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ENVIRONMENTAL FACTORS AND POLYCYSTIC OVARIES

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ABSTRACT

This study was designed to investigate the effect of environmental factors on the appearance of polycystic ovaries (PCO) during the first two decades of life.

Ninety-four female-female twins who underwent a transabdominal ultrasound at the Royal Hospital for Women were sent a questionnaire asking about their birth details, feeding history as a baby, childhood illnesses and vaccination as well as exercise patterns. Seventy-seven subjects returned the questionnaire. All of the variables were studied in two groups of subjects; those with ultrasound evidence of polycystic ovaries (US-PCO, n= 37) and those with normal ovaries (US-normal, n= 40). The data were also analyzed in a group of scan-discordant twins (7 pairs) in whom one of the twins had US-PCO and the co-twin had normal ovaries.

Analyzing the data from the whole database suggested that US-PCO subjects had lower birth weight compared to US-normals. Vaccination against mumps was also found to be significantly higher in the US-PCO group compared with US-normals. Matched results for scan-discordant twins did not confirm these results. Other environmental variables such as feeding history, type of delivery, birth order and physical activity during the first 20 years of age did not seem to have any significant influence on the prevalence of PCO. No significant difference was found in childhood illnesses between the groups.

In conclusion, this study examined the effect of some environmental factors during childhood and early adulthood. Analyzing the whole database and scan-discordant twins failed to show any particular environmental factor associated with PCO.

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Keywords: Polycystic ovary, Twin study, Environmental factors.

INTRODUCTION

It has been hypothesized that PCOS is a condition which may start during childhood or puberty or may develop during the teenage years, resulting in the typical clinical appearances and biochemical changes.[1] Changes in the ovaries may begin at an early stage of fetal development,[2,3] in infancy[4] or later during puberty.[5,6] Using the twin model, we recently showed that PCO may not be the result of a single gene defect and environmental factors may influence the incidence of PCO.[7] The role of environmental elements on the etiology of PCO is not clear. This study aims to investigate the possible effect of these factors during the first two decades of life.

MATERIAL AND METHODS

Twins were identified from the National Health and Medical Research Council (NH & MRC) twin register and

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were invited to participate in the study. All subjects gave written consent and the study was approved by the ethics committee of the Royal Hospital for Women, Sydney, Australia.

Ninety-four female-female twins underwent a transabdominal ultrasound using an ACUSON 128 machine and a 3.5 MHz linear transducer. Polycystic ovaries were diagnosed using Adam's criteria,[8] namely the presence of 10 or more peripheral small follicles. Ultrasound is a highly reliable method for diagnosing PCO.[9] Subjects were then sent a questionnaire which asked the subjects and their mothers about their birth details, feeding history, childhood illnesses and immunization as well as their exercise pattern from birth till 20 years of age. Exercise activities included running, swimming, and sport, and scoring was based on the frequency of exercise performance. Seventy-seven subjects (82%) returned the questionnaire. All the subjects were between 15 to 45 years of age. Subjects were divided into 2 groups based on an ultrasound diagnosis of PCO; a group of subjects with normal ovaries (n= 40) and a group of subjects with scan evidence of PCO (n= 37). Within these 2 groups, there were 7 pairs of scan-discordant twins (that is one twin had US-PCO and the co-twin was US-normal); 3 MZ and 4 DZ pairs. Fisher's exact test was used to compare any two variables. ANOVA test was used when more than two groups were compared. A p-value of 0.05 or less was considered significant.

RESULTS

Birth weight, gestational age, birth order and type of delivery

The mean birth weight of subjects with US-PCO (2436 g±520) was significantly lower than the US-normals (2650 g±558, p= 0.05). The distribution of these two populations is shown in Figure 1. The mean gestational age of the US-PCO subjects (33.91 weeks ±3.21) was similar to that of the US-normals (34.95 weeks ±2.23, p= 0.12), suggesting that difference in birth weight was not due to differences in gestational age. However, within the scan-discordant group, the mean birth weight (±SD) for US-normals (n= 7) was 2503 (+555) that did not differ significantly from that of US-PCO (n= 7) (2628±451) (p= 0.65) using the Student's t-test.

The inter-twin birth weight was calculated for discordant twins (n= 14), twin-pairs whom both had US-PCO (n= 18) and twins who were both US-normal (n= 22). Using ANOVA test no significant difference was found among the 3 groups (p= 0.318).

Figure 2 shows the mean values of inter-twin birth weight for the groups. Birth order was found to be similar between US-normals and US-PCOs (Table I).

Overall, 41 subjects had normal delivery, 8 had cesarean section and 8 were delivered by forceps. Sixteen subjects had breech presentation and spontaneous delivery, while 4 subjects were breech in presentation and were delivered by forceps (partial breech extraction). None of the subjects was delivered by vacuum extraction. When the subjects were classified into 2 groups of the US-PCO and US-normal, 49% of US-PCO subjects had normal delivery as opposed to 57.5% of US-normals (Table II). The two groups of US-PCO and US-normal did not differ significantly with respect to the complications of delivery. The numbers of US-normal subjects delivered by cesarean section were higher in percentages compared to the US-PCO group (12.5% vs. 8%), but the difference between these two groups was not significant (p= 0.40). The rate of breech and forceps delivery was not found to be significantly different between the two groups (Table II). Fifty-seven percent of scan-discordant twins (8 out of 14) were found to have normal delivery, 2 had cesarean section and 4 subjects were delivered by forceps. The type of delivery did not seem to differ between US-normals and US-PCOs within the discordant group (Table II).

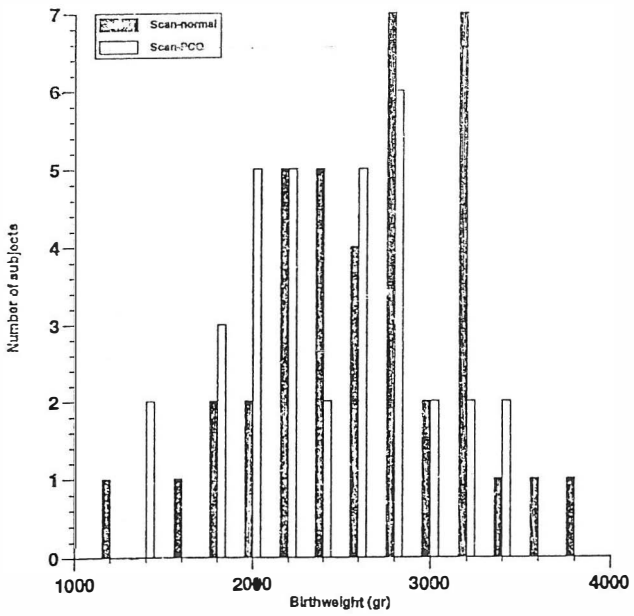

Fig. 1. Distribution of birth weights in two groups of US-normal (n= 40) and US-PCO (n= 37) subjects

Table I. The distribution of birth order in two groups of US-PCO and US-normal subjects.

Group	Twin 1	Twin 2
US-normal (n= 40)	21 (52.5%)	19 (47.5%)
US-PCO (n= 37)	16 (43%)	21 (57%)
Fisher's Exact Test	0.28	0.29

Table II. Type of delivery in two groups of US-PCO and US-normal subjects.

Group	Normal delivery	Cesarean section	Forceps	Breech
The whole database				
US-normal (n= 40)	23 (57.5%)	5 (12.5%)	3 (7.5%)	9 (22.5%)
US-PCO (n= 37)	18 (49%)	3 (8%)	5 (13%)	11 (30%)
Fisher's Exact Test (p)	0.29	0.40	0.31	0.32
Scan-discordant twins				
US-normal (n= 7)	5 (71%)	1 (14%)	1 (14%)	-
US-PCO (n= 7)	3 (43%)	1 (14%)	3 (43%)	-
Fisher's Exact Test (p)	0.29	0.77	0.28	-

Baby and infant feeding history

Seventeen subjects were only breast fed and 27 were only bottle fed. Thirty-three subjects were on both regimens. Table III shows that the percentage of subjects who were breast fed only, did not differ between those with US-PCO and the US-normals (24% vs. 20% respectively, p= 0.34). However, almost twice as many US-normal subjects were bottle fed in comparison with US-PCOs (p= 0.05). The duration of breast feeding ranged between 1 to 12 months as opposed to bottle feeding which lasted longer (3 to 36 month). When subjects were divided according to the length of time that they were breast fed (>3 months and <3 months), no significant difference was found between the two groups of US-normal and US-PCO. Similar results were obtained for bottle feeding when a 6 month interval was used as the classification marker. Solid food was given to the subjects starting from 2 to 8 months of age. Using the starting point of 4 months, subjects were then classified into two groups (>4 months and <4 months). Again, the incidence of PCO did not differ between these groups. Scan-discordant twins were fed similarly.

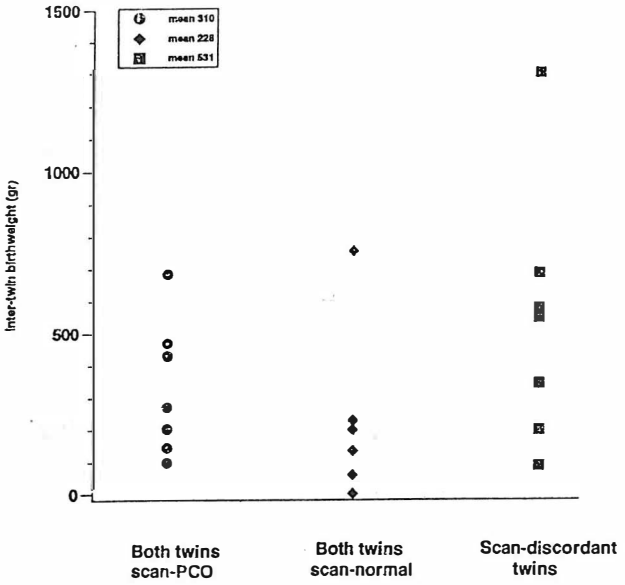

Fig. 2. A comparison of inter-birth weight between twin-pairs in 3 groups; both US-PCO (8 pairs), both US-normal (8 pairs), and scan-discordant twins (7 pairs).

Childhood illness and vaccination

Tables IV and V summarize the data of childhood illnesses and vaccinations. Overall, the two groups of US-normal and US-PCO were similar with respect to the prevalence of childhood illnesses. This was also true for vaccination. Vaccination against mumps was found to be higher in the US-PCO group (p= 0.04).

Subjects were then divided into 4 groups; those who had mumps during childhood but were not vaccinated against it (illness only), subjects who were vaccinated but were not affected by the illness (immunized only), subjects who have been vaccinated and were also affected by mumps during childhood (both) and finally a group of subjects who were not vaccinated and did not have mumps (none). As Table VI shows, 7 subjects were affected by the illnesses during childhood and also had vaccinations (for mumps). Six subjects were only vaccinated and all of them were in the US-PCO group (16%). Using Fisher's test the difference between the two groups of US-normal and US-PCO was significant (p= 0.04). Analyzing the data for scan-discordant twins, however, did not show any significant difference for mumps or

Table III. Feeding history in two groups of US-PCO and US-normal subjects.

Group	Breast feeding only	Bottle feeding only	Both
US-normal (n= 40)	8 (20%)	18 (45%)	14 (35%)
US-PCO (n= 37)	9 (24.3%)	9 (24.3%)	19 (51.4%)
Fisher's Exact Test	0.34	0.05	0.11

Table IV. Ten childhood illnesses in two groups of US-PCO and US-normal subjects.

Childhood illness	US-normal (n= 40)	US-PCO (n= 37)	p value
Measles	32 (80%)	23 (62%)	0.07
Mumps	23 (58%)	15 (41%)	0.10
Chickenpox	36 (90%)	29 (78%)	0.13
Rubella	16 (40%)	9 (24%)	0.11
Glandular fever	4 (10%)	6 (16%)	0.31
Appendicitis	9 (23%)	3 (8%)	0.08
Eczema (dermatitis)	1 (2.5%)	3 (8%)	0.27
Hepatitis	3 (7.5%)	2 (5%)	0.54
Swollen or aching joints	1 (2.5%)	-	0.52
Whooping cough	3 (7.5%)	2 (5%)	0.54

Table V. Vaccination pattern in two groups of US-PCO and US-normal subjects.

Vaccination pattern	US-normal (n= 40)	US-PCO (n= 37)	p value
Triple vaccine	31 (86%)	31 (84%)	0.34
Polio	32 (89%)	33 (89 %)	0.21
Measles	16 (44%)	13 (35%)	0.42
Rubella	32 (89%)	28 (76%)	0.42
Tetanus	30 (83%)	23 (62%)	0.17
Mumps	3 (7.5%)	9 (24%)	0.04
Hepatitis	13 (36%)	10 (27%)	0.39

any other examined childhood illness and/or vaccination between the two groups of US-normal and US-PCO. The age of infection also did not differ b etween the two groups of US-normal and US-PCO within the whole database.

Activity and exercise pattern

Physical activity during childhood and adolescence was classified into 4 age groups (Table VII). The intensity of physical activity in the first 5 years of age was categorized in three groups of quiet, inactive games; active physical behavior and a bit of both which was scored 0, 1 and 2 respectively. The physical activities for the second, third and fourth 5 years included running, sports and swimming. The frequency of performing the exercise was subdivided into 6 degrees (everyday, more than one hour; everyday less than one hour; 2-3 times a week, more than one hour each time; 2-3 times a week, less than an hour each time and hardly ever). Each level scored separately. The incidence of PCO did not seem to relate to physical activity during the first 15 years of age. Between age 16-20, subjects with US-PCO were found to be less active, compared with US-normals. However, this difference did not reach significance. Similar results were obtained from scan-discordant twins.

DISCUSSION

Birth weight, feeding behavior, childhood illnesses and activity are some of the factors which may affect growth

Table VI. Vaccination against mumps in two groups of US-PCO and US-normal subjects.

Mumps	None[a]	Illness only[b]	Immunized[c]	Both[d]
US-normal (n= 40)	17 (43%)	19 (48%)	-	4 (10%)
US-PCO (n= 37)	15 (41%)	12 (32%)	6 (16%)	3 (8%)
Fisher's Exact Test (*p*)	0.52	0.13	0.009	0.544

[a]Subject neither had mumps during childhood, nor was vaccinated against it.
[b]Subject had mumps during childhood but was not immunized.
[c]Subject was vaccinated only and was not infected by mumps during her childhood.
[d]Subject had been immunized against mumps and had the illness during her childhood.

Table VII. Activity of subjects since birth till 20 years of age in two groups of US-PCO and US-normal.

Activity and exercise pattern	US-normal (n= 40)	US-PCO (n= 37)	p value
Birth-5 (years)	17 (43%)	13 (35%)	0.33
6-10 (years)	26 (65%)	21 (57%)	0.31
11-15 (years)	23 (58%)	23 (62%)	0.43
16-20 (years)	20 (50%)	13 (35%)	0.41

and lead to adult diseases later as a programming phenomenon.[9] This in turn may lead to disturbances in the hypothalamic-pituitary-ovarian (HPO)-axis and PCO changes. The present study attempted to examine the effect of such factors on the etiology of PCO. All the examined parameters were analyzed in the whole database as well as in scan-discordant twins.

Lower birth weight may result in impaired endocrine system and PCO changes. Although analyzing the whole database suggested that scan-PCO subjects had lower birth weight than scan-normals, the mean birth weight of scan-discordant twins did not differ significantly between scan-normals and scan-PCOS.

Birth order and gestational age did not seem to have any influence in the prevalence of PCO. Our data suggests that the type of delivery has no effect on the prevalence of PCO. Bottle feeding has been hypothesized to be the cause of an elevated IGF-I which in turn results in hypersecretion of insulin and PCO changes.[4] Our study does not support this theory, since the number of subjects who were bottle fed during infancy was lower in the scan-PCO group (24%) compared to the scan-normal subjects (45%). Similar results were obtained from scan-discordant twins.

It has been suggested that an autoimmune mechanism is responsible for PCO changes, at least in some cases.[10,11] It could be hypothesized that active immunization or viral infections that activate the immune system may interact with the endocrine system. If this theory is true, then differences in the incidence of childhood illnesses would be expected to differ between subjects with scan-PCO and those with normal scans. The incidence of childhood illness was higher in scan-normal subjects in comparison with scan-PCOs. However, the difference between the two groups was not significant for any of the childhood illnesses. The same pattern was observed for vaccinations except for mumps. The number of subjects who were vaccinated for mumps and with no illnesses during their childhood were six times higher in the scan-PCO group ($p= 0.04$).

In conclusion, this study examined the effect of some environmental factors during childhood and early adulthood. Analyzing the whole database suggested that low birth weight and prematurity may have a significant impact on the neuroendocrine system that may lead to disturbance of the HPO-axis function, resulting in PCO during adulthood. However, matched results for scan-discordant twins did not agree with these results. Feeding behavior, type of delivery, birth order and physical activity during the first 20 years of age did not seem to have any significant influence on the prevalence of PCO. No significant difference was found in childhood illnesses between the groups. Vaccination against mumps was found to be significantly higher in the scan-PCO group. This result was not confirmed by scan-discordant results.

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