

## Cryptorchidism and Hypospadias in Sons of Gardeners and Farmers

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Cryptorchidism and hypospadias have been related to prenatal estrogen exposure in animal models. Some chemicals used in farming and gardening have been shown to possess estrogenic and other hormone-disrupting effects. Earlier studies have indicated increased risks of urogenital malformations in the sons of pesticide applicators. In the present study, parental occupation in the farming and gardening industry among 6,177 cases of cryptorchidism, 1,345 cases of hypospadias, and 23,273 controls, born live from 1983 to 1992 in Denmark, was investigated in a register-based case-control study. A significantly increased risk of cryptorchidism but not hypospadias was found in sons of women working in gardening (adjusted odds ratio = 1.67; 95% confidence interval, 1.14–2.47). The risks were not increased in sons of men working in farming or gardening. The increased risk of cryptorchidism among sons of female gardeners could suggest an association with prenatal exposure to occupationally related chemicals. *Key words:* case-control studies, cryptorchidism, hypospadias, pesticides. *Environ Health Perspect* 106:793–796 (1998). [Online 12 November 1998]

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There is evidence that male reproductive health has suffered impairment over the last decades. A possible decline in semen quality in several countries (1–5), which has been the focus of considerable controversy (6,7), parallels a well-established increase in the incidence of testicular cancer in young men in several countries (8–10). Increasing incidences of cryptorchidism and hypospadias have likewise been reported (11–14); however, time trends associated with these malformations may be difficult to interpret due to potential changes in diagnostic criteria and treatment routines (13). Recently, an association between fetal exposure to environmental estrogens and the impairment of male reproductive health has been suggested (15). In animal studies, estrogen exposure during pregnancy resulted in the development of cryptorchidism and hypospadias in the male offspring (16,17). Some pesticides have been reported to possess estrogenic or antiandrogenic properties (18–20). Prenatal exposure to such pesticides may therefore increase the risk of cryptorchidism and hypospadias. Although indicative of such associations, previous research on potential pesticide exposure and urogenital malformations is still too sparse for firm conclusions to be drawn (21–26).

Pesticides and additives used in formulations with pesticides reported to have estrogenic or antiandrogenic activity (18–20,27) have been used in Denmark in farming and gardening (28,29). The present register-based case-control study explores the hypothesis that maternal occupation in farming or gardening increases the risk of cryptorchidism and hypospadias in the male offspring. In addition, as most previous

studies have made no distinction between male and female exposure, we decided to investigate paternal occupation in farming and gardening as well. No attempt was made to explore occupations other than farming and gardening because we had no *a priori* hypothesis of exposure to hormone-disrupting substances in other occupations.

### Materials and Methods

**Subjects.** All residents of Denmark are provided with a personal identification number that follows the person throughout life; the number is recorded in the Danish Population Register. This registration provides a unique opportunity for epidemiological investigation. Data in The Danish National Patient Register, which nationwide covers all hospital discharge diagnoses and operations performed since 1977, were linked to the Fertility Database at Statistics Denmark, using patients' personal identification numbers. The Fertility Database holds a series of background variables on children and their parents obtained from other registers operated by Statistics Denmark (30).

In our study we included all males born live in Denmark from 1983 to 1992, who were discharged from a Danish hospital with a diagnosis of cryptorchidism or hypospadias, including all variants of both conditions as defined in the World Health Organization *International Classification of Diseases*, 8th and 10th revisions, or with an operation performed specifically for cryptorchidism or hypospadias. Cases were identified in the Danish National Patient Register, which at the time of retrieval included records of all discharge diagnoses until 1995 and all operations performed

until 1996 in Denmark. Using similar criteria, additional cases were identified in the Danish Malformation Register, where malformations observed in the first year of life may be recorded. The study was restricted to liveborn boys because the observation and registration of minor malformations is less complete in stillborn children. In addition, the relevant occurrence of cryptorchidism is difficult to assess in stillborn boys because the testes descend into the scrotum shortly before termination of normal gestation.

Of the 6,177 cases with cryptorchidism identified, 4,226 cases had a record of surgical treatment related to cryptorchidism and 206 cases were identified in the Danish Malformation Register only. Of the 1,345 cases with hypospadias identified, 650 cases had a record of surgical treatment related to hypospadias and 45 cases were identified in the Danish Malformation Register only. Ninety-two boys had a record of both cryptorchidism and hypospadias and were included as cases in both analyses.

All information about risk factors was obtained from the Fertility Database at Statistics Denmark (30). Data concerning parental occupation in the year of conception were obtained from tax authority information sheets on which the employer had indicated a previously agreed serial number corresponding to the employee's working place (31). Gardening included work in greenhouses, outdoor gardening, orchards, and nurseries. Landscape gardeners make no appreciable use of pesticides and were therefore included in the "other and not available" category, as were parents in unspecified service jobs associated with gardening and farming.

Risk factors were studied by comparison with one common control group from the Fertility Database ( $n = 23,273$ ), from which all incidentally occurring cases had been excluded. The control group was selected at random from the entire population of boys born in Denmark between 1983 and 1992.

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**Statistical analyses.** Statistical analyses were performed using contingency tables and unconditional logistic regression analysis. Year of birth was included as a covariate in all analyses. This was necessary because boys with different years of birth have different probabilities of being recorded with cryptorchidism or hypospadias due to different observation time. Hence, boys born in 1983 had an average of 12.5 years in which the diagnoses could be recorded; those born in 1992 had only 2.5 years. The inclusion of year of birth in the statistical analyses takes account of this difference between the birth cohorts.

Results are presented both with and without adjustment for birth weight. Further multivariate analyses included a number of covariates: gestational age, parity, twin birth, a maternal history of previous stillbirth, parental age, nationality and professional status (self-employed, salaried employee, skilled worker, unskilled worker), maternal occupation in farming or gardening, and the occurrence of the same malformation in an older brother.

## Results

Table 1 shows the risk of cryptorchidism and hypospadias in relation to parental occupations in farming and gardening. The risk of cryptorchidism was significantly

increased in the sons of women working in farming or gardening [odds ratio (OR) = 1.38; 95% confidence interval (CI), 1.10–1.73]. The risk was most pronounced in the sons of women working in gardening (OR = 1.67; CI, 1.14–2.47). Adjustment for birth weight had no material influence on the estimates. Paternal occupation in farming or gardening had no effect on the risk of cryptorchidism (OR = 1.08; CI, 0.97–1.22). The association between maternal occupation in gardening and cryptorchidism accounts only for a small fraction of the total occurrence of cryptorchidism in the population. With an OR of 1.7 and a prevalence of exposure of 0.4%, the attributable proportion is only around 0.3%.

Maternal or paternal occupation in farming or gardening had no significant effect on the risk of hypospadias.

The effects presented in Table 1 were not materially affected by adjustment for gestational age, parity, twin birth, maternal history of previous stillbirth, parental age, nationality and professional status (self-employed, salaried employee, skilled worker, unskilled worker), maternal occupation in farming or gardening, and the occurrence of the same malformation in an older brother.

To anticipate the risk of attenuation of the estimated parameters due to erroneous diagnosis or coding of the diagnosis, we

repeated all analyses on the subsets consisting of cases who had a record of surgical treatment related to cryptorchidism or hypospadias. These analyses excluded boys with spontaneous descent of the testes before 1 year of age, as orchiopexy was not routinely performed on children younger than this age. The results, presented in Table 2, were similar to the results in Table 1. A slight attenuation of the parameter estimates was seen, from 1.38 to 1.36 for maternal occupation in farming or gardening and from 1.67 to 1.52 for maternal occupation in gardening. Furthermore, the width of the confidence intervals of the estimated parameters increased, as was expected due to the decrease in sample size.

## Discussion and Conclusion

This register-based case-control study in Denmark was designed to determine the association between parental occupation in the farming and gardening industry and the occurrence of hypospadias and cryptorchidism in the male offspring.

We found a significantly increased risk of cryptorchidism in the sons of female gardeners and no effect of paternal work in gardening on cryptorchidism. Our results are coherent with earlier studies reporting an increased frequency of orchiopexy in areas with extensive use of pesticides in

**Table 1.** The occurrence of cryptorchidism and hypospadias in sons of gardeners and farmers

	Controls (%) (n = 23,273)	Cryptorchidism			Hypospadias				
		Cases (%) (n = 6,177)	OR <sup>a</sup>	OR <sup>b</sup>	CI <sup>b</sup>	Cases (%) (n = 1,345)	OR <sup>a</sup>	OR <sup>b</sup>	CI <sup>b</sup>
Mother in farming or gardening	1.3	1.8	1.35	1.38	1.10–1.73	1.6	1.22	1.27	0.81–1.99
Farming	0.8	1.0	1.21	1.28	0.94–1.73	0.8	1.10	1.26	0.68–2.33
Gardening	0.4	0.6	1.73	1.67	1.14–2.47	0.4	0.95	0.85	0.34–2.11
Other and not available	0.2	0.2	–	–	–	0.4	–	–	–
Father in farming or gardening	6.4	6.8	1.05	1.08	0.97–1.22	6.8	1.11	1.19	0.96–1.49
Farming	4.1	4.3	1.02	1.08	0.93–1.24	4.2	1.06	1.16	0.88–1.53
Gardening	0.3	0.4	1.26	1.28	0.80–2.04	0.5	1.41	1.47	0.63–3.39
Other and not available	2.0	2.1	–	–	–	2.2	–	–	–

Abbreviations: OR, odds ratio; CI, 95% confidence interval.

<sup>a</sup>Adjusted for year of birth.

<sup>b</sup>Adjusted for year of birth and birth weight.

**Table 2.** The occurrence of cryptorchidism and hypospadias in sons of gardeners and farmers, with analyses restricted to cases with a record of surgical treatment

	Controls (%) (n = 23,273)	Cryptorchidism			Hypospadias				
		Cases (%) (n = 4,226)	OR <sup>a</sup>	OR <sup>b</sup>	CI <sup>b</sup>	Cases (%) (n = 650)	OR <sup>a</sup>	OR <sup>b</sup>	CI <sup>b</sup>
Mother in farming or gardening	1.3	1.8	1.34	1.36	1.05–1.77	1.1	0.84	0.90	0.42–1.92
Farming	0.8	1.0	1.22	1.27	0.90–1.80	0.9	1.22	1.43	0.63–3.25
Gardening	0.4	0.6	1.57	1.52	0.96–2.40	0.2	0.41	0.37	0.05–2.70
Other and not available	0.2	0.2	–	–	–	0.0	–	–	–
Father in farming or gardening	6.4	6.8	1.04	1.08	0.94–1.23	6.5	1.05	1.15	0.83–1.58
Farming	4.1	4.5	1.08	1.13	0.96–1.33	3.7	0.94	1.04	0.69–1.58
Gardening	0.3	0.4	1.09	1.10	0.62–1.95	0.2	0.49	0.51	0.07–3.69
Other and not available	2.0	1.9	–	–	–	2.6	–	–	–

Abbreviations: OR, odds ratio; CI, 95% confidence interval.

<sup>a</sup>Adjusted for year of birth.

<sup>b</sup>Adjusted for year of birth and birth weight.

Spain (21) and an increased occurrence of cryptorchidism in boys born on Norwegian farms where pesticides had been in use (24). These studies made no discrimination between paternal and maternal exposure. A biologic effect mediated through paternal exposure seems less plausible than an effect on the embryo that acts through the mother. The inclusion of paternal exposure thus serves as a control because factors related to the lifestyle of agricultural families would lead to an apparent effect of both maternal and paternal exposure, while an effect seen only or predominantly in relation to maternal exposure provides a higher degree of evidence of a true effect.

Maternal estrogen exposure during pregnancy has been shown to cause cryptorchidism in the offspring of mice and rats (16,17), and prenatal exposure of rats to the antiandrogenic pesticide vinclozolin has also been associated with cryptorchidism (32). The increased risks of cryptorchidism among sons of female gardeners could therefore, in principle, be attributable to the action of estrogenic or antiandrogenic compounds, as pesticides with these effects (18–20) were used in Denmark in gardening during the study period (29). Furthermore, the estrogenic compound nonylphenol (27) was used in large amounts in formulations with pesticides during the same period (28); therefore, exposure to pesticides with endocrine activities was not necessary for exposure to estrogenic chemicals to occur in the gardening industry. Dermal and inhalation exposure to pesticides has been found to occur among workers in Danish greenhouses (33) and may be expected to have occurred in our study population as well. Furthermore, pesticide exposure in greenhouses has probably been considerably higher than in farming due to the manual working procedures applied in greenhouses. However, these conjectures remain speculative in the absence of measured or estimated exposures.

Women working in farming or gardening during pregnancy were not necessarily exposed to pesticides. If occupational exposure to fetotoxic chemicals was suspected to occur during pregnancy, Danish legislation permitted the pregnant woman to take paid leave. Information on the occupational status was available only for the year of conception and not at the exact time of conception. If prenatal exposure to pesticides truly increases the risk of cryptorchidism, these uncertainties in exposure assessment will tend to produce a bias in the estimated risks from the true value and towards unity.

Like cryptorchidism, hypospadias has been associated with maternal exposure to

estrogenic and antiandrogenic compounds in rodents (17,34). Along with an increased risk of cryptorchidism, a moderately increased risk of hypospadias was found among sons born on Norwegian farms where pesticides and tractor spraying equipment had been in use (24), whereas the risk of hypospadias was not increased among sons of agricultural workers in California (35). We were not able to detect an increased risk of hypospadias among sons of parents working in farming or gardening. Either the exposure was insufficient, the association of hypospadias with gardening or farming was too weak to be detectable among the available number of cases potentially exposed to pesticides, or no such association truly exists in humans.

We have observed a statistically significant increased occurrence of cryptorchidism in sons of female gardeners, but we emphasize that the increase is of moderate magnitude and that this association can only account for a small proportion of the total occurrence of cryptorchidism in the population. However, our finding substantiates earlier reports of an increased risk of urogenital malformations among boys potentially exposed to pesticides *in utero* and confines the increased risk to maternal occupation. It remains to be established whether this association is caused by prenatal exposure to occupationally related chemicals and, more specifically, estrogenic and other hormone-disrupting agents. Studies with detailed exposure assessment are warranted in order to explore these associations more fully.

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