Early physiological development of infants with intrauterine growth retardation

J A Jackson, M P Wailoo, J R Thompson, S A Petersen

Objectives: To assess the patterns of early postnatal physiological adaptation and maturation in intrauterine growth retarded (IUGR) infants by measuring changes in sleeping deep body temperature, heart rate, and concentrations of urinary cortisol.

Setting: At home.

Patients: Sixty five IUGR babies and 127 controls matched for sex, social class, and levels of parental smoking.

Results: Night time sleeping deep body temperature, heart rate, and cortisol excretion fell with age, eventually establishing an adult type diurnal rhythm of physiological function. Minimum overnight temperature showed a linear decline with age (\( p < 0.001 \)), but the IUGR infants and the controls had significant differences in intercept (\( p = 0.007 \)) and slope (\( p = 0.02 \)). The estimated rate of decline per week was 0.020°C for IUGR infants and 0.031°C for controls. Maximum temperature did not show similar changes. IUGR infants had a mean (SE) age adjusted minimum overnight heart rate that was 4.2 (1.5) beats/\( \text{min} \) (\( p = 0.005 \)) higher than controls. Overnight cortisol/creatinine ratios declined with age at a rate of 4.1% per week (log ratio \(-0.421\) (0.165), \( p = 0.01 \)), but the ratio for IUGR infants was on average 42% higher (log ratio \(0.35\) (0.11), \( p = 0.002 \)) than for controls of the same age. Morning cortisol concentrations did not show a similar pattern.

Conclusions: Postnatal physiological adaptation and maturation of IUGR infants is slower than normal and therefore remain in a physiologically immature state for longer. The higher heart rates and greater cortisol excretion in such infants may be precursors to hypertension and cardiovascular disease seen in adults.
immunoassay (Coat a Count assay). All these techniques are safe, and full ethical approval was obtained for the study. Parents were asked to keep a detailed diary of all events that occurred on the night of the recording, including nappy changes, periods of waking and feeding, and any medication given to the infant. The following morning, the equipment was collected and the recorded measurements were downloaded to a computer for analysis. The recordings were scrutinised for evidence of lost probes or technical problems, and affected data were removed before further analysis. For each night, measurements were abstracted at 30 minute intervals, the rectal temperature for the period from one hour before bedtime until eight hours later, and the heart rate for the period from bedtime until six hours later. For each IUGR infant, data on matched control infants who had identical physiological measurements were taken from an existing database. The IUGR infants and controls were individually matched for sex, social class, method of feeding, and maternal smoking behaviour.

The measurements were analysed by mixed normal regression models fitted by REML. The models incorporated a random subject term to allow for the correlation between repeated measures on the same infant. Cortisol/creatinine ratios were positively skewed and so the log of the ratios was analysed.

RESULTS

Sixty five infants with IUGR were identified. They were monitored for temperature, heart rate, and cortisol/creatinine ratio on an average of 4.2 occasions between the ages of 6 weeks and 21 weeks. Matched controls were chosen from a large database of healthy children who had been studied previously using the same methodology.

Temperature

The analysis included 64 IUGR infants and 127 controls. Overnight rectal measurements were discarded when the probe became loose, when there were missing data in the first four hours after bedtime, or when the infant was monitored on a night after an immunisation. On average, each IUGR infant was successfully monitored 4.0 times, and each control infant 3.5 times between the ages of 6 weeks and 21 weeks, providing a total of 712 temperature recordings, 258 for the IUGR infants and 454 for the controls. Figure 1 shows the ages at which the IUGR infants and their controls were monitored. Most monitoring took place between 7 and 15 weeks of age.

Table 1 shows the quality of the matching. The mothers of controls tended to be of slightly higher social class and to be marginally more likely to be non-smokers. Counting the number of variables by which the IUGR infants and their matched controls differed and treating social classes that differ by more than one category as being a mismatch, the average difference between a control and their IUGR infant was 0.5 of a variable.

Temperatures were extracted from the continuous recording at 30 minute intervals between bedtime and four hours after bedtime. From the resulting nine temperature readings for a given night, the maximum and minimum temperatures were calculated. Figure 2 shows the means of the minimum and maximum temperatures across all IUGR infants and across their controls.

Models for the minimum temperature showed a linear decline (p < 0.001) and no significant deviation from linearity (p = 0.57). The lines for IUGR infants and controls showed significant differences in intercept (p = 0.007) and slope (p = 0.02). The intercepts differed by a mean (SE) of 0.051 (0.019)˚C, and the estimated decline for IUGR infants was 0.011 (0.005) ˚C a week steeper. Patterns of linear trend require careful interpretation and they sometimes show good local fit when the model does not extrapolate. In this study an alternative model for the data would be that IUGR infants are similar to controls until about 10 weeks. They then show

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**Table 1**

<table>
<thead>
<tr>
<th>Matched factors</th>
<th>IUGR (n = 64)</th>
<th>Controls (n = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>46%</td>
<td>44%</td>
</tr>
<tr>
<td>Feeding (breast)</td>
<td>48%</td>
<td>45%</td>
</tr>
<tr>
<td>Maternal smoking (yes)</td>
<td>54%</td>
<td>47%</td>
</tr>
<tr>
<td>Social class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>21%</td>
<td>30%</td>
</tr>
<tr>
<td>II In or IIIm</td>
<td>52%</td>
<td>46%</td>
</tr>
<tr>
<td>IV or less</td>
<td>29%</td>
<td>24%</td>
</tr>
<tr>
<td>Unmatched factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>27.8 (5.0)</td>
<td>28.6 (4.8)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>38.7 (1.5)</td>
<td>39.8 (1.5)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2663 (453)</td>
<td>3448 (506)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or percentages.

IUGR, Intrauterine growth retarded; III In, social class III, non-manual; III m, social class III, manual.
less of a decline in minimum temperature but catch up about a month later. A post hoc definition of the 10–15 week interval as being where the groups differ produces a significant interaction (p = 0.02) with a mean difference between groups within those ages of 0.092 °C, but not otherwise. As this interval is derived from these data, the finding requires confirmation in another study.

The maximum temperatures showed a declining trend (p = 0.003) but there was also a suggestion of non-linearity (p = 0.02). Adjusting for the age difference between IUGR infants and controls was of marginal significance (p = 0.07), with the maximums for the IUGR infants on average 0.44 (0.024) °C lower than for the controls. There was no suggestion of a difference in slope (p = 0.53) or of a difference between 10 and 15 weeks that was absent elsewhere (p = 0.48).

Heart rate

All of the 54 IUGR infants were matched with a control. Table 2 shows the quality of the matching. The control infants for whom heart rate was available tended to come from poorer social backgrounds (p = 0.06) and to be less likely to have been breast fed (p = 0.05). Counting mismatches in the four variables that were used for matches, on average the IUGR infant and their control differed by 0.9 of a variable.

The 54 IUGR infants included in the heart rate analysis had been monitored successfully over 211 nights, and the 54 controls on 142 nights. Half hourly readings were extracted from the continuous recordings taken over the four hours after bedtime, and the minimum and maximum of these values were calculated. Figure 3 shows the means.

The analysis of minimum heart rate showed a decline with age averaging 1.0 (0.2) beats/min a week. Adjusting for age, the IUGR infants had a higher minimum heart rate by a mean (SE) of 4.2 (1.5) beats/min (p = 0.005). There was an inconclusive suggestion of a difference in slope between IUGR infants and controls (p = 0.07), but no evidence of a different pattern in weeks 10–15 compared with other ages (p = 0.65). The maximum heart rates also showed a decline with age, which in this case averaged 1.5 (0.22) beats/min a week, but there was no suggestion of a difference between IUGR infants and controls (p = 0.22).

To compensate for the poor matching of social class, the minimum heart rate was reanalysed including a term for social class based on the groupings shown in table 2. The rate of change with age stayed at 1.0 (0.2) beat/min a week, and the mean age adjusted difference between IUGR infants and controls increased to 4.9 (1.7) beats/min (p = 0.005).

Cortisol

Cortisol and creatinine concentrations were measured in urine samples collected overnight and again in the morning. Cortisol/creatinine ratios were then calculated. Two controls were sought for each IUGR infant.

Overnight cortisol

Thirty nine of the IUGR infants had at least one bedtime measurement and could be matched to at least one control with a bedtime measurement. Cortisol was measured in all the 39 IUGR infants on 114 occasions and in the 58 matched controls on 160 occasions. Table 3 shows a summary of the quality of the matching.
Early physiological development of IUGR infants

Table 4 Comparison of matching and other variables: morning cortisol to creatinine ratio

<table>
<thead>
<tr>
<th>IUGR (n = 31)</th>
<th>Controls (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched factors</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>65%</td>
</tr>
<tr>
<td>Feeding (breast)</td>
<td>55%</td>
</tr>
<tr>
<td>Maternal smoking (yes)</td>
<td>39%</td>
</tr>
<tr>
<td>Social class</td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>39%</td>
</tr>
<tr>
<td>III or IV</td>
<td>35%</td>
</tr>
<tr>
<td>V or less</td>
<td>26%</td>
</tr>
<tr>
<td>Unmatched factors</td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>39.0 (5.5)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>38.5 (1.4)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2694 (520)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or percentages.
IUGR, Intrauterine growth retarded.

Figure 4 shows the average bedtime cortisol/creatinine ratios. On analysis of the log of the ratio, there was a suggestion of a decline with age of 4.1% a week (log ratio = −0.0421, SE = 0.0165, p = 0.01) and strong evidence that IUGR infants had higher cortisol/creatinine ratios. The IUGR infants had ratios that were 42% higher (log ratio = 0.35, SE 0.11, p = 0.002) than the controls. There is no suggestion of a difference in the rate of decline with age depending on the IUGR status of the child (p = 0.92).

Morning cortisol
Thirty one of the IUGR infants had at least one morning measurement and could be matched to at least one control with a morning measurement. Cortisol was measured in all 31 IUGR infants on 85 occasions and in the 44 matched controls on 104 occasions. Table 4 shows a summary of the quality of the matching.

The mean morning cortisol/creatinine ratios (fig 5) were far more variable than the bedtime ratios. There was no suggestion of a decline with age (p = 0.80), but there was evidence that IUGR infants have higher cortisol/creatinine ratios (estimated to be 48% higher; log ratio = 0.391, SE 0.116, p < 0.001).

DISCUSSION
On the face of it, growth restricted infants appear to be physiologically different during the first postnatal months from other infants. The changes we have measured (the slowing of heart rate, the fall in deep body temperature with sleep, and the excretion of cortisol in the urine) are definitely related to the growth restriction per se and not to some other factors. Excretion of mela-tonin, also rhythmically and age related, is delayed in growth restricted infants22 in a way that fits with the findings of this study.

There is every likelihood that IUGR infants are subjected to some intrauterine stress and programming, which may be compounded by postnatal infant and parental behaviours. When awake, IUGR infants tend to be more passive, difficult to arouse, and prone to more frequent changes of waking state,23 and, when asleep, they change states more frequently.24 These differences may persist for at least six months24 and may be visible expressions of the altering physiological state of the infants. It has been found that the mothers of IUGR babies may be more irritable and less affectionate than normal towards their babies in the first few months.25 This raises the question of whether such differences can affect the changes in deep body temperature, heart rate, and cortisol.

The pattern of adult cortisol secretion, diurnal with relatively low night time and high waking-morning concentrations, is slowly achieved by most infants, but more slowly by IUGR infants, who continued to excrete more cortisol than controls up to the time when measurements ceased in this study. In view of the assertions of Barker et al26 that adults who were growth restricted infants tend to develop more cardiovascular and hypotensive illness, and may also have persistently higher serum concentrations of cortisol,27 we speculate that the early physiological changes seen in this...
study may well be the result of early fetal programming which persists into adulthood.

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Authors’ affiliations

J A Jackson, Department of Child Health, University of Leicester and University of Warwick, UK

M P Wailoo, Department of Child Health, University of Leicester

J R Thompson, Department of Ophthalmology, University of Leicester

S A Petersen, Department of Medical Education, University of Leicester

REFERENCES
