Higher weight at birth is related to decreased maternal amino acid oxidation during pregnancy1–3

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ABSTRACT

Background: Small size at birth is associated with cardiovascular disease in adult life. Decreased fetal growth may result from a limitation in the nutrient supply to the fetus. Net tissue deposition in the mother and fetus increases the demand for nitrogen, but because maternal consumption of protein does not increase, there must be a change in the partitioning of amino acids, away from oxidation and toward deposition.

Objective: Our objective was to characterize amino acid oxidation in pregnancy and to investigate whether the relative partitioning of amino acids was related to fetal growth.

Design: We determined amino acid oxidation as urea production in 25 women during mid (17–19 wk) and late (26–29 wk) gestation. Urea production was measured from urinary [15N-15N]urea excretion over 48 h after a single oral dose of [15N,15N]urea. We measured the infant’s size at birth.

Results: For the group as a whole, urea excretion decreased and amino acid oxidation remained similar between mid and late pregnancy, but there was wide variation between the women. Heavier infants were born to the mothers in whom amino acid oxidation decreased the most during pregnancy (slope of regression line: $-80 \text{ g} \cdot \text{g N}^{-1} \cdot \text{d}^{-1}$; 95% CI: $-129$, $-31$; $P = 0.003$). After adjustment for length of gestation and the infant’s sex, the change in maternal amino acid oxidation explained 34% of the variation in birth weight.


KEY WORDS Nutrition, pregnancy, amino acid oxidation, urea production, birth weight, fetal origins, white women

INTRODUCTION

A significant body of epidemiologic evidence shows that growth and development during fetal life may have important effects on health in adult life. Many studies have shown that smaller size at birth is associated with a higher risk of developing cardiovascular disease, type 2 diabetes, and hypertension later in life (1–3). Graded associations are seen across the normal range of birth weight. Many studies have shown that small size at birth is associated with cardiovascu-lar disease in adult life. Decreased fetal growth may result from a limitation in the nutrient supply to the fetus. Net tissue deposition in the mother and fetus increases the demand for nitrogen, and amino acids (5). It is estimated that 925 g protein is accumulated, and recommendations suggest that protein intake should be increased by 6–10 g/d throughout pregnancy (6–8). However, women do not appear to increase their protein consumption as pregnancy advances (9), and therefore to enable net protein deposition, there must be a change in the partitioning of amino acids away from oxidation and toward deposition.

In the present study, we measured urea production as an index of amino acid oxidation. Previous researchers assessed amino acid oxidation from measurements of urinary nitrogen excretion (10). It is now recognized that not all the urea produced is excreted in urine: a portion passes into the colon where it is hydrolyzed by the colonic microflora. Hence, urea excretion underestimates the extent of amino acid oxidation (11, 12).

We studied women twice during pregnancy to characterize changes in amino acid oxidation and to investigate whether the relative partitioning of amino acids was related to the growth of the fetus. Because body mass index (BMI; in kg/m$^2$) has been shown to influence aspects of protein metabolism (10, 13), we studied women with a BMI of 21.0–28.9.

SUBJECTS AND METHODS

Subjects

We recruited 30 healthy, nonsmoking, multiparous white women from 2 hospitals and a health center in the Southampton area when the women attended a midwives’ antenatal booking clinic. To be eligible for the study, subjects had to be multiparous, aged between 24 and 33 y, and nonsmokers and had to have a height of 1.58–1.68 m and a BMI of 21.0–28.9. Length of gestation was estimated from the first day of the last menstrual period. The study was approved by the local ethics committee, and informed, written consent was obtained from each subject. The

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women were studied in their own homes with the use of noninvasive methods suitable for free-living individuals (14).

**Study design**

Each subject was studied twice during pregnancy: at 17–19 wk gestation (mid pregnancy) and at 26–29 wk gestation (late pregnancy). On both occasions, measurements of amino acid oxidation and anthropometric measurements were carried out. In mid pregnancy each woman completed a 3-d food diary. When the subject delivered, the infant’s body size was measured within 48 h.

**Amino acid oxidation**

The rate of urea production is a direct measure of the rate of amino acid oxidation. Urea production was measured from the recovery in urine of a single oral dose of $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$. A sample of urine was collected before administration of the isotope to determine the background abundance of $^{15}\text{N}$. Each subject ingested 100 mg $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$ (99 atom%; Bioquote Ltd, York, United Kingdom) dissolved in 10 mL tap water between 0730 and 0930 (14). Urea was collected in 4 samples of 12 h each for the next 48 h. The urine was collected directly onto 98% (by wt) thymol (Sigma-Aldrich Co Ltd, Dorset, United Kingdom), the total urine volume was measured, and a 60-mL sample was acidified with 100 μL of a 6-mol HCl/L solution and frozen at $-20^\circ\text{C}$ until analysis. Isotopic enrichment was measured in each 12-h sample.

**Biochemical analysis**

The urinary urea concentration was measured by the Berthelot method (15). Urea was chromatographically isolated from urine for mass spectrometry with the use of a short ion-exchange column (16). Nitrogen gas was liberated from urea by reaction with alkaline hypobromite in a monomolecular reaction: 2 nitrogen atoms from urea yield a single molecule of nitrogen gas. Thus, the relative proportions of $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$, $[^{15}\text{N}]{^{14}\text{N}}\text{urea}$, and $[^{14}\text{N}]{^{14}\text{N}}\text{urea}$ can be determined. Measurements of enrichment were carried out in a triple collector isotope ratio mass spectrometer (SIRA 10; VG Isogas Instruments, Cheshire, United Kingdom).

**Calculations**

Urea production was measured with the use of a stochastic model in which the recovery in urine of a single oral dose of $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$ is determined, assuming a biological quasi-steady state (14). In this method it is presupposed that the oral dose of $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$ is absorbed from the upper bowel and mixes freely with the urea pool within the body and hence that the fate of the $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$ effectively traces the fate of unlabeled urea. There are 2 possible fates for the urea within the body pool. It can be excreted in urine as $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$ and lost from the body, or it can pass to the lower bowel, where it is hydrolyzed by the microflora, in which case the nitrogen is returned to the body pool for further potential metabolic interaction. Hence the proportion of the dose recovered in urine is presumed to be the same as the proportion of endogenously produced urea that passes into urine. If the amount of urea excreted in urine over a defined period is known, it is possible to derive the production of urea over an equivalent period. Thus, if labeled urea reliably traces endogenous urea, production can be derived from

$$\text{eu30/d30} = \text{Eu/P} \quad (1)$$

where eu30 is the excretion of $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$ in mg, d30 is the dose of $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$ in mg, Eu is the total urine excretion in mg/48 h, and P is urea production in mg/48 h. On the assumption that urea that is not recovered in urine has been hydrolyzed in the colon, it is possible to derive colonic hydrolysis ($T$) from

$$T = P - \text{Eu} \quad (2)$$

The nitrogen derived from the hydrolysis of urea is retained within the body and has 1 of 2 fates (17). A small proportion returns to urea formation, whereas a greater proportion is incorporated into the metabolically active pool of nitrogen within the body.

The period over which urine is collected must be long enough to ensure that all of the $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$ has been cleared from the body pool and recovered in the urine. Earlier experience has suggested that 48 h is sufficient (14).

In 2 women, amino acid oxidation was very high (>3 SDs greater than the mean value for the group), raising the possibility that they were infected with *Helicobacter pylori*, in which case the dose of $[^{15}\text{N}]{^{15}\text{N}}\text{urea}$ would have been hydrolyzed before absorption, thus producing erroneous results. Excessive hydrolysis of an oral dose of labeled urea is used as a diagnostic test for infection with *H. pylori*. There was no increase, however, in the excretion of $[^{15}\text{N}]{^{14}\text{N}}\text{urea}$ in either subject, making it unlikely that they had an active, ongoing infection; therefore these 2 women were not excluded from the analyses (18).

**Protein intake and test diet**

Current energy and protein intakes were assessed with the use of the 3-d food diary (19). To enable accurate assessment of intake during the study period, food comprising items such as cereal, milk, bread, ready-prepared meals (eg, lasagna), vegetables, and fruit was supplied for the duration of the 48-h study period; this food provided an amount of energy and protein similar to that of the food reported in the food diary. Additional food was available at the woman’s request.

**Anthropometry**

Maternal height was measured with a Harpenden pocket stadiometer (Chasmos Ltd, London) to the nearest 0.1 cm, and weight was measured with Seca portable digital scales (Seca, Hamburg, Germany) to the nearest 100 g. At birth, each infant was weighed to the nearest 5 g with the use of digital scales. Using a Harpenden neonatometer (Holtain, Crymych, United Kingdom), 2 trained research nurses measured each infant’s crown-to-heel length 3 times to the nearest 0.1 cm, and the mean value was used in the analysis. We calculated the ponderal index at birth as birth weight/length$^3$ (in kg/m$^3$). The placenta was weighed on digital scales after removing the umbilical cord and membranes (9).

**Statistical analysis**

Results are expressed as means ± SDs. Paired $t$ tests were used to detect statistically significant differences between measurements in mid and late pregnancy. Linear regression analysis was used to explore the associations between maternal amino acid oxidation and the infant’s size at birth. In late pregnancy, there was a significant positive association between urea production and the length of gestation at the time of the measurement and between urea excretion and the length of gestation at the time of the measurement. Therefore, both were adjusted to the mean length of gestation at the time of measurement (28.3 wk). Measurements of urea hydrolysis were positively skewed and were
Results are expressed as g nitrogen/d. It was assumed that 1 g nitrogen is equivalent to 6.25 g protein. The statistical package SPSS version 7.5 (SPSS Inc, Chicago) was used for statistical analyses.

RESULTS

Of the 30 women who agreed to take part in the study, 1 miscarried and 2 dropped out for medical reasons. Of the remaining 27 women, 25 and 26 completed the 48-h urine collection in mid pregnancy (mean gestation: 18 wk) and late pregnancy (mean gestation: 28 wk), respectively. The maximum number of subjects possible was included in each analysis.

The pattern of isotope excretion over the 48 h of measurement for the studies completed in mid pregnancy is shown in Figure 1. In this time the dose of \([^{15}\text{N}-^{15}\text{N}]\)urea had been cleared from the body pool and recovered in the urine.

Anthropometry and amino acid oxidation

The anthropometric characteristics, dietary protein intake, and amino acid oxidation of the women over the 48-h study period are shown in Table 1. Dietary protein intake and amino acid oxidation in late pregnancy were not significantly different from those in mid pregnancy, but urea excretion decreased significantly from mid to late pregnancy. In both mid and late pregnancy, amino acid oxidation was greater than urea excretion. The amount of urea hydrolyzed in the colon was not significantly different between mid and late pregnancy. For the male and female infants, respectively, birth weight was \(3.90 \pm 0.42\) and \(3.52 \pm 0.43\) kg, birth length was \(52.3 \pm 1.6\) and \(50.3 \pm 1.5\) cm, the ponderal index (in kg/m\(^3\)) was \(27.3 \pm 1.9\) and \(27.7 \pm 2.4\), and placental weight (in 26 women) was \(543 \pm 50\) and \(497 \pm 100\) g.

Intraindividual variability

Although for the group as a whole there was no significant difference in either mean protein intake or amino acid oxidation between mid and late pregnancy, the variation between individuals was substantial at each time point. The CVs for protein intake in mid and late pregnancy were 20.1% and 16.8%, respectively, and the CVs for amino acid oxidation in mid and late pregnancy were 22.5% and 22.0%, respectively. Furthermore, the response to pregnancy also varied between individuals. The change (\(\Delta\)) in amino acid oxidation between the 2 time

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**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All women ((n = 27))</th>
<th>Mid pregnancy ((n = 25))</th>
<th>Late pregnancy ((n = 26))</th>
<th>Paired difference(^1) ((n = 25))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>30.6 (\pm) 2.3(^2)</td>
<td>67.9 (\pm) 6.8</td>
<td>73.0 (\pm) 7.2</td>
<td>5.0 (\pm) 1.8 (4.3, 5.8)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 (\pm) 0.03</td>
<td>25.7 (\pm) 2.4</td>
<td>27.6 (\pm) 2.5</td>
<td>1.9 (\pm) 0.7 (1.6, 2.2)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>—</td>
<td>13.9 (\pm) 2.8</td>
<td>14.3 (\pm) 2.4</td>
<td>0.4 (\pm) 1.7 (0.3, 1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>—</td>
<td>10.8 (\pm) 2.9</td>
<td>11.0 (\pm) 2.0</td>
<td>0.27 (\pm) 1.65 (0.41, 0.95)</td>
<td>0.4</td>
</tr>
<tr>
<td>Protein intake (g N/d)</td>
<td>—</td>
<td>8.4 (\pm) 1.4</td>
<td>7.7 (\pm) 1.4</td>
<td>(-0.7 \pm 1.3 (-1.3, -0.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Energy intake (MJ/d)</td>
<td>—</td>
<td>12.0 (\pm) 2.7</td>
<td>11.8 (\pm) 2.6</td>
<td>(-0.3 \pm 2.6 (-1.3, 0.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>Urea excretion (g N/d)</td>
<td>—</td>
<td>3.3 (\pm) 1.5</td>
<td>3.7 (\pm) 1.5</td>
<td>—</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\(^1\)95% CI in parentheses.  
\(^2\)\(\bar{x}\) \(\pm\) SD.  
\(^3\)Geometric \(\bar{x}\) \(\pm\) SD. The paired difference as a percentage was 13.1 \(\pm\) 65.1% (95% CI: -8.0%, 39.2%).
Fetal growth

The difference between the women in the metabolic response to pregnancy was explored in relation to the size of their infants at birth. All of the infants (21 females and 6 males) were delivered after 38.7 wk gestation (271 d). Birth weight, length, and placental weight were higher in the infants who had a greater gestational age at birth and were higher in the males than in the females. We therefore adjusted these 3 variables for length of gestation and the infant’s sex in the following analyses. The ponderal index was higher in the infants who had a greater gestational age at birth and was therefore adjusted accordingly.

There was no relation between either maternal BMI in early pregnancy or weight change between early and late pregnancy and birth size. There was also no relation between amino acid oxidation at either time point in pregnancy and the infant’s length, ponderal index, or placental weight. The women who had lower amino acid oxidation in late pregnancy, but not during mid pregnancy, tended to have heavier babies. As amino acid oxidation in late pregnancy decreased by 1 g N/d, there was a trend for the infant’s birth weight to increase by 49 g (95% CI: 7, 104 g · N⁻¹ · d⁻¹; \( P = 0.08 \)). However, when \( \Delta \) amino acid oxidation from mid to late pregnancy was considered, the association with birth weight was strongly significant. The mothers in whom amino acid oxidation decreased more between mid and late pregnancy had heavier babies (slope of the regression line: \(-80 \text{ g · N}^{-1} \cdot \text{d}^{-1}\); 95% CI: \(-129, -31 \text{ g · N}^{-1} \cdot \text{d}^{-1}\); \( P = 0.003 \)). This relation is shown in Figure 3, in which the women are divided into 4 groups on the basis of \( \Delta \) amino acid oxidation for clarity of presentation. The women in whom amino acid oxidation decreased more between mid and late pregnancy also had fatter babies, as measured by the ponderal index (slope of the regression line: \(-0.41 \text{ kg}^{-1} \cdot \text{m}^{3} \cdot \text{g}^{-1} \cdot \text{d}^{-1}\); 95% CI: \(-0.72, -0.10; P = 0.01 \)). There was no relation between \( \Delta \) amino acid oxidation and birth length or placental weight.

The predictive value of amino acid oxidation late in pregnancy and \( \Delta \) amino acid oxidation was investigated in the following way. Because the late pregnancy value of amino acid oxidation is correlated with \( \Delta \) amino acid oxidation, it is statistically inappropriate to include both these variables in a multivariate analysis. Therefore, the mean amino acid oxidation for each subject was calculated and used in the multivariate analysis. The association between \( \Delta \) amino acid oxidation and birth weight remained and was independent of the absolute amino acid oxidation (Table 2). For this group of women, the range of \( \Delta \) amino acid oxidation (calculated as the mean ± 2SD) predicted a difference in birth weight of 832 g. After adjustment for length of gestation and the infant’s sex, \( \Delta \) amino acid oxidation explained 34% of the variation in birth weight.
Because \( \Delta \text{protein intake} \) predicted \( \Delta \text{amino acid oxidation} \), the association between \( \Delta \text{protein intake} \) and birth weight was investigated. As \( \Delta \text{protein intake} \) decreased by 1 g N/d, the infant’s birth weight increased by 86 g (95% CI: 0.7, 171 g · N \( \cdot \) d \( ^{-1} \); \( P = 0.05 \)). In a simultaneous analysis that included both \( \Delta \text{amino acid oxidation} \) and \( \Delta \text{protein intake} \), \( \Delta \text{amino acid oxidation} \), but not \( \Delta \text{protein intake} \), remained a significant predictor of birth weight (Table 2). In this analysis, a total of 65% of the variation in birth weight was explained by the predictor variables. Length of gestation and the infant’s sex explained 43% of the variation in birth weight. When \( \Delta \text{amino acid oxidation} \) was added, an additional 20% of the variation was explained, and \( \Delta \text{protein intake} \) explained an additional 2%.

### DISCUSSION

We measured amino acid oxidation in 25 pregnant women at 17–19 and 26–29 wk gestation. There was wide variation between the women in amino acid oxidation at both times and in the change over the 10-wk period. In previous studies substantial variation between women has been found, the basis of which is not clear (20–23). The present study is the first one in which the possible implications of this variation were explored in relation to the growth of the fetus. We showed that mothers in whom amino acid oxidation decreased more between mid and late pregnancy had heavier babies. This finding was independent of any change in protein intake. The change in amino acid oxidation in the mother, length of gestation, and the infant’s sex explained 63% of the variation in birth weight. There are few other markers of metabolism in normal pregnancy that can account for such a large proportion of the variation in birth weight; Catalano et al (24) showed that measures of insulin sensitivity are strongly associated with birth weight \( (R^2 = 0.28) \). The results of the present study suggest that the relative partitioning of amino acids between oxidation and deposition during this period may be crucial with respect to the nutrient supply to the fetus.

During pregnancy complex metabolic changes take place at different times to support the changing needs of the developing fetus. We chose to study the period between 18 and 28 wk gestation. At the beginning of this time, the velocity of fetal growth in length is at its greatest (25). The period of maximum increase in absolute weight, however, occurs later, after 30 wk gestation. In agreement with other evidence (20), our data show that there are important changes over this period and suggest that changes in maternal nitrogen metabolism may anticipate the needs of the fetus because those changes occur in advance of any increase in fetal demand. This may explain why we found an association between the mother’s amino acid oxidation and the infant’s weight, but not length. A progressive decrease in amino acid oxidation from mid to late pregnancy would reflect effective conservation of amino acids and nitrogen, with preferential partitioning toward net deposition. In some women in our study, amino acid oxidation increased, implying a net degradation of protein. The babies born to these women were lighter. We did not have measures of the infant’s fat or lean body mass, but we used the ponderal index as a measure of thinness. Because the infant’s length was not associated with amino acid oxidation, these infants were also thinner. It will be important to understand how amino acid oxidation relates to the availability of amino acids to the fetoplacental unit and to the growth and body composition of the fetus.

The values obtained for amino acid oxidation in the present study were similar to the values we obtained previously with the use of the same method (22, 23). Kalhan (20) has reported a significant decrease in urea synthesis expressed relative to body weight between the first and last trimesters, and others have shown that ureogenesis is lower in the last trimester than it is post partum (21, 26). Our data suggest that this apparent decrease is more likely to reflect changes in maternal body weight than an absolute decrease in urea synthesis. When we expressed our data per kilogram weight, we also found a significant decrease in amino acid oxidation. Expressing the data in this way, however, did not remove the variation between individuals.

The measurement of amino acid oxidation in the present study does not differentiate between the contribution from the maternal tissues and that from the fetal tissues, but it is unlikely that the relation between \( \Delta \text{amino acid oxidation} \) and birth weight can be explained on the basis of changes in the fetal compartment alone. Fetal urea production has been estimated at 540 mg urea · kg \( ^{-1} \) · d \(^{-1} \) at term (25 mg N · kg \( ^{-1} \) · d \(^{-1} \)) (27), similar to values measured in newborn infants (28). In the present study birth weight was 3.6 kg, and therefore urea production in the fetus at term would have been 1.94 g urea/d (0.91 g N/d). This is <8% of the total. At 28 wk gestation, when the fetus would have weighed about 1 kg, the total fetal contribution would have been <3%. This is insufficient to account for either the variability between the women or the change between mid and late pregnancy. It appears that the change in the partitioning of amino acids takes place predominantly in the mother in anticipation of increased demands by the fetus.

It is not clear what drives the overall partitioning of amino acids in the mother between deposition and oxidation. The fetus utilizes amino acids both as precursors for the synthesis of protein and other metabolically active compounds, such as DNA, RNA, creatine, and neurotransmitters, and as a source of energy. It is possible therefore that amino acid partitioning may be affected by the needs of the fetus for energy (29). We did not have any information on the mother’s glucose or insulin physiology, but it is possible that the mothers in whom urea production decreased during pregnancy were those who had higher plasma glucose concentrations. In nondiabetic women, increased plasma glucose concentrations within a normal range are associated with greater infant size (30, 31). A second explanation for the observed relation between amino acid oxidation and birth weight may be that oxidation reflects the goodness of fit between the pattern of amino acids provided in the diet and the needs of the fetus. Although the fetus requires an adequate supply of essential amino acids, the

### TABLE 2

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>( \beta^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta ) amino acid oxidation (g N/d)</td>
<td>(-80 (-130, -30))</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean amino acid oxidation (g N/d)</td>
<td>(-12 (-68, 44))</td>
<td>0.7</td>
</tr>
<tr>
<td>( \Delta ) protein intake (g N/d)</td>
<td>(-69 (-125, -13))</td>
<td>0.02</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted for the infant’s sex and length of gestation.

\(^2\) Gram change in birth weight per unit increase in the independent variable. 95% CI in parentheses.
greatest demand quantitatively is for certain nonessential amino acids (32). Those amino acids in excess of requirements for synthetic processes must be catabolized. This may underlie our observation that the women whose protein intake increased more during pregnancy had smaller infants, because higher intakes of protein were associated with higher amino acid oxidation and because increased oxidation may result when the fit is poor (33). Epidemiologic studies have shown that a high energy intake from protein is associated with low birth weight (34).

In summary, we found that amino acid oxidation varied widely during pregnancy in a group of well-nourished women. These metabolic differences may reflect the various abilities of individual women to adapt to pregnancy and conserve nitrogen. Understanding the ability of a woman to adapt metabolically during pregnancy and how this interacts with her body composition and diet may have implications for establishing dietary recommendations in pregnancy.

We thank the women who took part in this study; the staff of the antenatal clinic, labor ward, and postnatal ward at the Princess Anne Maternity Hospital and Romsey Hospital, Romsey, Hampshire and the staff of the antenatal clinic at Bitterne Health Centre, Southampton for their assistance; and the consultants at the Princess Anne Hospital for allowing us to include their patients. J Hammond, S Beare, V Davill, and L Greenaway assisted with the fieldwork. A Shiell gave statistical advice, and DJP Barker advised on the preparation of the paper.

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