A case-control study of the aetiology of cryptorchidism

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SUMMARY A study of cryptorchidism was undertaken based on patients identified through the Oxford Record Linkage Study. The cumulative lifetime incidence of archidopexy among males in the study area was estimated to be 3.38%; 88% of orchidopexies were performed on males aged 5 years and over and 32% on those aged 10 and over. In a case-control study with 146 cases ascertained at orchidopexy and 146 matched controls there was a substantially increased risk of cryptorchidism for those who had undergone breech labour. Raised risks of cryptorchidism were found for boys born to mothers who were primigravidas or aged under 20, and a significantly reduced risk was found for boys whose mothers were of B blood group. There was a gradient of increasing risk with decreasing birth weight and a significantly raised risk associated with clinical inguinal hernia. Since cryptorchidism and testicular cancer share several risk factors, it may be profitable to study newly identified risk factors for cryptorchidism in relation to testicular cancer.

Testicular maldescent is the most common disorder of sexual differentiation¹ and one of the most commonest congenital abnormalities in males.² The condition is particularly important because of its strong associations with infertility^{2,3} and testicular malignancy²⁻⁷. In nearly all cases the aetiology of cryptorchidism is unknown.¹

This investigation used data extracted from the files of the Oxford Record Linkage Study (ORLS) to investigate the role of prenatal and perinatal factors in the aetiology of cryptorchidism. The ORLS^{8,9} was begun in 1962, and since that time data have been collected on all hospital and domiciliary births, all hospital admissions and operations, and all deaths of residents in Oxfordshire and, since 1966, West Berkshire—that is, a total population of about 800 000 and about 14 000 births a year. The Registrar General notifies ORLS of all deliveries within the area covered by the study; recording of births is therefore probably virtually complete. Trained clerks abstract information about the pregnancy, delivery, and puerperium of the mother, and about the child at birth, from hospital notes or, for domiciliary births, midwives' notes.

Methods

The ORLS records of hospital admissions for the years 1976–8 (the most recent years available) were searched to identify all patients who had had a

diagnosis of cryptorchidism and the operation orchidopexy. The birth records of such patients who were born in 1970–2 were then sought in the ORLS birth files. The items of information included in the ORLS birth records have been altered and expanded periodically, and the period 1970–2 was chosen as the most recent for which consistent data were available and which would include a fairly large number of births of patients operated on in 1976–8. Singleton born patients whose birth records were located—that is, those singletons born within the ORLS area—formed the cases for the study. For each case, one matched control birth was chosen randomly from the file of birth records: each control was matched to the case for year of birth, hospital of delivery (or, for domiciliary deliveries, geographical area of domiciliary delivery), male sex baby, singleton birth, live birth, and not neonatal death. For each case and control, information about the pregnancy, birth, and puerperium, and about the baby, was extracted from the records. Differences between cases and controls with respect to these factors were tested for statistical significance by analysing the data as matched pairs using McNemar's test¹⁰ and linear logistic regression.¹¹ For cases, the ORLS records were also searched for all hospital admissions between birth and the index orchidopexy operation; all recorded diagnoses at these admissions and at the admission for orchidopexy were noted. The matched controls from the case-

control study would not have been satisfactory as controls for this analysis because they were not known to have remained in the study area after birth; the frequencies of diagnoses in cases were compared therefore with published data on the frequencies of such diagnoses. Seasonal variations in the month of birth of cases and in the month of last menstrual period of mothers of cases were tested for significance by the method of Walter and Elwood.¹² For births, correction was made for monthly variation in the total numbers of births in the ORLS area during 1970–2. For last menstrual periods, 1970–2 data for the area were not available, and corrections were based instead on last menstrual periods for all births in the ORLS area during 1973–8.

Results

A total of 813 admissions for orchidopexy for cryptorchidism were recorded in residents in the ORLS area in 1976–8, mainly of boys aged 6 to 10 years (fig). Fifty seven of the patients were admitted for the operation twice within the period—that is, 756 residents underwent orchidopexy in the area. The cumulative life time risk of archidopexy for males in the area, assuming 1976–8 rates of admission, was 3.38%.

In the ORLS area during 1976–8, 221 boys born in 1970–2 had orchidopexies. The birth records of 150 (68%) of these boys were traced in the ORLS files: the other 71 could not be traced and presumably were born outside the area. Four of the 150 boys traced were twins (3.38 cases born from multiple pregnancies would be expected on the basis of all births in the ORLS area during 1970–2) and these were excluded from the study. Thus 146 singleton born cases and 146 controls were included in the case-control study.

Number of orchidopexies for cryptorchidism by age at operation: residents operated on within the Oxford Record Linkage Study area, 1976–8.

DEMOGRAPHIC FACTORS AND MEDICAL CHARACTERISTICS OF THE MOTHER

Table 1 shows the distribution of cases and controls with respect to various characteristics of their parents. The social class distribution of cases and controls did not differ significantly. Nevertheless, the risk for cryptorchidism was lower for boys in social class I than for those in other social classes. Maternal age at birth was not significantly related to risk of cryptorchidism, but the risk was highest for those whose mothers were under 20. There were no notable differences between cases and controls with respect to the marital state or religion of the mother (not shown in table 1). The sons of blood group B mothers were at low risk compared with those whose mothers were in other blood groups ($p < 0.01$). One possible explanation of this finding that needs consideration is that an abnormally high proportion of blood group B mothers might have been included, by chance, in the control group. Nevertheless, when the distribution of blood groups among the mothers of the cases was compared with that of all mothers delivering in the ORLS area in 1970–2 broadly similar results were obtained (relative risk (RR) for sons of blood group B mothers compared with sons of all other blood group mothers = 0.29; $p < 0.025$). The rhesus blood group of the mother showed no significant association with risk of cryptorchidism in the son (table 1). The only notable differences in the frequency of non-obstetric diseases recorded between mothers of cases and of controls were with respect to diabetes mellitus: three cases but no controls had mothers with this condition recorded in the obstetric notes; non-endocrine obesity: four mothers of controls but no mothers of cases; and congenital genitourinary abnormality: one mother of a case but no mothers of controls (the mother of the case had a double uterus and vagina). None of these differences was statistically significant.

OBSTETRIC HISTORY

There was no significant difference between cases and controls with respect to the parity of the mother, the number of previous stillbirths, or number of previous miscarriages (table 2); risk was highest for sons of nulliparous mothers compared with parous mothers, but this was not statistically significant, and there was no gradient of risk with parity among parous mothers.

SEASONALITY

Neither month of last menstrual period ($\chi^2_1 = 2.13$) nor month of birth ($\chi^2_1 = 2.27$) of cases had distributions significantly different from expectations based on the corresponding measures in all women delivering in the ORLS area.

Table 1 Parental characteristics

Risk factor	No (%) of cases with risk factor*	No (%) of controls with risk factor*	Relative risk†	Chi square (significance)†
Social class of father at index birth:				
I	10 (7.4)	18 (14.3)	1.00	$\chi^2_4 = 4.25$ (NS) χ^2_1 Trend = 2.71 (NS)
II	26 (19.1)	25 (19.8)	2.10	
III	69 (50.7)	61 (48.4)	2.21	
IV	22 (16.2)	16 (12.7)	2.65	
V	9 (6.6)	6 (4.8)	2.34	
Total	136 (100)	126 (100)		
Age of mother at index birth (years):				
<20	14 (9.6)	5 (3.4)	1.00	$\chi^2_4 = 5.34$ (NS) χ^2_1 Trend = 0.82 (NS)
20-24	47 (32.2)	54 (37.0)	0.29	
25-29	60 (41.1)	60 (41.1)	0.33	
30-34	17 (11.6)	17 (11.6)	0.33	
≥35	8 (5.5)	10 (6.9)	0.28	
Total	146 (100)	146 (100)		
Blood group of mother:				
ABO A	66 (46.8)	59 (40.4)	1.00	$\chi^2_4 = 14.80$ (p<0.01)
B	4 (2.8)	23 (15.7)	0.18	
AB	4 (2.8)	2 (1.4)	2.93	
O	67 (47.5)	62 (42.5)	0.95	
Total	141 (100)	146 (100)		
Rhesus +	124 (87.9)	118 (80.8)	1.00	$\chi^2_1 = 2.66$ (NS)
-	17 (12.1)	28 (19.2)	0.58	
Total	141 (100)	146 (100)		

* Based on all individuals for whom the information was recorded.

† Based on analysis of matched pairs.

PREGNANCY

No significant differences were found between the pregnancies involving the cases and controls with respect to time from last menstrual period to booking, number of antenatal attendances, number of radiographs taken during pregnancy, maximum recorded systolic and diastolic blood pressures of the mother, albuminuria in pregnancy, rhesus incompatibility, and complications of pregnancy, (in particular, 24 cases and 24 controls had pre-eclampsia, eclampsia, or toxemia; one case and one control were recorded with hyperemesis gravidarum;

and nine cases and seven controls had an antenatal haemorrhage).

DELIVERY

Ten cases but only two controls presented in the breech position before delivery (RR = 5.0; p<0.05). Eight of the 10 cases were delivered vaginally and two by caesarian section, of whom one underwent the operation during labour and the other was an elective caesarian. The relative risk for those experiencing

Table 2 Obstetric history of mother

<i>Risk factor</i>	<i>No (%) of cases with risk factor*</i>	<i>No (%) of controls with risk factor*</i>	<i>Relative risk†</i>	<i>Chi square (significance)†</i>
Parity:				
0	69 (47.3)	55 (37.7)	1.00	$\chi^2_s = 2.74$ (NS) χ^2_1 Trend = 1.88 (NS)
1	42 (28.8)	49 (33.5)	0.68	
2	23 (15.7)	28 (19.2)	0.67	
≥ 3	12 (8.2)	14 (9.6)	0.67	
Total	146 (100)	146 (100)		
Previous stillbirths:				
0	144 (98.6)	143 (97.9)	1.00	$\chi^2_1 = 0.20$ (NS)
≥ 1	2 (1.4)	3 (2.1)	0.67	
Total	146 (100)	146 (100)		
Previous miscarriages:				
0	121 (82.9)	118 (80.8)	1.00	$\chi^2_s = 1.07$ (NS) χ^2_1 Trend = 0.01 (NS)
1	19 (13.0)	24 (16.4)	0.76	
≥ 2	6 (4.1)	4 (2.7)	1.46	
Total	146 (100)	146 (100)		

* Based on all individuals for whom the information was recorded.

† Based on analysis of matched pairs.

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breech labour was 4.5 ($p = 0.065$). Two of the four cryptorchid boys who were twins born in the ORLS area 1970-2 had undergone breech birth. Six of the nine mothers of cases undergoing breech labour were nulliparous; the birth weights of these cases ranged from 2.3 kg to 3.5 kg. Five cases but only one control (not statistically significant) underwent Keilland's rotation, and nine cases and six controls were delivered by caesarian section. For significantly fewer cases than controls was labour induced ($RR = 0.55$; $p < 0.05$), the risk of cryptorchidism being reduced similarly for surgical induction (RR compared with no surgical induction = 0.52; $p < 0.05$) and hormonal induction (RR compared with no hormonal induction = 0.58; NS). Cases did not differ notably from controls for complications of delivery other than those mentioned above, use of forceps or vacuum extraction, operations on the mother after delivery, and maternal complications in the puerperium.

THE BABY

Cases tended to have lower birth weights than controls but this trend was not significant (table 3). Risk varied with gestational period ($p < 0.025$), with a high risk in those born under 36 weeks, and a low risk in those born 36-37 weeks (table 3). The blood group of the baby was known for too few patients (12 cases and 15 controls) for useful analysis. Cases and controls did not differ notably for Apgar score at birth, nor for diseases noted at birth other than three hernias in cases (one inguinal, two umbilical) and none in controls, and 12 cases but no controls with genital anomalies (nine cases with cryptorchidism, three with other genital anomalies). Seven cases and eight controls were noted at birth to have other congenital defects. The coding of ORLS birth records

allowed space for only one disease for each patient at birth; therefore the above figures for specific diseases may underestimate the numbers actually diagnosed, although there is no reason to believe that the underestimation is biased between cases and controls except for those cases with cryptorchidism recorded at birth. Since 97 of the cases had no disease recorded at birth, at most 49 (34%) cases may have been diagnosed cryptorchid at birth.

Twenty-two (15%) of the 146 cases had had a hospital diagnosis of inguinal hernia by 1978, in all but one instance undergoing herniorrhaphy. Up to 1978 six of the cases had a hospital diagnosis of hydrocoele and one had a diagnosis of a renal disease (acute nephritis). The expected number of cases with these associated diseases is difficult to determine because the presence of cryptorchidism, and operation for it, may have led to the diagnosis of associated conditions that might otherwise have remained undetected. Various studies suggest a prevalence of clinical hernia in boys in the general population in England of about 1-2%^{13 14}; assuming that all the hernias operated on in the present series were clinically significant, the relative risk of cryptorchidism for boys with clinically significant hernia was about 11 ($p < 0.01$).

Discussion

The estimated cumulative lifetime risk of operated cryptorchidism in the ORLS area (3.38%) is much greater than the prevalence of cryptorchidism after infancy found in studies reported in the 1960s in England^{15 16} and Denmark¹⁷ (around 0.8%); earlier studies had given widely varying estimates.^{2 18} The actual prevalence of cryptorchidism after infancy in the ORLS area may be greater than 3.38% because

Table 3 Birth weight and gestation of index child

<i>Risk factor</i>	<i>No (%) of cases with risk factor*</i>	<i>No (%) of controls with risk factor*</i>	<i>Relative risk†</i>	<i>Chi square (significance)†</i>
Birth weight (kg):				
<2.5	7 (4.9)	6 (4.1)	1.00	$\chi^2_4 = 2.09$ (NS)
2.5–2.9	26 (18.1)	22 (15.2)	1.09	
3.0–3.4	48 (33.3)	42 (29.0)	0.97	
3.5–3.9	45 (31.2)	49 (33.8)	0.81	
≥4.0	18 (12.5)	26 (17.9)	0.65	χ^2_1 Trend = 1.87 (NS)
Total	144 (100)	145 (100)		
Gestation (weeks):				
<36	6 (4.5)	1 (0.7)	1.00	$\chi^2_4 = 11.98$ (p<0.025)
36–37	10 (7.5)	7 (5.6)	0.12	
38–39	37 (27.8)	35 (27.8)	0.52	
40–41	56 (42.1)	66 (52.4)	0.53	
≥42	24 (18.1)	17 (13.5)	0.44	χ^2_1 Trend = 0.74 (NS)
Total	133 (100)	126 (100)		

* Based on all individuals for whom the information was recorded.

† Based on analysis of matched pairs.

the present study was confined to operated cases, and because possible coding errors were interpreted conservatively when validation was not possible. Recent data from the Hospital In-patient Enquiry on a 10% sample of NHS hospital patients in England and Wales¹⁹ also suggest a far higher prevalence of cryptorchidism than in England in the 1960s: estimation of cumulative lifetime incidence of orchidopexy in England and Wales from published estimated operation rates for 1978¹⁹ would give a figure of 3.07%. This figure requires correction because it probably omits some patients who underwent another operation as well as orchidopexy during the same hospital admission, and because the operation rates are based on unlinked data—that is, patients admitted for the operation more than once during the year are counted on each occasion. The latter correction would probably be small: in the ORLS linked data over 90% of orchidopexy operations in a year were on different patients. Estimates of the prevalence of cryptorchidism based on ORLS and the Hospital In-patient Enquiry must be treated cautiously because the data are for operated cases only and rely on ascertainment and coding in information systems whose data are extracted from routine hospital records. Nevertheless, prevalence of cryptorchidism in England has probably risen substantially, which requires further investigation by clinical screening studies. There is some evidence for an increasing secular trend in the prevalence of cryptorchidism in the United States also.⁷

The distribution of age at operation in the present study is similar to that in recently reported series in England²⁰ and Scotland²¹ and to that for orchidopexies in England and Wales overall where, in 1978, for the broad age groups published, 9% of orchidopexies were before age 5 years and 78% from age 5 to 14 years.¹⁹ In these series most of the operations were performed at an older age than that usually recommended.^{20–23} There seems to be a strong case for more systematic screening of young boys for undescended testis to allow earlier orchidopexy.

A major problem in studying epidemiologically the aetiology of cryptorchidism is the difficulty of diagnosing the condition. The present study was confined to operated cases, which has the advantage that operation is likely to be the most reliable point of diagnosis of cryptorchidism in records of routine clinical practice. Another advantage of studying operated cases is that since such patients are almost all over 1 year of age, spontaneous descent of their cryptorchid testes is unlikely to occur.^{15–17} It is for such “permanently” cryptorchid patients that risks for testicular cancer and infertility have been shown.

Study of operated cases, however, introduces some case selection that may, for example, lead to social class bias.

The most striking finding of the study was the high risk of cryptorchidism for those presenting in the breech position. Breech delivery is known to cause severe injuries that may be fatal, but the implications of lesser injuries for future health are not clear.²⁴ Prolapse of the scrotum of a male fetus through a partially dilated cervix may cause severe congestion and necrosis of the scrotal skin.²⁴ Ráliš conducted postmortem examinations on 49 boys who died during or soon after breech delivery and found that trauma to the testes was frequent and that in two cases there was a severely damaged testis within the inguinal canal.²⁵ There have been reports of scrotal bruising and changes in the size, consistency, and sensation of testes of infants after non-fatal breech birth,^{26–27} with abnormalities sometimes persisting for up to a few years,²⁶ and reports of otherwise unexplained testicular atrophy in two older individuals who had been breech born.²⁸ It has not been shown previously, however, whether breech birth may be a cause of serious long term testicular abnormality.

Breech birth is associated with several major congenital abnormalities^{29–30} for which it is unlikely to be aetiological. Such associations are thought to occur because the abnormal morphogenesis or function, or both, associated with the abnormalities reduces the chance that the fetus will assume the vertex position.³⁰ It seems improbable, however, that this explains the association of cryptorchidism with breech birth, and it seems more likely that the association results from trauma from the breech position. If this is so other birth and postnatal traumas might also cause cryptorchidism. If future studies confirm the association between obstetric trauma and cryptorchidism the possible protective role of caesarian section will require consideration.

Several lines of evidence make it reasonable to suppose that hormonal factors are important in normal testicular descent and that abnormalities of them might be a cause of cryptorchidism,^{1–2} but there is no convincing evidence that hormonal abnormalities are commonly a cause of cryptorchidism in man. Seasonal variation in numbers of births of cryptorchid boys in Hungary has been adduced as evidence for a hormonal aetiology³¹; however, as that study included no correction for normal seasonal variation in births it is difficult to interpret. The present study found no evidence of seasonal variation in births of cryptorchid boys.

The small rise in risk for those of low birth weight (table 3) accords with previous data,^{15–17} suggesting that some raised risk persists beyond infancy in this

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group, even though this risk is probably less than that for such boys at birth.^{15 32} A raised risk in boys of low birth weight might reflect the absence of maternal hormonal stimulus for descent in those already born at the normal time of testicular descent (mainly around eight months' gestation¹⁸).

If a hormonal abnormality of the mother or baby is responsible for a substantial proportion of cases of cryptorchidism the abnormality must be a subtle one—neither the case mothers nor the cases in the study showed an excess of hospital diagnoses of conditions likely to be associated with endocrine abnormality, nor have such abnormalities been noted previously other than for the small minority of cases of cryptorchidism in patients with rare disorders that include abnormal gonadotrophin production, androgen secretion, or androgen action.¹

The low risk of cryptorchidism for boys born after induction has not been reported previously, and needs further study. Risk of cryptorchidism by age and parity of the mother has been reported upon by Czeizel *et al*,³¹ who found no substantial excess in young mothers or primiparae. The analysis of social class in the present study is potentially biased, firstly, because greater migration out of the area after birth by higher social class cases could have left an excess of lower social class native cases resident in the area by 1976–8 and, secondly, because presentation and ascertainment might be worse in the lower classes; however, in another case-control study of cryptorchidism³¹ the cases had significantly less well educated parents and mothers of cases had significantly less well qualified occupations than the controls, suggesting that the social class gradient in the present study may well be real.

An association of cryptorchidism with inguinal hernia and hydrocoele is to be expected on anatomical grounds.² In clinical series inguinal hernia has been reported in most cases of cryptorchidism.^{23, 33–35} In very few cases, however, does the hernia cause symptoms requiring operation.^{2 34} This low clinical importance may be the reason for the low prevalence of hernia in the present study compared with other series, since the present data reflect routine recording of diagnoses by clinicians not engaged in special study of the associations of cryptorchidism.

Cryptorchidism is the main known risk factor for testicular cancer.⁶ The cause of the association is unknown: cryptorchidism might be a cause of testicular cancer or the two conditions might have causes in common, or both. The raised risk of testicular cancer in normally descended testes opposite cryptorchid testes suggests some degree of common aetiology.⁶ Around 90% or more of cases of testicular cancer occur in men who are not

cryptorchid.^{5–7, 36} Therefore, even if cryptorchidism is a cause of testicular cancer, factors that increase the risk of cryptorchidism may well not be detected in studies based on all cases of testicular cancer. If the two conditions share common causes, however, they might be expected to have some epidemiological risk factors in common. Several risk factors have been found for both testicular cancer and cryptorchidism, which supports the latter hypothesis: inguinal hernia is probably associated with testicular cancer,^{4–7, 37} and its association with cryptorchidism has already been discussed; abnormalities of the urinary tract may well be associated with both testicular cancer^{4, 38} and cryptorchidism³⁹; there is some evidence that prenatal hormones may be a risk factor both for testicular cancer^{6 7 40} and cryptorchidism^{41–44}; both testicular cancer⁴⁵ and cryptorchidism⁴⁶ are rare in United States negroes compared with United States whites; sons of mothers of blood group B were at much reduced risk of cryptorchidism in the present study, and at reduced risk of childhood testicular cancer in one study.³³ It would be of value to investigate in future studies of testicular cancer whether breech birth and the other prenatal factors leading to a raised risk of cryptorchidism in the present study are also risk factors for testicular cancer.

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