Pattern of Pregnancy Weight Gain in Homozygous Sickle Cell Disease and effect on Birth Size

M Thame, J Lewis, I Hambleton, H Trotman, G Serjeant

ABSTRACT

Objective: To assess pregnancy weight gain and newborn anthropometry in mothers with homozygous sickle cell (SS) disease and normal controls.

Methods: An eleven-year retrospective review at the University Hospital of the West Indies, Kingston, Jamaica, revealed 128 singleton deliveries in women with SS disease who were matched by maternal age and birth date with 128 controls with a normal AA phenotype. Restriction to those commencing antenatal care before 16 weeks gestation resulted in the final study group of 80 SS patients and 115 AA controls. Weight and height were measured at first antenatal visit and weight at 20, 25, 30, 35 and 38 weeks gestation. Longitudinal regression used mothers’ weight as the outcome, genotype as a predictor and gestational age as a random effect. Regression analyses of maternal weight on childhood anthropometry were repeated in separate maternal genotypes. Neonatal indices included gestational age, birthweight, head circumference and crown-heel length.

Results: Mothers with SS disease had lower weight and body mass index at first antenatal clinic visit (p < 0.001). Total weight gain was 6.9 kg for SS women and 10.4 kg for AA controls (p < 0.001) and weekly weight gain 0.263 kg (95% CI 0.224, 0.301) and 0.396 kg (95% CI 0.364, 0.427) respectively. A significant relationship occurred between birthweight and maternal weight gain at 25–30 weeks gestation in AA controls but this relationship appears delayed in SS disease.

Conclusion: Different patterns of maternal weight gain in SS mothers and normal controls may have significance for the lower birthweight in SS mothers.

Keywords: Birthweight, sickle cell disease, maternal weight gain

Patrones de Ganancia de peso Gestacional y Tamaño al nacer en los casos de Anemia de células Falciformes

M Thame, J Lewis, I Hambleton, H Trotman, G Serjeant

RESUMEN

Objetivo: Evaluar la ganancia de peso gestacional y la antropometría neonatal en madres con anemia de células falciformes (CF) homocigóticas y en controles normales.

Método: Un examen retrospectivo de once años en el Hospital Universitario de West Indies West Indies, Kingston, Jamaica, reveló la ocurrencia de 128 partos únicos (e.d. de un solo bebé) en mujeres con la enfermedad de CF, que fueron comparadas sobre la base de la edad materna y la fecha de nacimiento, con 128 controles de fenotipo AA normal. A partir de restricciones a las gestantes que comenzaron el cuidado prenatal antes de las 16 semanas de gestación, se llegó finalmente al grupo de estudio de 80 pacientes con CF y 115 controles con AA. El peso y la altura se midieron en la primera visita prenatal, y el peso a las 20, 25, 30, 35 y 38 semanas de gestación. La regresión longitudinal usó el peso de las madres como resultado, el genotipo como predictor, y la edad gestacional como efecto aleatorio. Los análisis de la regresión de peso materno sobre la antropometría fueron repetidos en genotipos maternos separados. Los índices neonatales incluyeron la edad gestacional, el peso al nacer y la circunferencia cefálica.

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Introduction

Pregnancy in homozygous sickle cell (SS) disease is associated with a low birthweight, with values below 2.5 kg occurring in 42% of SS mothers in the Jamaican Cohort Study compared with 19% among controls with a normal haemoglobin genotype (1). Two features characteristic of mothers with SS disease likely to contribute to this low birthweight are the low pre-pregnancy body mass index (2,3) and the tendency to deliver at an earlier gestational age (1,4). The anthropometry of SS disease is characterised by a low body weight and normal or increased height so that the body mass index (BMI) is usually low. However, in mothers without sickle cell disease and with a low BMI, gestational weight gains (GWG) of 14.5 and 15.7 kg (5,6) far exceed those seen in mothers with SS disease. The lower gestational age at delivery in most pregnancies of SS mothers contributes to the low birthweight but compared with controls with a normal haemoglobin (AA) genotype, birthweights in SS mothers remained lower for each gestational age (1) implying that other factors must contribute to the low birthweight in SS mothers. One possibility is that the increased metabolic rate typical of SS disease (7) competes with the metabolic demands of the fetus and delays gestational weight gain. This possibility has been explored by examining the relationship between pre-pregnancy BMI, GWG, gestational age and the longitudinal weight gain at different stages of pregnancy in mothers with SS disease and in matched controls with a normal haemoglobin genotype.

Subjects and Methods

There were 128 women with SS disease and singleton deliveries at the University Hospital of the West Indies (UHWI) in the 11-year period (1 January 1992 – 31 December 2002). Each was matched by maternal age and date of delivery to a control with an AA phenotype without known chronic disease. The final study group was 80 SS and 115 AA controls after further restriction to women with live deliveries and who first attended antenatal clinic at or before 16 weeks gestation (ensuring baseline values which allowed calculation of pregnancy weight gain). The subjects’ records were examined for maternal height and weight at the first antenatal visit and maternal weight at 20, 25, 30, 35 and 38 weeks gestation. The pre-pregnancy BMI was calculated from height and weight at the first antenatal clinic visit. Birth data included gestational age, birthweight, head circumference, crown-heel length, calculated ponderal index and placental weight. Faculty of Medical Sciences, The University of the West Indies/UHWI Ethics Committee approved the study.

Statistical Methods: Expression of the relationship between maternal weight gain and birthweight was complicated by repeated observations and variable weight-gain trajectories in each participant. Maternal weight gain was examined using a longitudinal regression model with mother’s weight as the outcome and with gestational age as a random effect. Weight differences between patients and controls were examined, and the interaction between genotype and gestational age explored to determine whether the weight gain trajectories differed between SS and AA women. Weights predicted from this model were used as potential predictors of birthweight, crown-heel length and head circumference. For direct comparison of weight change, the predicted weights were converted to SD scores (z-scores) with a mean of 0, and a standard deviation of 1. Body mass index was calculated as weight (kg)/height (m) squared and ponderal index as weight/height cubed. Stata statistical software was used to perform all analyses (Release 10, StataCorp LP, College Station, Texas, USA).

Results

At the first antenatal visit, weight and body mass index were lower, and height greater in SS mothers compared to controls (Table 1). Average weekly weight gain was 0.263 kg (95% CI 0.224–0.301) in SS women and 0.396 kg (95% CI 0.364–0.427) among controls (p < 0.001). Overall mean weight gain between visit 1 (average 11.7 weeks) and visit 6 (average 37.8 weeks), derived from the fitted model, was 6.9 kg for SS women and 10.4 kg for AA women (p < 0.001) (Table 2). Weight gain between individual visits calculated from the fitted weights (Table 2) is displayed graphically in the Figure. In AA controls compared to SS mothers, greater gestational weight gain occurred at all intervals during pregnancy prior to 30 weeks gestation and the genotype difference was most

Resultados: Las madres con la enfermedad de CF tenían más bajo peso e índice de masa corporal en la primera visita clínica prenatal (p < 0.001). La ganancia de peso total fue 6.9 kg para las mujeres con CF y 10.4 kg para los controles AA (p < 0.001) y la ganancia de peso semanal 0.263 kg (95% CI 0.224–0.301) y 0.396 kg (95% CI 0.364–0.427) respectivamente. Una relación significativa tuvo lugar entre el peso al nacer y la ganancia de peso materna en las semanas 25–30 de gestación en los controles AA, pero esta relación parece demorada en la enfermedad de CF.

Conclusión: Los patrones diferentes de ganancia de peso materno en las madres con CF y los controles normales, pueden tener importancia significativa para las madres con CF.

Palabras claves: Peso al nacer, enfermedad de células falciformes, ganancia de peso materno

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Table 1: Maternal characteristics at first antenatal clinic visit

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SS</th>
<th>AA</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n mean (SD) range</td>
<td>n mean (SD) range</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>80 11.7 (1.8) 7.4 – 14.9</td>
<td>115 11.7 (1.5) 7.4 – 14.9</td>
</tr>
<tr>
<td>Age of mother (years)</td>
<td>80 26.6 (4.8) 18.6 – 39.5</td>
<td>114 26.2 (5.3) 17.6 – 38.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 54.5 (7.1) 40.0 – 79.0</td>
<td>110 67.6 (14.7) 39.6 – 127.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>80 165.2 (7.8) 137.2 – 186.7</td>
<td>89 162.5 (6.6) 132.1 – 174.0</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>80 20.1 (3.0) 15.2 – 30.4</td>
<td>86 25.2 (5.1) 15.0 – 40.0</td>
</tr>
</tbody>
</table>

*Based on linear regression with adjustment for gestational-age at baseline

Table 2: Maternal weight and weight gain throughout pregnancy in SS disease and AA controls

<table>
<thead>
<tr>
<th>Visit</th>
<th>Weeks Mean (SD)</th>
<th>Subject number</th>
<th>Mean weight (SD)</th>
<th>Fitted weight, SE</th>
<th>p-value</th>
<th>Weight gain (kg)*</th>
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<tr>
<td></td>
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<td>SS AA</td>
<td>SS AA</td>
<td>SS AA</td>
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<tr>
<td>1</td>
<td>11.7 (1.6)</td>
<td>80 111</td>
<td>54.6 (7.1) 67.6 (14.7)</td>
<td>54.9,1.41 67.3,1.18</td>
<td>&lt;0.001</td>
<td>2.7 3.0</td>
</tr>
<tr>
<td>2</td>
<td>20.2 (1.6)</td>
<td>73 110</td>
<td>57.3 (7.1) 70.6 (15.0)</td>
<td>57.1,1.44 70.7,1.20</td>
<td>&lt;0.001</td>
<td>1.4 2.4</td>
</tr>
<tr>
<td>3</td>
<td>25.3 (1.7)</td>
<td>74 104</td>
<td>58.7 (7.2) 73.0 (14.7)</td>
<td>58.5,1.46 72.7,1.21</td>
<td>&lt;0.001</td>
<td>1.0 2.0</td>
</tr>
<tr>
<td>4</td>
<td>30.0 (1.6)</td>
<td>74 108</td>
<td>59.7 (7.1) 75.0 (14.4)</td>
<td>59.7,1.48 74.6,1.23</td>
<td>&lt;0.001</td>
<td>2.0 1.7</td>
</tr>
<tr>
<td>5</td>
<td>35.1 (1.4)</td>
<td>70 106</td>
<td>61.7 (6.9) 76.7 (13.5)</td>
<td>61.0,1.52 76.6,1.26</td>
<td>&lt;0.001</td>
<td>-0.8 0</td>
</tr>
<tr>
<td>6</td>
<td>37.8 (1.2)</td>
<td>36 91</td>
<td>60.9 (7.3) 76.7 (12.9)</td>
<td>61.8,1.53 77.7,1.28</td>
<td>&lt;0.001</td>
<td></td>
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</tbody>
</table>

*derived from actual weight data

Figure: Weight increase during pregnancy among 80 SS mothers and 115 AA controls derived by random effects linear regression with fixed effects component.

marked between 20 and 30 weeks. Furthermore, weight gain between 25–30 weeks gestation was significantly associated with birthweight (coefficient 1.31, 95% CI 0.36, 2.25; p = 0.007) in AA mothers but not in SS disease (coefficient 0.34, 95% CI 1.34, 2.00; p = 0.69). In SS mothers, the period of weight gain most closely related to birthweight was 30–35 weeks (coefficient 1.39, 95% CI -0.19, 2.97; p = 0.08). Although this regression analysis loses statistical power when restricted to separate maternal genotypes, complete data were available in 74% of the initial sample (87 AA and 50 SS subjects) over the critical period between visits 1–5. Examining the effects of pre-pregnancy weight, gestational age (GA) and gestational weight gain (GWG) on birthweight in SS mothers indicated that 57% of variance in birthweight was explained by GA and GWG whereas the corresponding figure for normal controls was 39%. In both genotypes, there was little additional contribution from the pre-pregnancy weight.

Infants born to SS mothers had lower gestational age, birthweight, head circumference and crown-heel length but ponderal index did not differ from controls (Table 3). Placental weight was lower in SS pregnancies. Birthweight was influenced by gestational age (0.10 kg/week, 95% CI 0.08, 0.12, p < 0.001), placental weight (0.19 kg/100 g of placental weight, 95% CI 0.15, 0.24, p < 0.001), and maternal genotype (0.22 kg greater in AA than SS, 95% CI 0.10, 0.34, p < 0.001).

Head circumference was associated with gestational age (0.29 cm/week, 95% CI 0.17, 0.40, p < 0.001), placental weight (0.43 cm/100 g of placental weight, 95% CI 0.23, 0.63, p < 0.001), and maternal genotype (0.50 cm larger in AA than SS, 95% CI 0.02, 1.02, p = 0.06). The relationship
between head circumference and maternal weight gain showed a similar pattern to birthweight, significant relationships occurring between 25–30 weeks in AA mothers (p = 0.02) and between 30–35 weeks gestation in SS mothers (p = 0.03).

Crown-heel length was associated with gestational age (0.45 cm/week, 95% CI 0.20, 0.71, p < 0.001), placental weight (0.53 cm/100 g of placental weight, 95% CI 0.09, 0.98, p < 0.001), and maternal genotype (1.06 cm longer in AA than SS, 95% CI 0.09, 2.21, p = 0.07). No relationships occurred between crown-heel length and gestational period in either maternal genotype.

**DISCUSSION**

The lower birthweight in children of mothers with SS disease is long established but the present study has also shown differences in the pattern of gestational weight gain. Weight gain was similar in SS and AA mothers from 12–20 weeks, 2 kg less among SS mothers from 20–30 weeks and similar again after 30 weeks. The relationship of gestational weight gain to final birthweight also showed genotype differences, birthweight being significantly related to gestational weight gain between 25–30 weeks in normal controls but not in SS disease whereas there was a trend for birthweight to be related to gestational weight gain between 30–35 weeks in SS mothers.

These differences appear consistent with the hypothesis that the increased resting metabolic rate in SS mothers competes with the fetal requirements for growth which is delayed in pregnancies of SS mothers. The resting metabolic rate is increased in SS disease (8) and the greater metabolic demands of the mother are not met by an increased nutritional intake (9, 10). Pregnancy imposes further metabolic demands in these women which may not be fully met because of the limited reserves.

The substrate needs of the fetus are small before 20 weeks gestation but between 20–24 weeks, linear growth reaches peak velocity and fetal weight gain rises rapidly after 30 weeks gestation, peaks at 32–37 weeks gestation and falls thereafter (11). In haematologically normal mothers, the mean daily fetal weight gain exceeds 30 g/day at 34–38 week gestation, falls to 18 g/day at 40 weeks gestation and to 10 g/day by 42 weeks gestation, (12–14) later growth rate being constrained by uterine size (11). Figures derived from the present study show weight increases of 45 g/d (SS) versus 50 g/d (AA) from 12–20 weeks, 39 g/d versus 67 g/d from 20–25 weeks, 30 g/d versus 61 g/d from 25–30 weeks, and 56 g/d versus 48 g/d from 30–35 weeks. Weight gains at later gestational ages are lower but variable because of the declining number of observations.

Observing the relation between gestational weight gain and fetal growth, both birthweight and head circumference correlated positively with weight gain between 25–30 weeks gestation in AA mothers, consistent with the observations of Scholl et al (15), but not among SS mothers. A similar correlation may occur in SS mothers at 30–35 weeks but did not reach significance because of the smaller numbers of subjects. Whatever the responsible mechanisms and recognising the relative statistical frailty due to the smaller numbers when regressions were performed in separate maternal genotypes, these observations suggest that the lower weight gain from 25–30 weeks gestation in SS mothers may contribute to the lower birthweight in their offspring. It is tempting to postulate that the delayed weight gain in SS mothers is a consequence of SS disease, the growing fetus having to compete with the greater metabolic demands of the bone marrow and cardiovascular activity in the mother.

The lower pre-pregnancy weight in mothers with SS disease is an obvious candidate for influencing the lower birthweight of offspring but despite observations on the effect of pre-pregnancy weight on birthweight in other groups, (16–18) the current study showed that after allowing for gestational age and gestational weight gain, the pre-pregnancy weight accounted for only a small additional proportion of the variance.

Another unexplained and potentially important observation in the current study is that women with SS disease commence antenatal care later than woman with the AA genotype (19). The first antenatal clinic visit occurred at or before 15 weeks in 63% of the initial 128 SS women com-

<table>
<thead>
<tr>
<th>Infant Genotype</th>
<th>n</th>
<th>Male</th>
<th>Female</th>
<th>Combined</th>
<th>n</th>
<th>Male</th>
<th>Female</th>
<th>Combined</th>
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</thead>
<tbody>
<tr>
<td>SS mother</td>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td>mean (SD)</td>
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<tr>
<td>Gestational age</td>
<td>38</td>
<td>37.3 (2.8)</td>
<td>34</td>
<td>37.7 (2.3)</td>
<td>72</td>
<td>37.4 (2.6)</td>
<td>57</td>
<td>39.0 (2.5)</td>
</tr>
<tr>
<td>Placental weight (g)</td>
<td>37</td>
<td>542 (125)</td>
<td>33</td>
<td>514 (102)</td>
<td>70</td>
<td>529 (115)</td>
<td>57</td>
<td>630 (111)</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td>38</td>
<td>2.61 (0.57)</td>
<td>34</td>
<td>2.51 (0.50)</td>
<td>72</td>
<td>2.57 (0.54)</td>
<td>56</td>
<td>3.18 (0.49)</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>30</td>
<td>33.1 (1.9)</td>
<td>29</td>
<td>32.6 (1.9)</td>
<td>59</td>
<td>32.9 (1.9)</td>
<td>49</td>
<td>34.3 (1.4)</td>
</tr>
<tr>
<td>Crown-heel length (cm)</td>
<td>30</td>
<td>48.8 (3.5)</td>
<td>29</td>
<td>47.8 (3.8)</td>
<td>59</td>
<td>48.3 (3.6)</td>
<td>49</td>
<td>50.3 (3.8)</td>
</tr>
<tr>
<td>Ponderal Index (kg/m²)</td>
<td>30</td>
<td>23.5 (4.6)</td>
<td>29</td>
<td>24.1 (4.5)</td>
<td>59</td>
<td>23.8 (4.6)</td>
<td>48</td>
<td>25.5 (5.1)</td>
</tr>
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</table>

1 Difference in birth outcomes assessed by normal linear regression after adjustment for gestational age and gender of child.
pared with 88% of controls. Part of this difference may be artefactual since at the University Hospital, women perceived to be at ‘high risk’ may be accepted for antenatal care at later gestational ages than normal women who may be referred to other institutions for care and delivery. However, it is important to identify the reasons for later attendance among SS women in order to improve comprehensive clinical care. A further source of bias in this study results from the selection criteria which excluded early fetal losses common in women with SS disease, (4, 19) inevitably introduces a bias towards better pregnancy outcome.

Poor maternal weight gain could be argued as either a cause or an effect of the low fetal weight but the apparent importance of weight gain at gestational ages of 25–30 weeks in AA controls suggests that this period should be closely monitored in SS subjects to seek interventions to improve maternal weight gain and ultimately fetal growth. It is unknown whether nutritional supplementation at this stage of pregnancy will promote greater maternal weight gain or whether such weight gain would be reflected in increased birthweight but these questions should be addressed. In conclusion, maternal weight gain between 25–30 weeks gestation correlates positively with birthweight in children of AA mothers but this relationship may be delayed beyond 30 weeks in SS mothers. The mechanisms for this difference are important and require further investigation.

REFERENCES