Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity

K A Neville, J L Walker

Background: Perinatal stress is thought to underlie the Barker sequelae of low birth weight, of which precocious pubarche may be a manifestation.

Aims: To explore whether prematurity as well as smallness for gestational age (SGA) predisposes to precocious pubarche, and the potential role of excess weight gain during childhood.

Methods: Retrospective chart review of 89 children (79 girls) with precocious pubarche.

Results: Sixty five per cent were overweight/obese at diagnosis, compared with 19–24% of Australian children. Thirty five per cent had a history of SGA and 24% of prematurity. Weight SDS increased from birth to diagnosis in 91% of children. The mean change in weight SDS from birth to diagnosis was greater in those who were SGA (2.8, 95% CI 2.2 to 3.4) versus AGA (1.7, 95% CI 1.3 to 2.2), with no difference in the incidence of overweight/obesity. The latter was lower among children born premature (40% versus 72% term) but was associated with a mean increase in weight of 1.3 SDS during childhood. Nine out of ten girls and boys with precocious pubarche had at least one of the three risk factors studied.

Conclusions: Both prematurity and SGA were associated with precocious pubarche, as was overweight/obesity, irrespective of size or gestation at birth. Excess weight gain in childhood may predispose to precocious pubarche in susceptible individuals.

Patients and Methods

A retrospective chart review was performed of all patients presenting between December 1988 and May 2001 who were coded in the database of the Endocrine Department of Sydney Children’s Hospital as having precocious pubarche. Precocious pubarche was defined as the onset of sexual hair at less than 8 years for girls and 9 years for boys, with sufficient duration of follow up and clinical and/or laboratory data to exclude other pathology, including the development of true precocious puberty.

Eighty nine children (79 girls) were identified as having a diagnosis of precocious pubarche and included in the study. Potential adrenal pathology was excluded biochemically in 85/89 children with an adrenal hormone profile and/or ACTH stimulation test, with the diagnosis resting on clinical grounds in the remaining four. The median age of onset of precocious pubarche in girls was 6.7 years (range 2.7–8.0) and boys 8.0 years (range 5.4–8.6). Of the seven girls aged <4 years, all had adrenal pathology excluded on biochemical grounds, a median bone age (BA) advance of 0.8 years (range 0–2.3 years) and a median follow up period of 4 years (range 3.3–6.0 years). Data obtained for analysis from the patients’ files included height and weight at diagnosis, gestational age (available in 84/89), birth weight (81/84), birth length (58/81), and BA (84/89).

Birth weights were expressed as a standard deviation score (SDS) and percentile for GA using recent Australian standards. Where a birth length was also available, a Ponderal Index (PI; weight/length3) was calculated and was classified as either above or below the 10th centile for Australian neonates. Because the PI relates weight to

Abbreviations: AGA, appropriate for gestational age; BA, bone age; BMI, body mass index; BW, birth weight; GA, gestational age; PI, Ponderal Index; SDS, standard deviation score; SGA, small for gestational age
height, it may be a better indicator of nutritional constraint in utero and intrauterine growth retardation than birth weight alone.\textsuperscript{23} Children were classified as small for gestational age (SGA) if the birth weight and/or Ponderal Index were less than the 10th centile for GA. Prematurity was defined as a GA less than 37 weeks.

Weight, height, and BMI (weight/height\textsuperscript{2}) at diagnosis were expressed as SDS and centiles in accordance with published data.\textsuperscript{20–21} The difference between the chronological age (CA) and BA at diagnosis was calculated. Using the BMI at diagnosis, children were defined as overweight or obese according to the recently developed and published Cole standards.\textsuperscript{25} These standards relate a child's age and sex-adjusted BMI SDS to a BMI of 25 kg/m\textsuperscript{2} (overweight) or 30 kg/m\textsuperscript{2} (obese) at age 18 years and therefore allow comparison across populations and over time. Gain in weight during childhood was assessed by comparing the difference between birth weight SDS and diagnosis weight SDS.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 11.0 for Windows). Anthropometric measures were expressed as either mean (95% CI) or median [range] unless otherwise indicated. Means between groups were compared by independent \(t\) tests. Categorical data were analysed using cross-tabulation and the \(\chi^2\) test. Pearson's correlation coefficient was used to describe the correlation between two continuous variables. Statistically significance was defined as a \(p\) value less than 0.05.

RESULTS

At initial presentation for precocious pubarche the group was tall with a mean height SDS of 0.8 (0.6 to 1.1), consistent with the mean bone age advance over chronological age of 0.9 years (0.7 to 1.1). The mean weight SDS was 1.7 (1.3 to 2.0; table 1). Thirty of the 89 children were overweight or obese (33.7%) and 28/89 obese (31.4%). Fifty eight (65.1%) children were therefore overweight or obese (table 1) compared with the recently published rate of overweight/obesity in the general Australian child population (p<0.001, one way \(\chi^2\)).

The mean gain in weight (\(\Delta\)Wt) SDS from birth to diagnosis was 2.0 (1.7 to 2.4), with 90% (80/89) experiencing an increase in weight SDS. When analysed according to size at birth, there was no difference in weight SDS, BMI SDS, or incidence of overweight/obesity comparing those who were originally SGA to those who were appropriate for gestational age (AGA) (table 1). However, as by definition the mean birth weight SDS of the SGA children was lower than that of the AGA children, their "gain in weight" during childhood was significantly greater, with a mean \(\Delta\)Wt SDS from birth to diagnosis of 2.8 (2.2 to 3.4) versus 1.7 (1.3 to 2.2) for the AGA group (p = 0.005, table 1). The mean gain in weight SDS from birth to diagnosis in the children who were premature was significantly less than for the term group (1.3 (0.7 to 1.9) versus 2.3 (1.9 to 2.7); p = 0.02, table 1).

Seventy eight of the 89 (88%) children studied were overweight/obese and/or had a history of SGA and/or prematurity. Of the 31/89 children who were of normal weight at diagnosis, GA was recorded in 30 and birth weight +/− length in 29/30. Forty per cent (12/30) were premature and 41% (12/29) were SGA, with 67% (20/30) premature and/or SGA. Their mean gain in weight SDS from birth to diagnosis was 0.8 (0.3 to 1.2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Auxological parameters in 89 children with precocious pubarche according to their weight status, gestation, and birth weight</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Whole group n = 89</td>
</tr>
<tr>
<td>Weight SDS†</td>
<td>1.7 (1.3 to 2.0)</td>
</tr>
<tr>
<td>BMI SDS†</td>
<td>2.4</td>
</tr>
<tr>
<td>% overweight/obese (n)</td>
<td>65% (58)</td>
</tr>
<tr>
<td>% premature (n)</td>
<td>24% (8)</td>
</tr>
<tr>
<td>Birth weight SDS†</td>
<td>−0.4 [−0.7 to −0.2]</td>
</tr>
<tr>
<td>% SGA (n)</td>
<td>35% (28)</td>
</tr>
<tr>
<td>Gain in weight SDS†</td>
<td>2.0 [1.7 to 2.4]</td>
</tr>
<tr>
<td>% normal weight+</td>
<td>12% (11)</td>
</tr>
</tbody>
</table>

†Mean (95% CI), ‡median [range].
*p < 0.05, *p < 0.01, **p < 0.001.
What is already known on this topic

- Low birth weight increases the risk of a number of adult diseases, as originally postulated by the Barker hypothesis.
- Precocious pubarche has been associated with low birth weight and hyperinsulinism, and therefore may form part of the spectrum of disease encompassed by the Barker hypothesis.

Because of the small number of boys (consistent with published sex ratios\(^1\)), statistical analysis was repeated after their exclusion with similar results (data not shown). When the 10 boys with precocious pubarche were analysed separately, the rate of overweight/obesity was 80% (8/10), 30% (3/10) had a past history of prematurity, and 33% (3/9) were SGA. Only 1/10 was not overweight/obese, premature, or SGA, as was the case when boys and girls were analysed together (table 1).

DISCUSSION

Compared with published Australian standards, the children in our study with precocious pubarche had an increased incidence of overweight/obesity and an increased likelihood of having been SGA or premature, with 9/10 girls and boys presenting with at least one of these factors. The novel observation that prematurity is associated with an increased risk of precocious pubarche is consistent with the precocious pubarche being one of the sequelae of low birth weight and perinatal stress. The increase in weight SDS documented from birth to diagnosis in all groups (table 1) suggests that excess weight gain in childhood may provide the trigger for the development of precocious pubarche as is thought to be the case for other manifestations of the Barker hypothesis.

The prominence of overweight/obesity in the children studied is consistent with the postulated role for weight gain in the modulation of adrenal androgen secretion.\(^2\) The mean gain in weight during childhood of 2 SDS (table 1) in our study greatly exceeded that of 0.3 SDS shown in the ALSPAC longitudinal study of children followed from birth to 5 years.\(^3\) Sixty five per cent of the children presenting with precocious pubarche were overweight or obese, three times the rate of overweight/obesity in the Australian child population.\(^4\) The frequency of obesity (31%) we observed was similar to that recently reported in French children presenting with precocious pubarche.\(^5\) In children, the greatest increase in urinary DHEAS secretion occurs in the same year as the greatest increase in BMI,\(^6\) and in adults, experimentally induced fluctuations in weight have been shown to correlate directly with urinary adrenal androgen secretion.\(^7\) Insulin has been implicated in the regulation of adrenal androgen secretion in in-vitro studies.\(^8\) The increased plasma insulin concentrations and decreased insulin sensitivity associated with increasing weight may underlie the link between adrenal androgen production and body mass.

A history of SGA and/or prematurity was also more frequent among the children presenting with precocious pubarche than expected in the general Australian population,\(^9\) \(^10\) \(^11\) \(^12\) \(^13\) \(^14\) \(^15\) \(^16\) with 34% born SGA and 24% premature. Moreover, two thirds of the 31 children who were of normal body weight at presentation had a history of SGA and/or prematurity. Previous studies have described an association between SGA and the later development of precocious pubarche,\(^\) but have not explored the potential effect of prematurity alone. Hormonal studies of premature infants born small or appropriate for gestational age have yielded conflicting results;\(^17\) \(^18\) \(^19\) \(^20\) \(^21\) however it is possible that the prenatal and/or postnatal stresses to which premature infants are subjected induce similar permanent reprogramming of the endocrine and metabolic pathways as is proposed for growth restricted infants. Of note, large population studies\(^22\) \(^23\) \(^24\) \(^25\) \(^26\) \(^27\) \(^28\) \(^29\) examining the Barker hypothesis have linked low birth weight per se with later disease, without discriminating between children born prematurely or growth retarded.

Weight gain during childhood may be critical to the development of precocious pubarche in susceptible individuals. Epidemiological studies suggest that in children with low birth weight, relatively small increases in weight SDS and BMI during childhood magnify the risk of metabolic and endocrine sequelae.\(^30\) In twins discordant for birth size studied in late childhood, the lower birth weight twin had higher plasma concentrations of DHEAS than the higher birth weight twin if there had been catch-up in weight SDS of a degree similar to that observed in our study.\(^31\) Although our children with a past history of prematurity had a smaller increase in weight SDS during childhood (1.2 SDS) and a lower rate of overweight/obesity (40%) than children born at term (table 1), both were higher than predicted by population studies.\(^32\) \(^33\) Even among the 20 premature and/or SGA children of normal weight at diagnosis, the median increase in weight SDS of 0.8 SD was greater than that observed in the ALSPAC study.\(^34\) Our data do not allow us to determine the independent contributions of low birth weight and increase in weight SDS during childhood to the development of precocious pubarche; however the effects of low birth weight and increased weight gain during childhood might be expected to be additive if the common underlying mechanism is hyperinsulinism. Decreased insulin sensitivity has been documented in children with a history of low birth weight\(^35\) and in girls of normal body weight with precocious pubarche,\(^36\) especially if there is a history of low birth weight. Moreover, a recent study\(^37\) showed that treatment with an insulin sensitisier of normal weight girls with a history of precocious pubarche and low birth weight improved body composition, decreased lipid abnormalities, and prevented progression to polycystic ovarian disease, suggesting that hyperinsulinism contributes to the pathogenesis of precocious pubarche in children of low birth weight.

A caveat to our conclusion that overweight/obesity and perinatal stress predispose to the development of precocious pubarche is the known ascertainment bias of hospital based studies.\(^38\) Children who are overweight, or have a history of other problems (for example, prematurity or SGA) may be more likely than other children to present to a hospital outpatient clinic, simply because they suffer from another condition and may have more encounters with medical practitioners leading to their referral. The relevance of the

What this study adds

- Prematurity as well as smallness for gestational age is more frequent than expected in children with precocious pubarche.
- Overweight/obesity is more frequent in children with precocious pubarche than in the general population.
- The association of precocious pubarche with SGA, prematurity, and with excess weight gain in childhood suggests that precocious pubarche may be a marker for hyperinsulinism.
diagnosis of precocious pubarche, however, lies with whether it is a marker for something else because it is not a condition for which treatment is either required or available. The associations we observed are consistent with data suggesting that precocious pubarche may be a clinical marker for decreased insulin sensitivity, and this has implications for the counselling and follow up of affected children.

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