Seasonal variations in cryptorchidism

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SUMMARY The month of birth of boys undergoing orchidopexy in the Oxfordshire Health District during the years 1974–83 was analysed. A significant seasonal variation with a peak in April was found for those boys operated upon by paediatric surgeons at a young age (0–4). Possible causes of this variation and its relationship to the aetiology of cryptorchidism are discussed.

Cryptorchidism is a condition in which one or both testes fail to descend to a normal position in the scrotum. It is one of the commonest congenital abnormalities in males and there is evidence that it is becoming more common.^{1–3} Cohort analysis of Hospital In-Patient Enquiry data suggests that the cumulative rate to age 15 of discharge for undescended testis has risen from 1.4% for the 1952 birth cohort to 2.9% for the 1977 birth cohort.³ This is of particular importance as failure of descent usually leads to operative correction (orchidopexy) and carries an increased risk of subfertility and testicular malignancy.^{1 4–7}

The aetiology of cryptorchidism is not known but there is some evidence that the hormonal environment of the developing fetus may be important.⁸ A cyclic seasonal variation in the month of birth of boys with cryptorchidism has been reported,⁹ with a maximum in March and a minimum in October, and it has been suggested that this may reflect seasonal changes in hormone levels.

In this study, the month of birth of a group of boys undergoing orchidopexy in one health district was examined. Separate analyses were conducted for boys operated upon by general surgeons and those operated on by paediatric surgeons because it seemed possible that characteristics of the patient or of the diagnostic practice of the surgeons might vary between the two groups.

Method

Data were extracted from the files of the Oxford Record Linkage Study database (which collects data on all individuals admitted to hospital in a defined area in the Oxford Region), on boys coded as

undergoing orchidopexy in the period 1974–83 in the Oxfordshire Health District. All boys included in the study were undergoing orchidopexy for the correction of a cryptorchid testis rather than torsion of the testis (about 5% of orchidopexies in the age group 0–14 years are for testicular torsion (Oxford Record Linkage Study data)). Cyclic seasonality by month of birth in the Oxford data was then analysed by the method of Edwards¹⁰ after ascertaining the fit of the data to a harmonic curve¹¹ (since Edwards test is inappropriate if the data are significantly non-cyclic). Harmonic seasonality of cryptorchid births was then calculated by the method of Walter and Elwood,¹¹ adjusting for expectations from the number of male births per month in England and Wales for the period 1974–83 (local birth data for the same period were not available).

The analysis was performed separately on those cases operated upon by the paediatric surgeons working in the John Radcliffe Hospital in Oxford since their policy towards diagnosis of cryptorchidism was known to include a minimum of two examinations of the child before orchidopexy and repeated searching for the absent testis with examination both lying and squatting. These data were compared with those for all non-paediatric surgeons in the study area.

Results

The numbers of orchidopexies, in the age groups 0–4, 5–14 and 0–14 years, performed by the Oxford paediatric surgeons and by the non-paediatric surgeons during 1974–83, subdivided by month of birth and age at operation, are shown in table 1. Table 2 presents statistical analysis of seasonality of month of birth adjusted for “expectations” from England and

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Wales births seasonality (none of the data was significantly non-harmonic); very similar results were obtained in the unadjusted analyses which have not therefore been presented in the table. The summed data showed a significant degree of seasonality ($p=0.04$) with a peak in late March. When analysed by age group, the 0-4 years group was mainly responsible for producing this effect. The data for the Oxford paediatric surgeons showed a statistically significant peak for the fitted harmonic curve in early April for all ages ($p=0.03$) and for the age-group 0-4 years in mid April ($p=0.01$). For those older than 5 years at operation, the peak was in mid March, and seasonality was not statistically significant ($p=0.45$).

The data for all non-paediatric surgeons showed no significant seasonality either overall or after analysis

by age at operation. The significant seasonality in the summed data is thus due to the marked seasonality in the Oxford paediatric surgeons 0-4 years age group.

Discussion

The results for Oxford paediatric surgeons' young (0-4 years) orchidopexy patients support the findings of Czeizel⁹ of a significant seasonal fluctuation in the incidence of cryptorchidism as indicated by orchidopexy, with a peak in the spring. A smaller study² of orchidopexies, partly overlapping the present cases, reported no significant birth seasonality, but the peak of the harmonic curve, allowing for population fluctuations was in the spring,

Table 1 *Orchidopexy by age at operation and month of birth in the Oxford Health District and male births by month in England and Wales 1974-83*

Age at operation (yr)	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
Paediatric surgeons													
0-4	16	14	21	32	17	12	16	19	9	10	16	8	190
5-14	35	32	51	39	36	31	36	31	38	33	34	29	425
Total	51	46	72	71	53	43	52	50	47	43	50	37	615
All non-paediatric surgeons													
0-4	8	9	4	5	7	6	8	7	3	10	3	5	75
5-14	30	31	30	36	34	29	37	30	31	23	28	37	376
Total	38	40	34	41	41	35	45	37	34	33	31	42	451
All surgeons													
0-4	24	23	25	37	24	18	24	26	12	20	19	13	265
5-14	65	63	81	75	70	60	73	61	69	56	62	66	801
Grand Total	89	86	106	112	94	78	97	87	81	76	81	79	1066
Percentage of male births nationally 1974-83 by month	8.27	7.72	8.80	8.37	8.78	8.41	8.71	8.47	8.46	8.29	7.81	7.91	100.0

Table 2 *Statistical analysis of seasonality**

	Age group	Number of cases	Date of peak	Amplitude	χ^2	p value
Oxford paediatric surgeons	0-4	190	15 April	0.31	9.59	0.01
	5-14	425	11 March	0.09	1.58	0.45
	Total	615	2 April	0.14	6.83	0.03
All non-paediatric surgeons	0-4	75	27 Sept	0.04	0.04	0.98
	5-14	376	24 March	0.06	0.67	0.72
	Total	451	20 March	0.05	0.57	0.75
All cases	0-4	265	11 April	0.23	7.31	0.03
	5-14	801	16 March	0.08	2.23	0.33
	Total	1066	29 March	0.10	6.30	0.04

* Figures adjusted for seasonality expected from births in the general population (Walter and Elwood's test¹¹).

and 18.5% of births were in March. A recent study¹² which examined the month of birth of men with cancer of the testis also found a significant seasonal variation with a prominent peak in April as well as a prominent notch in November. This is of particular interest in view of the strong association between cryptorchidism and testicular cancer (an approximately eightfold risk⁶).

There are no obvious biases which could explain the findings for the Oxford paediatric surgical cases. In particular, a secular increase or decrease in incidence could produce artefactual seasonality, but this was not responsible for the seasonality in these data.

The lack of significant seasonal variation in month of birth of boys undergoing orchidopexy by non-paediatric surgeons may reflect differing diagnostic criteria from those used by the paediatric surgeons, for example, if more boys with retractile rather than truly undescended testes were being operated on, possible seasonal variation in those truly cryptorchid might be diluted sufficiently to be undetectable. The ease of diagnosis of cryptorchidism varies by age within young boys, but this does not appear to explain the present differences between paediatric and non-paediatric surgeons since the mean age at operation within the 0-4 years age group was similar (age at diagnosis was not available). Paediatric surgeons may well be referred, on average, more complex surgical problems than their non-paediatric colleagues (such as multiple abnormalities or abdominal testes) and the aetiology of cryptorchidism in these cases may differ.

Cyclic variation in the month of last menstrual period or of month of birth has been found for hypospadias in some studies^{13,16} but not all.^{17,19} The peak month of birth for boys with hypospadias was June or July in three studies,^{13 15 16} and April in one.¹⁴ Hypospadias, like cryptorchidism, may be of hormonal aetiology^{5 19 20} and may be increasing in prevalence.^{21 22}

Possible explanations for seasonality of cryptorchid births could lie with either antenatal or postnatal effects. Antenatal effects might occur if there were a seasonal variation in some basic biological function in pregnant mothers which affected the aetiology of congenital abnormalities, or if there was a seasonal variation in some risk factor in the environment such that greater or more prolonged exposure occurred during pregnancy at certain times of year.

There is some evidence that excessive unbound exogenous or endogenous oestrogen exposure in the first trimester of pregnancy can induce cryptorchidism and testicular cancer in humans^{6 8} and that exposure to exogenous hormones in early pregnancy may lead to an increased risk of hypospadias in male offspring.^{5 19 20} The first trimester of pregnancy is the period when the testes and external genitalia differentiate and

develop in the human,^{23 24} and the last trimester is the period when descent of the testes into the scrotum normally occurs.²⁵ Embryological differentiation of the testes begins at about 6-7 weeks post-conception whereas differentiation of the external genitalia and formation of the penis in the male does not begin until 11-13 weeks (ie, about six weeks later).²⁶ This is a similar time interval to that between the peaks found for births of boys with cryptorchidism (April) and hypospadias (June), which would be consistent with the suggestion that both conditions could be associated with seasonal antenatal hormonal effects with a peak at the same time of year. There appears to be no evidence that environmental risk factors for abnormalities of the male genitourinary system, notably exogenous antenatal oestrogen exposure, exhibit seasonal variation which could account for these findings.

Various lines of evidence do suggest, however, that endogenous sex hormone levels can vary seasonally, and this could potentially be responsible for seasonal variation in both cryptorchid and hypospadiac births. Firstly, many mammals, for example, sheep, deer, and hamsters, show seasonal variations in reproductive behaviour which appear to be associated with the functions of the pineal gland and its hormone melatonin. Melatonin can produce changes in the secretion of LH, FSH, and prolactin by the anterior pituitary gland.²⁸ Secondly, there is some direct evidence of seasonally changing plasma concentrations of various hormones in women. Halberg *et al.*²⁹ found that the amplitude of daily rhythmic oscillations of plasma prolactin, 17-hydroxyprogesterone, and oestrone increased in winter and spring compared to summer and autumn. Indirect evidence for hormonal seasonality has also been found in that the level of oestrogen receptors in breast cancer in women varies, with higher values in late autumn and lower values in the spring.³⁰

Seasonal variations in hormonal function affecting prevalence of cryptorchidism might also occur postnatally in the child. There is some evidence in adult human males³¹ that there is seasonal variation in serum testosterone levels with a peak in September and a trough in March. It has been suggested³² that a testosterone surge at or just after the time of birth may be necessary for normal testicular descent (about two thirds of testes which are undescended at birth descend in the 6 months of life³³). Thus it may be that infants born in spring have a reduced testosterone surge which leads to an increased incidence of incomplete testicular descent. Postnatal events cannot, however, have any role to play in the aetiology of hypospadias. Since an antenatal effect could potentially act on a 'catchment' population consisting of all male fetuses whereas a postnatal effect could only act on that 4% of boys

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whose testes were undescended at birth,³³ the postnatal effect would, in terms of the proportion of its catchment population affected, need to be about 25 times as strong as an antenatal effect to produce the same degree of seasonality.

The explanation for the seasonal variations described in this paper is not clear but there is increasing evidence that they are a real phenomenon. Further elucidation of the cause of these seasonal variations would be aided by an improved understanding of the antenatal and postnatal control of normal genital development.

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