Women with Inflammatory Polyarthritis Have Babies of Lower Birth Weight

ANDREW P. BOWDEN, JENNIFER H. BARRETT, WENDY FALLOW, and ALAN J. SILMAN

ABSTRACT. Objective. To assess the effect on fetal outcome, and development of the child over the first 8 months of life, of rheumatoid arthritis (RA) during pregnancy.

Methods. Women with RA or undifferentiated inflammatory polyarthritis (IP) were recruited from throughout the UK and followed prospectively from late pregnancy to 8 months postpartum. Matched controls were obtained from general practitioners. The babies’ health at birth and development at 8 months were monitored by the weight, head circumference, and length. Potential confounding variables were noted.

Results. One hundred thirty-three women with RA or undifferentiated IP took part in the study. There were 5 (4%) admissions for hypertension during pregnancy and no cases of preeclampsia. Cesarean section was common (23%). Matched controls were found for 103 (77%) subjects. There were no significant differences between groups in head circumference or length at birth. Babies born to women with arthritis had lower mean birth weight than controls [3.3 kg (standard deviation 0.5) compared to 3.5 kg (0.4); p = 0.004], even after adjustment for potential confounding factors. Within the patient group those whose arthritis was in remission had significantly heavier babies than those with active disease [mean 3.5 kg (0.5) compared with 3.3 kg (0.5); p = 0.04]. This trend was still apparent at 8 months, but differences were no longer statistically significant.

Conclusion. This is the first relatively large prospective study of the effects on mother and baby of RA during pregnancy. The results suggest that, although disease improves in most women during pregnancy, it is still sufficiently active to have a modest negative effect on birth weight.

Key Indexing Terms:
RHEUMATOID ARTHRITIS             PREGNANCY             BIRTH WEIGHT

During pregnancy women with rheumatoid arthritis (RA) typically experience an improvement in symptoms1-6, although in a recent prospective study we have shown that complete remission is relatively rare7. Since there is generally some continuing disease activity, albeit milder than prior to pregnancy, the question arises whether this affects fetal growth by influencing the placental blood supply. We investigated the influence on birth weight of inflammatory arthritis in a prospective study of 133 pregnant women. The results show that this disorder is associated with a lower weight at birth, which is still present after 8 months, but the effect is restricted to those women with active disease during pregnancy.

There have been relatively few reports of the effects of RA on fetal development, and most have been either case reports8,9 or small, retrospective, nonstandardized studies5,10,11. One exception is the study by Skomsvoll, et al12, which used records of all births in Norway over a 30 year period to demonstrate an increased risk of preeclampsia, prematurity, cesarean section, and small-for-gestational-age babies in women with inflammatory arthritis. The classification of subjects was based on a diagnosis being recorded on the birth notification and did not involve any clinical assessment to confirm diagnosis or disease activity.

We aimed to test the hypothesis that having RA or other inflammatory polyarthritis (IP) in general, and active inflammation in particular, during pregnancy adversely affects the outcome for the baby, primarily measured by birth weight. We carried out a nationwide study, following women with confirmed IP and their babies prospectively from late pregnancy until 8 months postpartum.

MATERIALS AND METHODS
Subjects and design. A matched case-control study design was used to compare outcome in babies born to women with a prior diagnosis of RA or IP to a control group. Women with RA or IP who had recently given birth were identified from a prospective study of pregnant arthritis patients we recently conducted. This study1 examined the change in disease activity from late pregnancy to 6 months postpartum. In brief, subjects were recruited from throughout the UK and were included in the study if they were currently pregnant and had a prior diagnosis of RA or undifferentiated...
IP affecting peripheral joints. Among the data collected was an assessment of disease activity during the last trimester of pregnancy by a research nurse. This included a standardized joint examination assessing 40 joints for tenderness and swelling. Detailed information about treatment was also obtained. This information was used to identify a subset of subjects whose disease was in complete remission, defined as having no currently swollen joints and the absence of antirheumatic therapy. Patients were classified into those who had definite RA according to the 1987 American College of Rheumatology (ACR) criteria\textsuperscript{13} and those with undifferentiated IP. This was done using information provided by the subject’s rheumatologist, including rheumatoid factor status and presence of radiographic erosions, and the clinical examination undertaken by the research nurse. We attempted to contact again all the study participants, and all those who agreed to take part formed the group of “cases” for the current study.

Control data were obtained by contacting the general practitioner or health visitor (a qualified nurse responsible in the UK for monitoring the health of all infants born in a particular area) of each of the cases and requesting anonymous information on the most recent birth in their practice. The aim of this approach was to obtain a control group matched for geographical region and social class.

Comparisons were made between case and control babies, and also within the case group, between subjects whose disease was in complete remission in the last trimester of pregnancy and those with active disease. The main analyses were repeated using only the subgroup of patients with confirmed RA.

The Central Manchester Healthcare Trust research ethics committee approved the study.

Data collection. Study participants were first contacted by letter. Where possible, data were then collected by telephone interview (by APB or WF) about 2 weeks later. The following information was collected: weight, head circumference, and length of the baby, both at birth and at 8 months of age; sex of the baby; duration of gestation; mode of delivery; reason for admission to hospital during pregnancy (if applicable); smoking history and parity. The decision to collect information on smoking history was not possible, data were then collected by telephone interview (by APB or WF) within the casenumber (%) of female babies 64 (58.2) 11 (47.8) 75 (56.4) 50 (48.5)

Table 1. Women with RA or IP were on average 2.7 years older than the control group (95% confidence interval, CI, for difference 1.5, 3.8). This was the first baby for 41% of cases and 52% of women in the control group, but differences in parity were not statistically significant. Gestational age was similar in all groups and was not significantly shortened in cases (p = 0.10). The percentage smoking in all

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RESULTS

A total of 133 women (from the 140 in the original study of pregnancy) were recruited into the study, and matched controls were found for 103 (77%) of these subjects. For 23 (17%) subjects, their disease was in complete remission during the last trimester of pregnancy. A subset of 89 (68%) subjects was identified who had definite RA according to the ACR criteria\textsuperscript{13}.

The characteristics of cases and controls are shown in Table 1. Women with RA or IP were on average 2.7 years older than the control group (95% confidence interval, CI, for difference 1.5, 3.8). This was the first baby for 41% of cases and 52% of women in the control group, but differences in parity were not statistically significant. Gestational age was similar in all groups and was not significantly shortened in cases (p = 0.10). The percentage smoking in all

Table 1. Characteristics of cases and controls.

<table>
<thead>
<tr>
<th></th>
<th>Not in Remission, n = 110</th>
<th>In Remission, n = 23</th>
<th>All cases, n = 133</th>
<th>Controls, n = 103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age at delivery, yrs</td>
<td>32.8 (4.5)</td>
<td>32.3 (5.3)</td>
<td>32.7 (4.6)</td>
<td>30.0 (4.5)</td>
</tr>
<tr>
<td>Number (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First baby</td>
<td>49 (44.6)</td>
<td>6 (26.1)</td>
<td>55 (41.4)</td>
<td>54 (52.4)</td>
</tr>
<tr>
<td>1 previous birth</td>
<td>41 (37.3)</td>
<td>13 (56.5)</td>
<td>54 (40.6)</td>
<td>38 (36.9)</td>
</tr>
<tr>
<td>≥ 2 previous births</td>
<td>20 (18.2)</td>
<td>4 (17.4)</td>
<td>24 (18.0)</td>
<td>11 (10.7)</td>
</tr>
<tr>
<td>Median (IQR) gestational age, wks\textsuperscript{a}</td>
<td>39 (38, 41)</td>
<td>40 (39, 41)</td>
<td>39 (38,41)</td>
<td>40 (39,40)</td>
</tr>
<tr>
<td>Number (%) smoking\textsuperscript{b}</td>
<td>11 (16.2)</td>
<td>0 (0)</td>
<td>11 (12.9)</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Number (%) of female babies</td>
<td>64 (58.2)</td>
<td>11 (47.8)</td>
<td>75 (56.4)</td>
<td>50 (48.5)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any, number (%)</td>
<td>28 (25.5)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids, number (%)</td>
<td>21 (19.1)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Gestational age was missing for one case (who was not in remission).

\textsuperscript{b}Smoking data were only available for 85 cases (68 not in remission, 17 in remission).

SD: standard deviation; IQR: interquartile range.
groups was small; it was higher in the patients with active
disease (16%) compared with none in the group in remis-
sion, but the difference did not reach statistical significance
(p = 0.11). Among cases, 56% of babies were female
compared to 49% in the control group (p = 0.23).
Among the cases only 5 (4%) women were admitted to
hospital for hypertension during the last trimester of preg-
nancy. No cases of preeclampsia were seen. Despite this
there were 31 (23%) instances of cesarean section, 15 of
which were emergency sections, mostly due to a combina-
tion of fetal distress and failure to progress.
There was no significant difference between groups in
head circumference at birth [mean 35.1 cm (standard devia-
tion, SD ± 1.8) in cases, 35.6 cm (2.5) in controls] or length
[51.8 cm (4.0) and 52.3 cm (2.3) in cases and controls,
respectively].

The principal outcome measures were the weight of the
baby at birth and at 8 months of age (Table 2). Babies born
to cases had a lower mean birth weight than controls. The
distribution of birth weights is shown in Figure 1. Similar
results were obtained when the 103 matched case-control
pairs only were analyzed. In this case the mean difference in
birth weight was 0.17 kg (95% CI for difference 0.05, 0.30;
p = 0.008). Further, there was no difference in mean birth
weight between those cases with and without controls (p =
0.6).

Within the case group there was a difference of similar
magnitude between those with active disease and those
whose arthritis was in remission, the latter group showing
no difference to controls (Figure 1). A linear regression
analysis did not reveal any relationship, within the active
group, between the number of tender or swollen joints and
birth weight (R² = 0.006). At 8 months of age, the difference
within the case group was no longer statistically significant,
although babies born to those in remission were still on
average almost 0.5 kg heavier. Weights at 8 months were not
available for babies of control subjects, but the mean weight
among babies of cases is similar to a sex adjusted control
value of 8.56 kg obtained from standard growth charts14.

Babies born to women with a definite diagnosis of RA
had a mean birth weight of 3.36 kg compared to 3.52 kg in
controls (p = 0.01). The disease of 12 (13%) subjects within
this group was in remission, and despite the small sample
size this group had significantly heavier babies than the
other 77 RA patients (3.74 vs 3.30 kg; p = 0.006).

To investigate whether the differences in birth weight
could be explained by confounding or intermediate factors,
regression analysis was carried out. In addition to gesta-
tional age, other factors with the potential to influence birth
weight include maternal age, parity, the sex of the baby,
maternal smoking, and the social class of the parents. We
attempted to exclude any effect of social class by matching
by general practitioner. The other factors were included in
the regression models.

The results of the linear regression models are shown in
Table 3. No relationship was found between any outcome
and maternal age, and this was dropped from the models
with little effect on parameter estimates. As expected, gesta-
tional age was the strongest predictor of birth weight in the
analysis of all cases and controls. However, after adjusting

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Table 2. Weights of babies at birth and at 8 months.

<table>
<thead>
<tr>
<th></th>
<th>Not in Remission, n = 110</th>
<th>In Remission, n = 23</th>
<th>Difference (95% CI), In Remission vs Not</th>
<th>All Cases, n = 133</th>
<th>Controls, n = 103</th>
<th>Difference (95% CI), Controls vs Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, kg, mean (SD)</td>
<td>3.30 (0.52)</td>
<td>3.54 (0.52)</td>
<td>0.25 (0.01, 0.49)</td>
<td>3.34 (0.53)</td>
<td>3.52 (0.39)</td>
<td>0.18 (0.06, 0.30)</td>
</tr>
<tr>
<td>Weight at 8 mo, kg*, mean (SD)</td>
<td>8.58 (1.13)</td>
<td>9.06 (1.29)</td>
<td>0.48 (-0.09, 1.06)</td>
<td>8.67 (1.17)</td>
<td>NA</td>
<td>—</td>
</tr>
</tbody>
</table>

*pWeights of babies at 8 months were only available for 106 cases (86 not in remission, 20 in remission).
SD: standard deviation; CI: confidence interval; NA: not available.

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Figure 1. Distribution of birth weights in different groups of babies. Horizontal lines (from bottom) indicate the minimum, lower quartile, median, upper quartile, and maximum, with the exception of outliers, which are marked by rings.

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for gestational age and parity, babies born to women in the control group were still on average heavier than babies born to cases, and this proved to be a more important factor than parity. None of those in remission smoked compared to 11 (16%) of those with active disease. In this group, however, there was no difference in birth weight between smokers: mean 3.27 kg (SD 0.48) and nonsmokers: 3.21 (0.54).

Parity and gestational age account for some of the difference in birth weight observed between babies born to women with disease in remission and those with active disease. After adjustment for these factors, the difference is no longer statistically significant. However, the number of women with disease in remission is relatively small, and some difference in mean birth weight cannot be excluded by our data.

There was no evidence of a difference in weight at 8 months between babies born to those with disease in remission and those with active disease, with or without adjustment for parity, gestation, and the sex of the baby.

**DISCUSSION**

We assessed the effects of RA and undifferentiated IP in pregnancy on maternal and fetal outcome and development. Women with arthritis in pregnancy were found to have babies with a slightly lower birth weight than control subjects, even after allowing for any reduced length of gestation and potential confounding factors. Furthermore, women whose disease was active during the last trimester of pregnancy had lighter babies than the minority (17%) whose disease was in complete remission, the latter group showing no difference to controls. Differences in weight were no longer statistically significant at 8 months of age, although babies born to those with active disease were still on average 0.5 kg lighter.

Women in our study had a high rate (11%) of emergency cesarean section, the reasons for which were split evenly between fetal distress and failure to progress in delivery. As this was an unexpected finding, we do not have comparable data from the control women. However, the recent Norwegian study by Skomsvoll et al. found an increased rate of surgical delivery in women with inflammatory arthritis. They also reported slightly higher rates of both preeclampsia and prematurity, whereas in our study there were no instances of preeclampsia, and we found no evidence of a difference in gestational age. The question is therefore raised whether active inflammatory arthritis increased the likelihood of intrapartum fetal distress and whether the latter is also associated with growth retardation. Although differences in the proportion of female babies were not statistically significant, females were most common in the active disease group. In a recent Polish study, 27 out of 43 babies (63%) born to women with early onset pauciarticular juvenile arthritis were female. These findings may indicate a higher rate of male fetal loss in the first and second trimester of pregnancy, resulting from the general catabolic stress of active disease favoring the harder female fetus.

There are a number of methodological issues to be considered in evaluating our results. First, inclusion in the study was not restricted to women whose disease satisfied the ACR criteria for RA. Restriction of recruitment to only those women who could be confirmed as satisfying the criteria would tend to bias selection to a more severely affected cohort. However we did analyze separately the subgroup with definite RA and found similar results to the whole cohort.

Second, because of the rarity of the co-occurrence of RA and pregnancy, a nationwide campaign was needed to recruit cases. It is likely that the study participants are not completely representative of pregnant women with RA and other IP in the UK; and in particular, as subjects volunteering to take part in a study, they may differ in social class composition. The main outcome measures of birth weight and weight at 8 months are known to be influenced by social class and also to differ across the country. For this reason matched controls were selected from the same general practitioner. This method provides a good adjustment for regional differences and is an attempt to match for social class. There may be residual confounding due to unmeasured differences in socioeconomic status between cases and controls, despite the matching.

Finally, it is not possible to determine from our study whether the differences observed are due to aspects of the disease itself or to the effect of treatment. During the last trimester of pregnancy, 28 (21%) of the women in the study were receiving some treatment for their arthritis, mainly in the form of steroids. These women had babies with lower birth weight than others with active disease (3.14 kg compared with 3.35 kg; p = 0.07), but it is also likely that the reason for their continued treatment was more severe

### Table 3. Results of linear regression models.

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Explanatory Variables</th>
<th>Regression Coefficient (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, kg, all cases and controls, n = 235</td>
<td>Cases ¹</td>
<td>-0.15 (-0.26, -0.03)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Multipara ²</td>
<td>0.08 (-0.03, 0.20)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Gestation, wks</td>
<td>0.11 (0.08, 0.15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth weight, kg, not in remission, n = 132</td>
<td>Not in remission ³</td>
<td>-0.16 (-0.37, 0.05)</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>Multipara ²</td>
<td>0.17 (0.01, 0.33)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Gestation, wks</td>
<td>0.13 (0.08, 0.18)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight at 8 mo, kg, all cases, n = 105</td>
<td>Not in remission ³</td>
<td>-0.37 (-0.94, 0.20)</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Female baby ⁴</td>
<td>-0.54 (-1.01, -0.08)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Multipara ²</td>
<td>0.16 (-0.30, 0.62)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Gestation, wks</td>
<td>-0.04 (-0.17, 0.09)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

¹Vs all controls.
²Vs primipara.
³Vs cases in remission.
⁴Vs male baby.
disease. In an observational study disease severity and treatment are too highly correlated to distinguish their effects.

These findings confirm for the first time in a prospective study the results of the recent retrospective study of pregnancy outcome in Norway\textsuperscript{12}, where babies born to women with inflammatory arthritides were found to be at increased risk of being small for gestational age. The regression analysis presented here suggests that lower birth weight is not attributable to shorter gestation, but it may be due to intrauterine growth retardation. Our study of the effect of pregnancy on disease activity\textsuperscript{7} revealed that even though most women experience amelioration of disease during pregnancy, few have total disease remission. The lower birth weight found in those whose disease is not in remission suggests that there is sufficient continuing disease activity to have a modest effect on fetal growth. The magnitude of the difference is small and is unlikely to affect the immediate health of the infant.

ACKNOWLEDGMENT
We thank UK consultant rheumatologists for referring patients and general practitioners for providing information.

REFERENCES