionally.

DISCUSSION

A number of animal studies have shown that *in utero* or perinatal exposure to industrial chemicals containing estrogenic properties or antiandrogens may cause hypospadias, cryptorchidism, reduced sperm count and testicular cancer in males, and may represent a symptom of an underlying developmental disease, the testicular dysgenesis syndrome.⁷ The list of chemicals that are known to affect reproduction in humans through endocrine mechanisms includes pesticides (DDT and its metabolites), polychlorinated biphenyls, dioxins, naturally occurring plant estrogens (phytoestrogens) and

mycotoxins. Several other chemicals (alkylphenols, phthalates and bisphenol A) have been shown to interfere with some endocrine-mediated processes.¹⁰

However, such clear effects of an endocrine-induced disruption of chemicals on reproductive organs have not yet been shown in humans. In a systemic review of epidemiological studies with implications for the estrogen hypothesis, Storgaard *et al.*¹¹ found no strong epidemiological evidence to indicate that prenatal exposure to estrogen is linked to disturbed development of the male reproductive organ, with the possible exception of testicular cancer. On the other hand, García-Rodríguez *et al.*¹² observed a link between the orchidopexy rate and use of pesticides in three of four different municipalities. Kirstensen *et al.*¹³ showed an increased risk among sons of farmers and gardeners in a nationwide cohort and Weidner *et al.*¹⁴ reported an increased risk among sons of mothers occupied with gardening. North and Golding¹⁵ found that a vegetarian diet was associated with hypospadias, perhaps because of the phytoestrogens in this type of diet. Published studies suggest that the incidence of these congenital anomalies has increased during the past half century in developed industrial countries, but not in less developed countries,⁷ and evidence suggests that there is geographical variation in the prevalence of cryptorchidism and hypospadias at birth.¹⁶ Regional and temporal trends may help to identify environmental factors that might be associated with these disorders.⁷

Industrial development has been remarkable over the past 40 years in South Korea, which has resulted in the spread of environmental pollution.⁹ In the current study, the national incidence of cryptorchidism and hypospadias in males aged 0–4 years showed an increased tendency from 5.01 to 17.43 per 10 000 persons and from 1.40 to 3.28 per 10 000 persons, respectively, between 2000 and 2005. The incidence of cryptorchidism in YC was significantly higher than the national incidence throughout the study period, whereas the incidence in the non-polluted area (CC) was significantly lower in 2001 and 2002. UL had a significantly increased rate of hypospadias in 2002 and YC in 2004, but it was difficult to compare the rates yearly and regionally because of a small number of the congenital anomaly. There are also indications that cryptorchidism may have increased in incidence in several countries.¹⁷ The reported values are 4–42 cases per 10 000 births. In England, the incidence of cryptorchidism increased by more than 60% between the 1950s and 1980s.¹⁰ The reported prevalence of hypospadias is 0.1–0.8 per 10 000 male births.¹¹ There is also some evidence for an increase in hypospadias rates during the last few decades.^{18,19} On the contrary, a recent report says that the incidence of cryptorchidism in a small cohort of newborns has not changed from the 1950s.²⁰ A review of the epidemiological data on the hypospadias amassed to date refutes claims for an increase in hypospadias rates,²¹

Table 4 Newly diagnosed incidence rate (per 10 000 persons) of hypospadias and exact Poisson 95% CI between 0 and 4 years of age in 2000–2005^a

Year	Incidence (95% CI)			
	National	Yeocheon	Ulsan	Chuncheon
2000	1.40	11.42 (0.29–63.6)	0.23 (0.01–1.26)	0 (0–4.31)
2001	2.59	0 (0–43.71)	1.19 (0.39–2.77)	0 (0–4.49)
2002	1.91	0 (0–54.65)	3.85 (2.15–6.35)	0 (0–4.67)
2003	2.99	15.82 (0.40–88.16)	2.21 (0.96–4.36)	2.68 (0.32–9.67)
2004	2.51	16.37 (0.41–91.19)	1.49 (0.48–3.47)	0 (0–5.28)
2005	3.28	14.14 (0.36–78.81)	2.93 (1.34–5.55)	0 (0–5.78)

Abbreviation: CI, confidence interval.

^a Yeocheon and Ulsan are two industrialized cities, while Chuncheon is a non-industrialized area.

and there was no statistical change in hypospadias rates in the New York State from 1992 to 2005.²² It is difficult to distinguish between cryptorchidism and retractile testes, and coronal and glandular hypospadias are indistinct and may cause underreporting of cases. Differences in case ascertainment may introduce variations in reported rates of the anomalies, but the extent of confounding by these differences is unknown. Moreover, assumptions are made about the number of reference subjects, who are all not examined for the anomalies. Hospital registry data have been shown to be unreliable.¹⁰ We believe that the institutionalized standardized system (HIS, MAP and NHIRA) in Korea minimized discrepancy in the reporting system between regions and increased the reliability of the data used, although the reported number of the cryptorchidism in this study seems to be smaller than western reports. The point that we stress here is that a region of petrochemical estates had a significantly higher incidence of cryptorchidism than a non-industrialized area. Hydrocarbon compounds encountered by petrochemical workers were reported to exert a detrimental effect on human spermatogenesis,²³ reduce sperm motility²⁴ and increase chromosomal aberrations in sperm.²⁵ Issues that remain to be resolved are appropriate measurement of exposure to multiple petrochemical compounds that act conjointly through mechanisms similar to endogenous hormones.

However, the results in this study had some limitations to be addressed. First, we could not avoid methodological limitations of the registry-based data. The duration of residence, occupational history of parents, exposure history of endocrine disruptors in daily life, defects among stillbirths and medical history such as low birth weight and prematurity were not included. Second, the increase in incidences might also be affected by other factors such as public recognition and physician's interest. Third, the small number of the congenital anomalies, particularly for hypospadias, may not represent trends in the incidences yearly and regionally.

In conclusion, the incidences of cryptorchidism have recently increased in Korea. The higher incidences of cryptorchidism in the areas of petrochemical complexes suggest that further community-based epidemiological studies using standardized diagnostic criteria and examination techniques are required to obtain a more precise estimation of the trends in the incidence of the anomalies and to confirm the association between petrochemicals and the anomalies.

AUTHOR CONTRIBUTIONS

All authors discussed the results and implications and commented on the manuscript at all stages. SCK developed the concept and designed the study, and wrote the paper. SKK gathered and analysed data. YPH interpreted and supervised its analysis, and edited the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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