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A maternal vegetarian diet in pregnancy is associated with hypospadias

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Objective To investigate the possible role of the maternal diet, particularly vegetarianism and consumption of phytoestrogens, in the origin of hypospadias, which is reported to be increasing in prevalence.

Subjects and methods Detailed information was obtained prospectively from mothers, including previous obstetric history, lifestyle and dietary practices, using structured self-completed questionnaires during pregnancy. Previously recognized associations with environmental and parental factors were examined, focusing particularly on the hypothesized hormonal link. Multivariate logistic regression was used to identify independent associations.

Results Of 7928 boys born to mothers taking part in the Avon Longitudinal Study of Pregnancy and Childhood, 51 hypospadias cases were identified. There were no significant differences in the proportion of hypospadias cases among mothers who smoked, consumed alcohol or for any aspect of their previous reproductive history (including the number of previous pregnancies, number of miscarriages, use of the contraceptive pill, time to conception and age at menarche). Significant differences were detected for some aspects of the maternal diet, i.e. vegetarianism and iron supplementation in the first half of pregnancy. Mothers who were vegetarian in pregnancy had an adjusted odds ratio (OR) of 4.99 (95% confidence interval, CI, 2.10–11.88) of giving birth to a boy with hypospadias, compared with omnivores who did not supplement their diet with iron. Omnivores who supplemented their diet with iron had an adjusted OR of 2.07 (95% CI, 1.00–4.32). The only other statistically significant association for hypospadias was with influenza in the first 3 months of pregnancy (adjusted OR 3.19, 95% CI 1.50–6.78).

Conclusion As vegetarians have a greater exposure to phytoestrogens than do omnivores, these results support the possibility that phytoestrogens have a deleterious effect on the developing male reproductive system.

Keywords Hypospadias, vegetarianism, iron supplements, phytoestrogen, male fetus, pregnancy

Introduction

There is evidence to suggest that male reproductive health has been declining over recent decades [1], a view supported by reports of declining sperm counts [2], although the evidence for this is still debated [3]. However, there is firm evidence for an increase in cancer of the testis [4] and suggestions of an increased prevalence of defects of the male genitalia, including hypospadias [5]. Several hypotheses have been proposed for the aetiology of this urogenital anomaly, including genetic [6–8], environmental [9] and maternal risk factors, including an early age at menarche [10], maternal age and parity [11]. Kallen *et al.* [11] showed that increasing maternal age (particularly of primiparae) was associated with a higher prevalence of hypospadias. Exposure to drugs in pregnancy, particularly involving sex hormones, was also a significant risk factor in several studies [9,10,12]. Links have been identified with twinning [12,13] and parental subfertility [14,15], such that families who experienced fertility problems were at an increased risk of having boys with hypospadias. Several of these factors support the hypothesis that exposure in pregnancy to environmental oestrogens may have a marked effect on the male reproductive system [16,17].

The role of maternal nutrition has received little investigation, but is another possible source of oestrogen and contaminant exposure. Phytoestrogens are available in many foodstuffs, although in low concentrations, with soya providing the richest source [18]; if consumed in significant quantities they may have a substantial oestrogenic effect which could contribute to the disruption of the developing male fetus.

Thus the aim of this study was to investigate the possible role of maternal nutrition in the origin of

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hypospadias. The associations with various environmental and parental factors that have previously been recognized were also examined, with particular attention to the possible oestrogen link. The data were derived from a large prospective cohort study of 7928 males.

Subjects and methods

The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) [19] is a population-based study investigating environmental and other influences on the health and development of children. Pregnant women resident in the three Bristol-based health districts of Avon, who had an estimated date of delivery between 1 April 1991 and 31 December 1992 were invited to take part; ≈85% of the eligible population enrolled. Detailed information was obtained from the mothers using self-completed questionnaires, administered during pregnancy at 8, 18 and 32 weeks of gestation, and after birth at various ages of the child.

Several sources were used to identify cases of hypospadias: (i) maternal reporting in postnatal questionnaires completed annually for the first 3 years of life, using the recorded reasons for medical referral and investigation, and reasons for hospital admission and/or surgery; (ii) birth notifications; (iii) records of examination by the neonatal paediatrician; and (iv) postmortem reports.

In questionnaires administered at 8 and 18 weeks' gestation, mothers were asked to provide the number of previous pregnancies and their outcome; this was used to determine whether their son was first-born (i.e. the offspring of the mother's first live birth or fetal death of $\geqslant$28 weeks' gestation). The age when menstruation began was also recorded (categorized as 8–11, 12–14 or $\geqslant$15 years). The mother was asked to identify whether it was possible that she might have taken oral contraceptives whilst she was pregnant and whether she had previously consulted her doctor with concerns about infertility. Finally, the duration of attempting conception ($<$0.5, 0.5–1, 1–2 and $\geqslant$3 years) and total duration of oral contraceptive use ($<$1, 1–2, 3–4 or $\geqslant$5 years) were established.

In the structured questionnaires that the mothers completed at 18 and 32 weeks' gestation, symptoms of ill-health, all medications taken (including dietary supplements) and general lifestyle habits such as smoking and drinking were noted. The 18-week questionnaire was considered to be the most informative, as male genital development is likely to have been completed by this time.

In the questionnaire completed by the mother at 32 weeks' gestation, current dietary behaviour was ascertained. Mothers were asked how often they were eating various types of food 'nowadays', including organically grown vegetables and whether they were currently vegetarian (i.e. during pregnancy) or had previously been so. The duration for which the mother had been a vegetarian was recorded.

The results were initially assessed using chi-squared analysis to detect any differences in the proportions of boys with hypospadias or not within the factors considered. Unadjusted logistic regression was used to calculate odds ratios (ORs) for significant factors, and finally multivariate logistic regression identified independent associations between factors and the risk of hypospadias.

Results

There were 51 boys with hypospadias in the population, giving an overall frequency of 64 per 10 000 male births. There were no significant differences in the proportion of offspring with hypospadias among mothers who smoked or consumed alcohol; nor were there significant differences with maternal age (mean 27.06 years for those with and 27.25 years for those with no cases) and no significant effect with twinning. There were 76 sets of same sex (male) twins, from which there was only one case. Among 62 sets of boy-girl twins, four boys had hypospadias.

There were no statistically significant differences in the incidence of hypospadias with previous obstetric history (Table 1). Hypospadias was no more evident in first-born boys or in those whose mothers had had previous miscarriages or previous stillbirths, mothers who had conceived within 6 months of trying, those who had been taking the contraceptive pill for $<$5 years and those who had consulted their doctor for possible infertility problems. Mothers whose age of menarche was $<$12 or $\geqslant$15 years had a smaller proportion of boys with hypospadias than those who began menstruating when aged 12–14 years, but this was not statistically significant.

Supplementing the diet with iron tablets in the first 3 months of pregnancy was associated with a significantly higher risk for hypospadias (Table 1); 1% of mothers who took iron tablets had boys born with hypospadias, compared with 0.6% of those who did not (P = 0.041). The most notable effect was with vegetarianism; 2.2% of mothers who stated that they were a vegetarian in pregnancy gave birth to hypospadiacs, which compared with 0.6% of omnivores (P = 0.001). The incidence of hypospadias in boys of omnivorous mothers who had previously been vegetarian (i.e. before pregnancy) was not significantly different from that in those who had never been (data not shown). The proportion of boys born with hypospadias was higher among mothers who drank soya milk (2.2%) and who regularly consumed soya products (1.8%), although not statistically significantly so. In

Table 1 Categorical factors studied in relation to hypospadias cases

Factor (population distribution, %)	*Cases, % (n)*	χ^2 (P)	*OR (95% CI)*
Previous obstetric history			
Previous miscarriages (n = 6692)			
Yes (21.7)	0.4 (6)		1.00 Ref
No (78.3)	0.8 (40)	2.05 (0.152)	1.86 (0.79, 4.38)
Previous stillbirths (n = 6672)			
Yes (1.0)	1.5 (1)		2.28(0.31, 16.78)
No (99.0)	0.7 (45)	0.69 (0.406)	1.00 Ref
Boy first born (n = 6610)			
Yes (42.8)	0.8 (22)		1.23 (0.69, 2.20)
No (57.2)	0.6 (24)	0.49 (0.485)	1.00 Ref
Age at menarche, years (n = 5714)			
8–11 (20.2)	0.6 (7)		1.58 (0.41, 6.13)
12–14 (66.2)	0.8 (30)		2.07 (0.63, 6.80)
$\geqslant$15 (13.6)	0.4 (3)	1.73 (0.420)	1.00 Ref
Possible use of the pill during pregnancy (n = 6358)			
Yes (5.4)	0.6 (2)		1.00 Ref
No (94.6)	0.7 (43)	0.08 (0.780)	1.22 (0.30, 5.07)
Seen doctor for possible infertility (n = 6333)			
Yes (12.8)	0.2 (2)		1.00 Ref
No (87.2)	0.8 (43)	2.85 (0.091)	3.18 (0.77, 13.12)
Duration of trying for pregnancy (years, planned pregnancies only) (n = 4660)			
<0.5 (73.7)	0.9 (31)		1.00 Ref
0.5–1 (13.8)	0.5 (3)		1.53 (0.21, 11.25)
1–2 (8.8)	0.2 (1)		0.81 (0.08, 7.82)
$\geqslant$3 (3.7)	0.6 (1)	2.89 (0.410)	0.43 (0.03, 6.82)
Total duration of pill use, years (n = 6184)			
<1 (9.2)	1.1 (6)		2.01 (0.79, 5.08)
1–2 (13.3)	0.9 (7)		1.61 (0.67, 3.86)
3–4 (22.5)	1.0 (14)		1.91 (0.95, 3.85)
$\geqslant$5 (55.0)	0.6 (18)	4.35 (0.226)	1.00 Ref
Maternal nutritional factors			
Taken iron tablets in first 18 weeks of gestation (n = 6228)			
Yes (22.8)	1.0 (16)		1.87 (1.02, 3.46)
No (77.2)	0.6 (29)	4.17 (0.041)	1.00 Ref
Vegetarian during pregnancy (n = 6296)			
Yes (5.1)	2.2 (7)		3.53 (1.56, 7.98)
No (94.9)	0.6 (37)	10.45 (0.001)	1.00 Ref
Drank soya milk during pregnancy (n = 6263)			
Yes (1.4)	2.2 (2)		3.67 (0.87, 15.44)
No (98.6)	0.6 (38)	3.61 (0.058)	1.00 Ref
Ate pulses during pregnancy (n = 6251)			
Never (76.7)	0.6 (30)		1.00 Ref
Once in 2 weeks (14.3)	0.4 (4)		0.72 (0.25, 2.04)
1–3 times/week (8.0)	0.8 (4)		1.28 (0.45, 3.64)
4 + times/week (1.1)	4.5 (3)	16.13 (0.001)	7.56 (2.25, 25.42)
Ate soya 'meat' during pregnancy (n = 6189)			
Never (92.3)	0.6 (36)		1.00 Ref
Once in 2 weeks (5.1)	0.6 (2)		1.01 (0.24, 4.22)
1 + times/week (2.7)	1.8 (3)	3.51 (0.173)	2.95 (0.90, 9.68)
Vegetarianism and iron supplementation (n = 6071)			
Omnivore, no iron (74.3)	0.5 (22)		1.00 Ref
Vegetarian, no iron (3.6)	2.3 (5)		4.81 (1.81, 12.84)
Omnivore, with iron (20.5)	1.1 (14)		2.32 (1.19, 4.55)
Vegetarian, with iron (1.6)	2.1 (2)	16.59 (0.001)	4.30 (0.99, 18.54)
Vegetarianism and iron supplementation (n = 6071)			
Omnivore, no iron (74.3)	0.5 (22)		1.00 Ref
Omnivore, with iron (20.5)	1.1 (14)		2.32 (1.19, 4.55)
Vegetarian (5.2)	2.2 (7)	16.54 (<0.001)	4.65 (1.97, 10.98)
Maternal health and medications taken			
Mother had influenza in first trimester (n = 6196)			
Yes (8.2)	1.8 (9)		3.08 (1.46, 6.48)
No (91.8)	0.6 (33)	9.78 (0.002)	1.00 Ref
Mother took 'codeine/Anadin®' in first trimester (n = 6154)			
Yes (3.2)	2.3 (5)		3.76 (1.47, 9.62)
No (96.8)	0.6 (41)	8.84 (0.003)	1.00 Ref

Table 2 Adjusted odds ratios for independent factors associated with hypospadias (considering iron supplementation and vegetarianism separately and combining iron supplementation with vegetarianism or not)

Factor (%)	*OR (95% CI)*	P
Model 1		
Vegetarian during pregnancy		
Yes (5.1)	3.88 (1.69, 8.92)	
No (94.9)	1.00 Ref	0.0014
Taken iron tablets during pregnancy		
Yes (43.0)	1.81 (0.92, 3.55)	
No (57.0)	1.00 Ref	0.0848
Mother had influenza in first trimester		
Yes (8.2)	3.24 (1.52, 6.88)	
No (91.8)	1.00 Ref	0.0020
Model 2		
Vegetarianism and iron supplementation		
Omnivore, no iron (74.3)	1.00 Ref	
Omnivore, with iron (20.5)	2.07 (1.00, 4.32)	
Vegetarian (5.2)	4.99 (2.10, 11.88)	0.0009
Mother had influenza in first trimester		
Yes (8.2)	3.19 (1.50, 6.78)	
No (91.8)	1.00 Ref	0.0026

addition, the consumption of pulses (e.g. dried peas, beans, lentils and chick-peas) four or more times a week resulted in a significantly larger proportion of cases (4.5%, $P = 0.001$). The consumption of any other types of foods had no significant effects. Only 163 mothers declared that they always bought organically grown vegetables. There were no cases of hypospadias among this group (1.07 cases would have been expected).

As iron supplementation is closely associated with vegetarianism (almost twice as many of the ALSPAC vegetarian mothers took extra iron tablets than did omnivores) this interrelationship was investigated. A new variable was created, initially categorized as (i) not vegetarian, no iron supplements; (ii) vegetarian, no iron supplements; (iii) not vegetarian, with iron supplements and (iv) vegetarian, with iron supplements. For univariate logistic regression, the largest group was used as the baseline (not vegetarian, no iron supplements). Compared with this group, vegetarian mothers who did not take iron were significantly more likely to give birth to boys with hypospadias, while omnivores who took iron were also more likely bear boys with hypospadias. The size of the effect for vegetarians who took iron was also large but was not significant. However, this was a particularly small group (only 1.6% of the sample). The incidence of hypospadias in vegetarians who supplemented their diet with iron did not differ significantly from that in vegetarians that did not do so, suggesting that the effect of iron supplementation was only significant among omnivores. The two vegetarian groups were therefore combined. The OR for the vegetarian group was then 4.65 (95% CI 1.97–10.98), using omnivores not taking iron as the baseline. This difference was also significant when using the other omnivorous group (taking iron supplements) as the baseline. This variable combination was used in the adjusted analysis.

A variety of possible medications taken in the first 3 months of pregnancy were investigated. Only one resulted in a significant effect; 2.3% of mothers who took codeine/'Anadin™' in pregnancy gave birth to a hypospadiac, compared with 0.5% of those who did not ($P = 0.003$). Similarly, only one aspect of health had a significant effect; three times as many mothers who reported influenza in the first 3 months of pregnancy (1.8%) had a boy with hypospadias compared with those who did not (0.6%).

To assess independent associations, two separate multivariate logistic regression models were built, the first using vegetarianism and iron supplementation as two separate variables, and the second combining these as previously described. All significant factors associated with hypospadias were entered. If mothers were vegetarian during pregnancy (model 1, Table 2), the risk for hypospadias remained significant after adjustment. Influenza was also independently associated with hypospadias. The effect of iron supplementation was no longer significant when influenza was added to the model. In the second model (Table 2) vegetarianism remained significant compared with omnivores who did not take iron; omnivores who took iron supplements were also statistically significant, but only just. Influenza was still significantly associated with hypospadias.

Discussion

Jensen *et al.* [16] hypothesized that the detrimental changes in male reproductive health that are becoming

more apparent may be caused by the developing fetus having an altered exposure to endocrine-disrupting chemicals with oestrogenic effects. Testosterone is responsible for the masculinization of the male reproductive tract and the external genitalia. It is thought that oestrogen may inhibit the production of testosterone and thus play a part in the development of urethral abnormalities such as hypospadias. Phytoestrogens have either oestrogenic or anti-oestrogenic activity depending on the biological environment and their individual chemical structures. The anti-oestrogenic effects have recently received wide coverage. As Bingham *et al.* [20] discussed, there are experimental findings suggesting that increased dietary intakes of phytoestrogens have a protective effect on the risk of various hormone-related diseases, particularly breast cancer, and therefore have an anti-oestrogenic effect.

The consumption of soya as a substitute for meat is increasing in the UK, partly as a result of the recent problems with beef and partly from concepts of 'healthy eating'. It is now widely used in the food industry, with the advent of vegetarian-style meals, and it provides the highest concentrations of phytoestrogens (particularly isoflavones) of all edible plant matter [18,21]. However, the estimated daily exposure to exogenous oestrogens by consumers of soya is minimal compared to, e.g. that from oral contraceptives. Such low levels of exposure would perhaps indicate small risks (or benefits), as the biological activity of phytoestrogens is considered to be low. Nevertheless, extended prolonged exposure may cause phytoestrogens in the body to reach biologically significant levels. The possible effects on humans should not be dismissed until more experimental data are available. MacLusky [22] discussed the more indirect role of phytoestrogens; rather than having a direct oestrogenic effect, they may interact with other factors in the diet and lead to an interference with 'normal oestrogen biosynthesis and action'.

The reported prevalence of hypospadias has varied among countries and with time. Czeizel *et al.* [8] reported a prevalence of 44 per 10 000 live male births in Hungary in 1978, while in Latin America a prevalence of only 7.6 per 10 000 live births was reported in 1981 [13]. More recently, Stoll *et al.* [7] reported a prevalence of 29 per 10 000 in French male newborns in 1990. The incidence of 64 per 10 000 (51 of 7928) boys in the present study is relatively high, supporting concerns about an increase. Several previous studies used specific classifications, but the present population-based study is unlikely to have included less severe cases, as the condition was only identified by investigations that were part of normal clinical care. Thus the high prevalence may even be an underestimate.

The ALSPAC study provided an ideal setting to test the effects of most factors that have previously been significant. However, none of those results was replicated here; indeed, at the time of analysis, the factors that had a statistically significant effect (vegetarianism, iron supplementation and influenza) had not been considered in previous investigations.

The present study has the advantage over many previous assessments of having collected the information prospectively, and is thus not influenced by biased recall. Information about events in early pregnancy, e.g. influenza, was elicited at 18 weeks' gestation and are likely to reflect accurately an infection in early pregnancy. However the dietary questions were asked at 32 weeks' gestation and concerned dietary habits at that time. These may not have reflected accurately the diet in the early stages of pregnancy. Vegetarianism is an exception; 92% of mothers who reported they were vegetarian at 32 weeks' gestation had been vegetarian from conception. The remaining 8% were recorded as having been vegetarian for 'less than one year', and it is likely that most of these had also been vegetarian since conception.

The association of hypospadias with a vegetarian diet was not obviously explicable by the components of a vegetarian diet. There were differences in the proportion of hypospadias cases born to mothers consuming soya milk or other products, but they were not significant, possibly because there were too few mothers who reported consuming such foods; only 1.4% regularly drank soya milk and 2.7% reported consuming soya 'meat' weekly. These interesting but statistically insignificant results warrant further investigation. One possible route would be to measure more accurately the amount of soya consumed in the diet. The present questionnaire did not explore other forms of soya in the diet, e.g. soya beans. However, the significant effect of vegetarianism could provide an indirect link to the increased consumption of soya and soya products compared with omnivores.

An alternative explanation for the association of hypospadias with vegetarianism might be related to the 'unnatural' chemicals (used as fertilizers and pesticides, and which act as endocrine disrupters) present in many fruits and vegetables. A way of assessing this might be to determine the association of hypospadias with the consumption of organic foods, where such chemicals are purportedly absent. Unfortunately, only 163 mothers 'always' bought organic vegetables; that none of these mothers had a son with hypospadias is of some interest, but only one case would have been expected. No reduction in risk was evident among those who 'sometimes' bought organic vegetables (0.8% had hypospadiacs, compared with 0.6% who never bought organically grown vegetables).

It is not possible to directly measure the amount of phytoestrogens consumed. Present tables of food contents provide inadequate information about phytoestrogen content and hence it is not possible to make substantive comments on their effects on hypospadias. It would therefore be beneficial to determine more precise levels of phytoestrogens, not only in soya and its products, but in other food substances commonly consumed in the UK. Presently, urinary levels of isoflavones are widely used as a surrogate estimate for the actual levels of consumption. Kelly *et al.* [23] found that the mean levels of isoflavones excreted increased from 2.5 mg to 17.4 mg after the diet was supplemented with soyabean. Among females, Aldercreutz *et al.* [24] found that the mean urinary excretion in American omnivores was 0.11 mg, which compared with 0.37 mg in lactovegetarians and 1.73 mg among the Japanese [25], where soybean products are a major component of the traditional diet.

A further aspect of the vegetarian diet which warrants investigation is a possible deficiency in one or more essential nutrients. The ALSPAC team obtained samples of maternal blood taken during pregnancy and intends to measure levels of these nutrients, phytoestrogens and pesticide residues, which can then be used in analyses of the hypospadias cases.

In conclusion, there was a higher proportion of boys with hypospadias born to mothers who were vegetarian during pregnancy ($P = 0.001$) and to those who had an episode of influenza in the first trimester of pregnancy ($P = 0.002$). Neither association appears to have been considered previously and these associations need to be tested elsewhere before they can be treated as causal. Nevertheless, it is important to note that there is biological evidence that vegetarians have a greater exposure to phytoestrogens [21] and thus a causal link is biologically feasible.

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