

# Effect of maternal asthma on birthweight and neonatal outcome in a British inner-city population

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## Summary

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During pregnancy, asthma-related alterations in placental function and the maternal immune system, and reduced growth affecting female but not male fetuses have been reported in a study of selected Australian women. The objective of this study was to evaluate the effect of asthma management, declared during pregnancy, on birthweight and neonatal outcome at an inner-city hospital in England. Between June 2001 and December 2003, women at antenatal clinics were questioned about asthma ( $n = 10\,983$ ). Women with asthma and singleton uncomplicated pregnancies ending at term were selected ( $n = 718$ ), with non-asthmatic controls ( $n = 718$ ).

Among asthmatic women using inhaled steroids and bronchodilators ( $n = 170$ ), 43% of the newborn boys had birthweights <10th centile, compared with 27% of controls ( $P = 0.011$ ; OR 2.51 [95% CI: 1.52, 4.14]). For girls, the proportions were 28% and 27%. In women using bronchodilators only ( $n = 178$ ) or those declaring no treatment ( $n = 370$ ), birthweights were not significantly reduced. Taking account of smoking, ethnicity, gestational age and parity, there was a mean birthweight reduction with inhaled steroids and bronchodilators of 118 g [95% CI 36.0, 199.0 g] compared with the control group. There was no interaction between the effect of asthma treatment and infant gender. Infants of asthmatic women in the three subgroups who required intensive care were more likely to exhibit transient tachypnoea of the newborn than infants of control women ( $P < 0.005$ ). In our population-based sample, the risk of low birthweight among asthmatic women did not depend on infant gender, while neonatal respiratory morbidity remains a significant health issue in boys and girls.

**Keywords:** maternal asthma, prenatal asthma medication, head circumference, birthweight, neonatal respiratory morbidity, transient tachypnoea of the newborn.

## Introduction

Asthma is a common pre-existing medical disorder encountered in pregnancy. It can affect 3.7% to 8.4% of pregnant women,<sup>1–3</sup> with about a third of them experiencing a worsening of symptoms.<sup>4</sup> Studies of asthma during pregnancy suggest an increased risk of adverse pregnancy outcomes, including low birthweight and transient tachypnoea of the newborn (TTN).<sup>5–11</sup> Prospective studies provide an emerging consensus that with well-controlled maternal asthma some adverse

perinatal outcomes are less likely to occur.<sup>12–17</sup> However, the mechanisms causing low birthweight are not understood. A group in Australia has recently described the relationships between maternal asthma, its treatment, placental function, fetal gender and low birthweight.<sup>18–21</sup> Specifically, while there was an increased risk of low birthweight among female fetuses if inhaled steroids were not used during pregnancy, the male fetus appeared to be remarkably insensitive to the inflammatory effects of maternal asthma,

with no changes in placental function or reduction in birthweight.<sup>20,21</sup>

In order to investigate whether these Australian results could be generalised to an unselected inner-city community in the UK, we identified a consecutive series of women with self-declared asthma who attended antenatal clinics at St Mary's Hospital, Manchester. In order to assess birthweight and other outcomes, using a representative comparator group, a group of women who did not self-declare asthma were selected from the same clinic. Our aims were, first, to examine whether infant gender modulated any effect of untreated or treated asthma on birthweight taking account of potentially confounding variables such as smoking<sup>22–25</sup> and ethnicity;<sup>26,27</sup> and second, to investigate whether the declared treatment of maternal asthma affects neonatal outcome as birthweight and neonatal outcome are likely to be correlated. We tested the hypothesis that birthweight adjusted for confounding variables is higher among female infants of asthmatic women who were treated with inhaled steroids than among male infants, leading to a difference in neonatal morbidity between the sexes.

## Methods

Approval for carrying out this study was given by the Local Research Ethical Committee and from the R&D Directorate of the Central Manchester and Manchester Children's University Hospitals NHS Trust.

## Participants

Each woman who attended antenatal clinics between 1 June 2001 and 31 December 2003 ( $n = 10\,983$ ) was routinely asked whether she had asthma or smoked during pregnancy. Those declaring asthma were asked about treatment ( $n = 873$ ). Information collected at the booking visit (about 12–14 weeks' gestation) to antenatal clinics was recorded on a database, including maternal age, height, weight, body mass index, blood pressure, ethnicity, gravidity and parity. In addition, at birth, the mode of delivery was recorded. Neonatal details recorded included gestational age, birthweight, head circumference, any medical condition and admission to the Neonatal Medical or Neonatal Surgical Unit (NMU/NSU). Gestational age was defined as completed weeks of gestation using menstrual dates and ultrasound scan data. Centiles for birthweight and head circumference were determined according to

gender and gestational age using national growth standards (Gairdner-Pearson charts<sup>28</sup>).

## Pilot study and power calculation

Four groups of women with uncomplicated singleton pregnancies ending at term (37–42 weeks' gestation) were included in a pilot study: (1) group C: non-asthmatic control women ( $n = 50$ ); (2) group A: asthmatic women with no declared treatment ( $n = 28$ ); (3) group AB: asthmatic women declaring treatment with inhaled bronchodilators only ( $\beta_2$  agonists) ( $n = 12$ ); and (4) group ABS: asthmatic women declaring treatment with bronchodilators and inhaled steroids (glucocorticoids) ( $n = 10$ ). The information entered on the database when checked against the case notes gave a reliability of 98% on every single item. Non-asthmatic controls with no recorded pregnancy complication were matched for 'smoking' and 'month of delivery'. Individualised birthweight centiles were calculated using the 'GROW' program that corrects for gestational age, gender of the baby, maternal height and weight at first booking.<sup>29</sup>

The pilot study showed that 3% of control infants had a birthweight <3rd centile while 14% of infants of asthmatic mothers had a birthweight <3rd centile. This difference in proportions was significant at the 5% level but was relatively underpowered. Using an approximation of 5% for the controls and 15% for the infants of asthmatic mothers, reference to table A3 in Fliess<sup>30</sup> indicated that 160 infants in each group would be required for a power of 0.8 and significance of 5%. Obtaining details of four times as many infants would allow us to carry out pre-planned subgroup analyses, e.g. by treatment status and neonatal outcome.

## Procedures

A total of 873 (8%) of 10 983 women declared that they had asthma. In total, 155 were excluded because they had medical conditions such as diabetes, hypertension, epilepsy or renal problems, or obstetric conditions, namely preterm delivery (<37 weeks' gestation), twins or pre-eclampsia. The remaining 718 asthmatic women with uncomplicated pregnancies ending at term were subdivided according to declared medication: group A (no treatment), AB (inhaled  $\beta_2$  agonists: salbutamol, terbutaline sulphate or salmeterol) or ABS (inhaled  $\beta_2$  agonists and inhaled glucocorticoids: beclomethasone dipropionate, budesonide, fluticasone propionate or a

compound preparation: seretide). No women declared medication with prednisolone, theophylline, or leukotriene receptor antagonists: montelukast or zafirlukast. For each case, a non-asthmatic control was chosen using the same exclusion criteria and matched for smoking status within the given month and year of delivery (group C,  $n = 718$ ). The controls were from the next births satisfying the criteria postnatally. An experienced paediatrician (S.D.S.) examined the case notes of infants who were admitted to the NMU/NSU, blinded to the infant allocation to the maternal asthma or control groups.

### Data analysis

SPSS version 12 software was used for statistical analysis, supplemented with GRAPH PAD PRISM for chi-squared tests for trend. The median and quartiles summarised continuous variables. Univariate analyses were performed using a Mann–Whitney *U*-test for continuous data or chi-squared test for categorical data.

Comparisons between categories were made using the Kruskal–Wallis test. Birthweight was likely to be confounded by several variables. In the main study, these were assessed individually (Table 1); the GROW program was not used. The confounding variables were taken into account using ANOVA.

All the potential confounding variables we had access to were included in the model, as sample attrition was not an issue and excluding variables that were correlated with the explanatory variable of interest might have introduced bias. If our sample was similar to the Australian sample, we would expect to see an effect of asthma group on birthweight that was limited to girls. That is, there would be an interaction between the effects on birthweight of asthma treatment group and infant gender. Categorical variables were entered as fixed factors; continuous variables were entered as covariates. We used a custom model. The only interaction that was included in this analysis was the one suggested by our study hypothesis, namely the interaction between asthma treatment

**Table 1.** Maternal characteristics

|                                  | Group C<br>( $n = 718$ ) | Group A<br>( $n = 370$ ) | Group AB<br>( $n = 178$ ) | Group ABS<br>( $n = 170$ ) | <i>P</i> -value |
|----------------------------------|--------------------------|--------------------------|---------------------------|----------------------------|-----------------|
| Age (years) <sup>a</sup>         | 27 (22, 32)              | 26 (20, 30)              | 27 (20, 32)               | 28 (23, 33)                | 0.001           |
| Height (cm) <sup>a</sup>         | 162 (158, 168)           | 163 (158, 168)           | 163 (157, 167)            | 163 (157, 167)             | 0.505           |
| Weight (kg) <sup>a</sup>         | 64 (56, 73)              | 65 (57, 75)              | 65 (57, 74)               | 64 (59, 75)                | 0.264           |
| BMI <sup>a</sup>                 | 24 (22, 27)              | 24 (22, 29)              | 25 (22, 29)               | 24 (22, 28)                | 0.116           |
| Systolic BP (mmHg) <sup>a</sup>  | 108 (100, 115)           | 110 (100, 115)           | 108 (100, 118)            | 110 (100, 118)             | 0.309           |
| Diastolic BP (mmHg) <sup>a</sup> | 62 (60, 70)              | 64 (60, 70)              | 64 (60, 71)               | 65 (60, 72)                | 0.022           |
| Gravidity <sup>a</sup>           | 2 (1, 3)                 | 2 (1, 3)                 | 2 (1, 3)                  | 2 (1, 3)                   | 0.137           |
| Parity <sup>a</sup>              | 1 (0, 2)                 | 0 (0, 1)                 | 1 (0, 2)                  | 1 (0, 2)                   | 0.055           |
| Gestation (weeks) <sup>a</sup>   | 40 (39, 41)              | 40 (39, 41)              | 40 (39, 41)               | 40 (39, 41)                | 0.134           |
| Smoking, $n$ (%)                 | 259 (36.1)               | 152 (41.1)               | 54 (30.3)                 | 53 (31.2)                  | 0.04            |
| Ethnicity, $n$ (%)               |                          |                          |                           |                            |                 |
| European                         | 424 (59.1)               | 263 (71.1)               | 130 (73.0)                | 124 (72.9)                 | <0.0005         |
| Asian                            | 143 (19.9)               | 40 (10.8)                | 25 (14.0)                 | 24 (14.1)                  |                 |
| Afro-Caribbean                   | 87 (12.1)                | 48 (13.0)                | 10 (5.6)                  | 13 (7.6)                   |                 |
| Other <sup>b</sup> /unknown      | 64 (9.0)                 | 19 (5.2)                 | 13 (7.3)                  | 9 (5.0)                    |                 |
| Delivery, $n$ (%)                |                          |                          |                           |                            |                 |
| Normal vaginal                   | 557 (77.6)               | 279 (75.4)               | 127 (71.3)                | 116 (68.2)                 | 0.046           |
| Ventouse                         | 31 (4.3)                 | 29 (7.8)                 | 17 (9.6)                  | 15 (8.8)                   | 0.011           |
| Forceps                          | 21 (2.9)                 | 12 (3.2)                 | 1 (0.6)                   | 8 (4.7)                    | 0.137           |
| Elective CS                      | 39 (5.4)                 | 17 (4.6)                 | 18 (10.1)                 | 14 (8.2)                   | 0.039           |
| Emergency CS                     | 70 (9.7)                 | 33 (8.9)                 | 15 (8.4)                  | 17 (10.0)                  | 0.929           |

Groups: C, controls; A, asthma, no medication; AB, asthma + bronchodilators; ABS, asthma + bronchodilators + steroids.

BMI, body mass index; BP, blood pressure; CS, caesarean section.

<sup>a</sup>Data are median (quartiles).

<sup>b</sup>Other: oriental, Middle East or mixed race.

group and infant gender. As the inclusion of continuous covariates precluded the use of *post hoc* tests, comparisons between the treatment groups specified in the overall study hypothesis were made using a simple contrast, with the control group acting as the reference group. The 'marginal means' function in SPSS was used to derive an estimate of the magnitude of significant differences between groups. Significance was assumed at  $P < 0.05$ .

## Results

### Maternal characteristics

The median maternal age differed by about 1 year between the control and asthma subgroups ( $P = 0.001$ ) (Table 1). In the control group, there were fewer Europeans than in the asthma subgroups: in group C, 59.1% were European as compared with 71.1%, 73.0% and 72.9% in groups A, AB and ABS respectively ( $P = 0.0005$ ). The median diastolic blood pressure was 2–3 mmHg higher in women with self-declared asthma than in the control group ( $P = 0.02$ ), but there was no difference in systolic values. The proportion of

smokers differed significantly between the asthma groups ( $P = 0.04$ ); 36.1% were smokers in group C as compared with 41.1%, 30.3% and 31.2%, respectively, in the asthma subgroups A, AB and ABS. More births in group C were by normal vertex vaginal delivery than in the asthma subgroups ( $P = 0.046$ ); 77.6% as compared with 75.4%, 71.3%, and 68.2% respectively. Conversely, births by ventouse assistance ( $P = 0.011$ ) or by elective caesarean section ( $P = 0.039$ ) were more frequent in the asthma subgroups than in group C.

### Size for gestational age

The infants were segregated into boys and girls (one group C infant was excluded, due to ambiguous genitalia), and birthweights were assessed using national growth standards (Table 2). Among the boys, there was a significant increase in the proportion of small-for-gestational-age (SGA; birthweight <10th centile; unadjusted results presented here). In group ABS, 43.3% of boys were SGA as compared with 27.8% in group C ( $P = 0.005$ , Fisher's exact test, two-tailed). For girls, the proportions were 27.5% and 28.8% respectively. In women using bronchodilators or those declaring no

**Table 2.** Small-for-gestational-age infants

|                             | Group C           | Group A           | Group AB          | Group ABS         | <i>P</i> -value <sup>a</sup> |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|------------------------------|
| Birthweight (g)             |                   |                   |                   |                   |                              |
| Boys, <i>n</i>              | 370               | 191               | 99                | 90                |                              |
| Median (quartiles)          | 3320 (3040, 3700) | 3360 (3075, 3620) | 3545 (3160, 3820) | 3250 (3000, 3510) |                              |
| <10th centile, <i>n</i> (%) | 103 (27.8)        | 56 (29.3)         | 22 (22.2)         | 39 (43.3)         | 0.011                        |
| <3rd centile, <i>n</i> (%)  | 38 (10.3)         | 25 (13.1)         | 6 (6.1)           | 7 (7.8)           | 0.249                        |
| Girls, <i>n</i>             | 347               | 179               | 79                | 80                |                              |
| Median (quartiles)          | 3240 (2885, 3585) | 3260 (2995, 3660) | 3220 (2960, 3600) | 3165 (2815, 3505) |                              |
| <10th centile, <i>n</i> (%) | 100 (28.8)        | 41 (22.9)         | 21 (26.6)         | 22 (27.5)         | 0.558                        |
| <3rd centile, <i>n</i> (%)  | 53 (15.3)         | 20 (11.2)         | 8 (10.1)          | 14 (17.5)         | 0.328                        |
| OFC (cm)                    |                   |                   |                   |                   |                              |
| Boys, <i>n</i>              | 323               | 170               | 86                | 79                |                              |
| Median (quartiles)          | 34.6 (34.0, 35.7) | 34.8 (34.0, 35.5) | 35.0 (34.5, 36.0) | 34.5 (34.0, 35.3) |                              |
| <10th centile, <i>n</i> (%) | 63 (19.5)         | 25 (14.7)         | 9 (10.5)          | 20 (25.3)         | 0.996                        |
| <3rd centile, <i>n</i> (%)  | 32 (9.9)          | 6 (3.5)           | 5 (5.8)           | 7 (8.9)           | 0.324                        |
| Girls, <i>n</i>             | 315               | 160               | 67                | 72                |                              |
| Median (quartiles)          | 34.1 (33.3, 35.0) | 34.4 (33.5, 35.0) | 34.2 (33.2, 35.0) | 34.0 (33.0, 35.0) |                              |
| <10th centile, <i>n</i> (%) | 68 (21.6)         | 34 (21.3)         | 10 (14.9)         | 16 (22.2)         | 0.653                        |
| <3rd centile, <i>n</i> (%)  | 28 (8.9)          | 4 (2.5)           | 5 (7.5)           | 4 (5.6)           | 0.206                        |

Groups: C, controls; A, asthma, no medication; AB, asthma + bronchodilators; ABS, asthma + bronchodilators + steroids.

Centiles were generated from growth charts in use in the hospital at the time of the study: these are unadjusted figures.

OFC, occipito-frontal head circumference.

<sup>a</sup>Chi-squared.

**Table 3.** Results of ANOVA for birthweight of infants born to mothers with self-declared asthma and to controls

| Variable                                                   | F-value                      | P-value           |
|------------------------------------------------------------|------------------------------|-------------------|
| Maternal smoking                                           | 41.1                         | <0.001            |
| Maternal ethnicity                                         | 29.2                         | <0.001            |
| Gestational age at delivery                                | 153                          | <0.001            |
| Maternal BMI                                               | 29.4                         | <0.001            |
| Mode of delivery                                           | 2.30                         | 0.058             |
| Parity                                                     | 7.34                         | 0.012             |
| Booking diastolic BP                                       | 0.968                        | 0.325             |
| Maternal age                                               | 0.006                        | 0.937             |
| Asthma treatment category                                  | 2.97                         | 0.031             |
| Results of contrast comparing controls with other groups   | Mean difference (g) [95% CI] |                   |
| Asthma: no medication                                      | -6.95 [-68.6, 54.7]          |                   |
| Asthma: inhaled bronchodilators only                       | 24.7 [-55.7, 105]            |                   |
| Asthma: inhaled steroids                                   | -112 [-193, -30.7]           |                   |
| Infant gender                                              | 9.42                         | 0.002             |
| Asthma treatment category * infant gender                  | 1.76                         | 0.153             |
| Estimated marginal means for asthma group by infant gender | Male                         | Female            |
|                                                            | Birthweight (kg)             | Birthweight (kg)  |
|                                                            | Mean [95% CI]                | Mean [95% CI]     |
| No asthma                                                  | 3.39 [3.32, 3.46]            | 3.26 [3.19, 3.33] |
| Asthma + no medication                                     | 3.32 [3.24, 3.40]            | 3.32 [3.24, 3.40] |
| Asthma + bronchodilators                                   | 3.42 [3.32, 3.53]            | 3.28 [3.16, 3.39] |
| Asthma + bronchodilators + inhaled steroids                | 3.26 [3.15, 3.37]            | 3.17 [3.06, 3.28] |

treatment, birthweights were not reduced in boys or in girls. The distribution of birthweights <3rd centile was not significantly different in the asthma subgroups and controls in either boys or girls. Head circumference values <10th centile, or <3rd centile, in the asthma subgroups compared with controls were not significantly different in boys or girls.

Table 3 shows the ANOVA model, which examined factors associated with birthweight with a representative comparator group. Birthweight was independently associated with gestational age, parity, infant gender, maternal smoking, ethnicity and asthma medication. There was no significant interaction between asthma treatment group (A, AB, or ABS) and infant gender. When this analysis was restricted to particular groups, the effect of maternal steroid use on birthweight among boys was found in European non-smokers but not for European smokers, or for non-Europeans (who were predominantly non-smokers) – data not shown.

### Neonatal outcome

The distribution of Apgar scores at 1 and at 5 min of age, meconium staining of liquor, or neonatal jaundice

in the asthma subgroups and in the controls was not significantly different – data not shown. The median duration of hospital stay in infants of asthmatic women was not statistically different from controls. There was, however, a significant increase in neonatal respiratory morbidity ( $P < 0.005$ ) and the frequency of admissions to the NMU/NSU in all asthma subgroups ( $P < 0.005$ ) as compared with controls (Table 4). We could not demonstrate in the small number of these cases with tachypnoea and grunting that the frequency of respiratory morbidity in boys and girls was statistically different. They had respiratory rates >60 breaths per minute within 6 h of birth and persistence of tachypnoea for at least 12 h. Those with TTN had a chest X-ray abnormality, consisting of hazy lung fields, increased parahilar vascular markings and frequently fluid in the horizontal fissure. Three neonatal deaths occurred, including one (cardiomyopathy) in group C, one (Ebstein's anomaly) in group A and one (pneumothorax, subdural haematoma) in group ABS.

### Discussion

We have demonstrated that in women with asthma and uncomplicated term pregnancies, the declared use

**Table 4.** Admissions to the Neonatal Medical Unit (NMU) or the Neonatal Surgical Unit (NSU)

|                                          | Group C  | Group A  | Group AB  | Group ABS | P-value <sup>a</sup> |
|------------------------------------------|----------|----------|-----------|-----------|----------------------|
| Boys and girls                           | 717      | 370      | 178       | 170       |                      |
| Hospital stay (days), median (quartiles) | 3 (2, 4) | 3 (2, 4) | 3 (2, 5)  | 3 (2, 5)  | 0.125                |
| NMU/NSU admissions, <i>n</i> (%)         | 42 (5.8) | 30 (8.1) | 23 (12.9) | 18 (10.6) | <0.005               |
| Reasons for admission, <i>n</i> (%)      |          |          |           |           |                      |
| Tachypnoea and grunting with:            |          |          |           |           |                      |
| TTN                                      | 3 (0.4)  | 8 (2.2)  | 6 (3.4)   | 5 (2.9)   | <0.005               |
| Other conditions <sup>b</sup>            | 2 (0.3)  | 4 (1.1)  | 2 (1.1)   | 4 (2.3)   | <0.05                |
| All                                      | 5 (0.7)  | 12 (3.2) | 8 (4.5)   | 9 (5.3)   | <0.001               |
| Sepsis                                   | 3 (0.4)  | 3 (0.8)  | 2 (1.1)   | 0         | 0.97                 |
| Congenital abnormality <sup>c</sup>      | 16 (2.2) | 3 (0.8)  | 4 (2.2)   | 6 (3.5)   | 0.47                 |
| Depressed condition/IPPV/acidosis        | 9 (1.3)  | 6 (1.6)  | 5 (2.8)   | 2 (1.2)   | 0.53                 |
| Remaining conditions <sup>d</sup>        | 9 (1.3)  | 6 (1.6)  | 4 (2.2)   | 1 (0.6)   | 0.96                 |

Groups: C, controls; A, asthma, no medication; AB, asthma + bronchodilators; ABS, asthma + bronchodilators + steroids.

TTN, transient tachypnoea of the newborn; IPPV, intermittent positive pressure ventilation; IUGR, intrauterine growth restriction.

<sup>a</sup>Chi-squared for trend, except for respiratory morbidities when *P*-value refers to Fisher's exact test for comparisons between group C and group ABS.

<sup>b</sup>Suspected sepsis, pneumothorax, congenital cytomegalovirus infection, meconium aspiration, hypothermia/hypoglycaemia.

<sup>c</sup>Complex cardiac defects, diaphragmatic hernia, gastroschisis, meningocoele, volvulus, tracheo-oesophageal fistula, cleft palate and micrognathia, cystic hygroma, extrophy of the bladder, exomphalos, and congenital adenomatous malformation of the lung.

<sup>d</sup>Jaundice, hypoxic-ischaemic encephalopathy, neonatal abstinence syndrome, vesicular rash, IUGR/hypoglycaemia, blood-stained vomit, myoclonic jerks, floppy infant.

of inhaled steroids and bronchodilators is associated with a lower birthweight. This reduction in birthweight was not influenced by whether the infant was a boy or a girl as there was no significant interaction between asthma treatment and the infant's gender. Additionally, in the small numbers of newborns with tachypnoea and grunting, infant gender does not modulate the effect of maternal asthma on neonatal respiratory morbidity (Table 4).

Our sample was comparable to those reported by other groups. For example, we found that in women from a multiethnic community attending antenatal clinics at our hospital, 8% declared asthma. This incidence is similar to that reported in some studies from outside the UK.<sup>1-3</sup> However, most prior studies have not focused on uncomplicated pregnancies because they did not exclude pre-eclampsia, hypertension and preterm births. We have replicated an association between maternal asthma and an increased incidence of respiratory morbidity in the immediate neonatal period.<sup>31-35</sup> Our analysis of factors associated with birthweight was based on comparisons with a control group that was matched for several confounding variables. We also examined centiles for birthweight and head circumference with growth standards used in the hospital during the study. The results underline the

need to have comparator groups that are representative of the study group, particularly in diverse clinical situations. The strengths of our study also include the sample size and the reliability of data collection, as clinical data were entered on the database on the day of discharge from hospital. Our sample size is larger than many studies on the effects of maternal asthma on neonatal outcome, and was based on a pilot study of the population we studied.<sup>12,36-38</sup>

However, these findings are not concordant with a recent report from Australia. According to Murphy *et al.*,<sup>20</sup> women with asthma who did not use inhaled steroids had a significantly higher proportion of SGA girls with birthweights <10th centile as compared with non-asthmatic controls. The expected interaction was not seen in our study: indeed, the effect of the declared use of inhaled steroids was more obvious in boys than in girls. The absence of an effect of infant gender on birthweight in our results is strengthened by our finding that infant gender may not modulate the effects of maternal asthma on neonatal respiratory morbidity (neonatal outcomes were not reported by the Australian group). In contrast to the data presented here, the Australian group found that boys were not affected by maternal asthma. The discrepancies between these two sets of results could arise from several differences

between the studies, including: (a) study design and methodology, (b) asthma management and (c) differences in the study populations.

### **Study design and methodology**

The current study was a comprehensive review of all cases booking for pregnancy care at one centre. General practitioners carried out the management of asthma in our study, the severity of asthma was not assessed clinically at antenatal clinics, and the data were analysed retrospectively. By contrast, in Australia, Murphy *et al.*<sup>20</sup> carried out a prospective study recruiting pregnant women with asthma during the first trimester with a defined protocol, but do not mention whether asthmatic women who developed pre-eclampsia or preterm labour were excluded. The Australian study does not provide any information about non-participants who had attended their antenatal clinics. It is possible that non-participants were different from participants in asthma severity, responsiveness to treatment, smoking status or use of inhaled steroids.

### **Asthma management**

In our study, the types of drugs used in the control of asthma were consistent with those in the British Thoracic Society and Scottish Intercollegiate Guidelines Network<sup>39</sup> on asthma management. We have no data on how well the women complied with the treatment declared, or whether the drugs used and the doses prescribed were adequate for optimal management. None of these women at antenatal clinics declared use of oral steroids, nocturnal and morning symptoms due to asthma, or hospitalisation.

In asthmatic pregnancies, the risks of maternal and fetal hypoxia are increased especially when asthma is poorly controlled and could potentially affect placental function and impair fetal growth.<sup>18</sup> Maternal inflammatory pathways can alter placental function and in poorly controlled asthma may contribute to reduced fetal growth.<sup>20</sup> This has been confirmed by studies in which well-controlled asthma with inhaled steroids is less likely to result in adverse outcomes, while worsening of symptoms during pregnancy and oral glucocorticoids (prednisolone) use was associated with reduced birthweight.<sup>40</sup> Hence, some effects of asthma on fetal outcome observed in our study may be related to asthma severity and the intensity of treatment requiring glucocorticoid therapy.

In the Australian study,<sup>20</sup> clinical asthma was rated mild, moderate or severe using Australian Asthma Management Guidelines. Furthermore, proper inhaler use and compliance was assessed in the Asthma Management Service, and the cumulative inhaled glucocorticoid dose was calculated for each trimester of pregnancy. The Australian study could be described as an 'efficacy' study carried out under ideal research conditions that favour adherence to treatment and follow-up.<sup>41</sup> For example, the instructions given to pregnant women who were treated for asthma and followed up might have been sufficient to enhance compliance to medication including inhaled steroids above that observed in routine clinical practice. On the other hand, our study reflects 'real life', in which, among other issues, the women manifested a range of symptoms, some of which may be mislabelled as asthma. Consequently, the gender-related effect of asthma on birthweight under controlled research conditions could be different from that observed in real life.

### **Background population**

The aetiology of asthma is likely to reflect complex interactions of genes and the environment that initiate and maintain the clinical features of the disease.<sup>42,43</sup> Current knowledge about how this altered immune responsiveness affects the placenta and fetal growth in different environments is limited. Similar issues have arisen when considering the incidence of intrauterine growth restriction irrespective of fetal gender, in the USA.<sup>17,37</sup> Drawing conclusions from the literature is difficult because differences in study design and asthma management may co-vary with the population differences. This is important because adversity unrelated to asthma could affect the relationship between fetal gender and fetal growth. Our finding provides one example that, among the offspring of European women, maternal smoking may neutralise the effects related to self-declared asthma on birthweight.

The Australian study found fetal gender-dependent differences in placental inflammatory markers.<sup>20</sup> Additionally, there were changes in the activity of placental enzymes (11 $\beta$ -hydroxysteroid dehydrogenase) that would lead to an increased fetal exposure to cortisol, which could inhibit fetal growth. However, 'female placentas' only were affected. The different effects of fetal gender that we report suggest that the placental findings may not be immediately generalisable. Just as a selected sample precludes generalising the clinical

results of the Australian study, so issues arising from study design and population differences could preclude generalising the biological results as well. Exploring the impact of population differences could suggest novel influences on placental function.

In 'real life' when women are prescribed treatment for asthma during pregnancy, the severity of asthma, poorly controlled asthma or the use of oral steroids may confound the apparent benefits reported with inhaled steroids.<sup>40,44</sup> As adequate data were not available at routine antenatal clinics, we could not exclude this possibility. A common finding between our study and the Australian study is that maternal asthma that is at the mild end of the asthma spectrum, can have an impact on birthweight. However, to appreciate fully the implications of this exciting finding, we need additional studies that take account of the issues represented in this discussion, including concerns about residual confounding especially by maternal smoking, which was associated with both the asthma group variables and birthweight. It is possible that controlling for smoking in more detail (more than just a binary variable) might attenuate the main findings. Studies closely resembling real life, controlled research conditions and somewhere in between therefore need to be performed and aggregated in a systematic manner.

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## Book review

**Health Psychology: Theory, Research and Practice**, 2nd edition. By D. F. Marks, M. Murray, B. Evans, C. Willig, C. Woodall and C. M. Sykes. London: Sage Publications, 2005, pp. 528, PB £24.99, \$50.95. ISBN 1412903378.

Although this is more of a textbook than a research treatise, it is useful for epidemiologists to catch up

with this burgeoning new field. The topics considered (e.g. social inequalities, diet, alcohol, cigarettes, exercise, stress) are in many instances identical to those that epidemiologists study. Nevertheless, the approach and focus is somewhat different and well worth epidemiologists becoming aware of.

JEAN GOLDING