Novel biomarkers in the pathogenesis of placental malaria in sub-Saharan Africa
Owens, S.

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Table 2. Multivariate linear regression analyses of the associations between dehydroepiandrosterone sulphate (DHEAS) (µg/dL) and haemoglobin levels (g/L) in pregnant women at delivery, and between DHEAS (µg/dL) and birth weight (g)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient (95% CI)</th>
<th>P</th>
<th>Regression coefficient (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEAS (µg/dL)</td>
<td>0.01 (-0.27, 0.28)</td>
<td>0.969</td>
<td>-3.2 (-10.2, 3.7)</td>
<td>0.358</td>
</tr>
<tr>
<td>Primiparity</td>
<td>-6.24 (-13.69, 1.20)</td>
<td>0.099</td>
<td>-261.1 (-450.1, -72.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Placental malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-infected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>-11.77 (-21.05, -2.48)</td>
<td>0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>-11.06 (-20.94, -1.18)</td>
<td>0.029</td>
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<tr>
<td>Reference</td>
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</tbody>
</table>

7. PLACENTAL MALARIA AND IMMUNITY TO INFANT MEASLES

Owens S a, Harper G a, Amuasi J b, Offei-Larbi G b, Ordi J c, Brabin B a, d

a. Child and Reproductive Health Group, Liverpool School of Tropical Medicine, Liverpool L3 5QA, United Kingdom

b. Komfo Anokye Teaching Hospital, Kumasi, Ghana

c. Departament d’Anatomia Patològica, Universitat de Barcelona, Villarroel 170, 08036, Barcelona, Spain

d. Emma Kinderziekenhuis, Academic Medical Centre, University of Amsterdam, 1100 DD Amsterdam, The Netherlands
The efficiency of transplacental transfer of measles specific antibody was assessed in relation to placental malaria. Infection at delivery was associated with a 30% decrease in expected cord measles antibody titres. Uninfected women who received anti-malarial drugs during pregnancy transmitted 30% more antibody than those who received no antimalarial drugs.

Malaria kills one million children each year, although a vaccine has been a component of the WHO Expanded Programme of Immunisation since 1985. The transplacental transfer of measles immunoglobulin G (IgG) from mother to fetus is a key component of infant immunity and partially determines the successful response to vaccination. We previously reported that 10% of babies born to mothers with heavy Plasmodium falciparum infections failed to acquire protective levels of tetanus antibody, despite adequate maternal levels. However, conflicting data on the effect of placental malaria on fetal acquisition of maternal antibodies were recently reported. Malaria is known to disrupt the placcental architecture, leading to a massive infiltration of monocytes, thickening of the basement membranes, and extensive fibrin deposition in the materno-fetal transfer membrane (syncytiotrophoblast). Placental malaria is a leading cause of low birthweight in Africa, especially in primigravidae, who lose previously acquired immunity and become particularly susceptible to parasitisation. We assessed the efficiency of transplacental transfer of measles antibody in 104 HIV negative mother-infant pairs living in Kumasi, Ghana, in relation to placental malaria and exposure to antimalarial drugs during pregnancy.

METHODS

Consenting women who delivered vaginally at the Komfo Anokye Teaching Hospital, Kumasi, Ghana were enrolled between April and June 2003. Demographic and retrospective antenatal data were obtained by questionnaire and from the antenatal health card. Babies and placentae were weighed to the nearest 50 g. Hypertensive women and those delivering stillborn infants, multiple births, or infants with congenital abnormalities were excluded.

Maternal and cord blood samples (10 ml) were obtained by venepuncture at delivery. Placental biopsies were obtained from an off-centre position and stored in 10% formaldehyde in phosphate buffer. Paraffin embedded sections were stained with haematoxylin-eosin and examined by light microscopy under polarised light. Placental malaria infection was defined by the presence of parasites and malaria pigment into non-infected, active infection, and past infection. Total IgG was assayed by laser nephelometry (Beckmann) and measles specific antibodies were measured by commercial enzyme linked immunoassay (ELISA). Anonymous HIV testing of maternal samples was undertaken by non-quantitative ELISA, and three HIV positive women were excluded. Maternal and cord blood haemoglobin was measured on Hemocue®. Ethical approval was obtained from both participating institutions before fieldwork was undertaken.

Log10 transformed cord measles antibody titres were regressed on log10 transformed maternal titres, and placental histological classification fitted to the linear model. The influence of key potential confounding variables (gestational age, birthweight, and maternal total IgG concentration) was assessed in a multivariate model. Ratios of cord:maternal antibody titres were calculated and then log10 transformed, generating geometric mean transfer ratios as a measure of transfer efficiency.

RESULTS

Placental malaria infection was detected in 33 of 104 subjects (31.7%), active infection in 18 of 104 (17.3%), past infection in 15 of 104 (14.4%), and no infection in 71 of 104 (68.3%). Placental malaria prevalence among primiparae was 50% and among multiparae 20.3% (odds ratio = 3.92 (95% confidence interval (CI), 1.65 to 9.35)). There were no cases of cord parasitaemia. During pregnancy, 51.5% of subjects took antimalarial drugs for prophylaxis or for empirical malaria treatment. There were no significant differences in antenatal attendance, maternal age, parity, nutritional status (indicated by mid-upper arm circumference), and placental malaria prevalence at delivery between subjects who did and did not use antimalarial agents.

Placental infection was associated with reduced maternal haemoglobin (104 v 117 g/l; p<0.001), lower birthweight (2.85 v 3.08 kg; p = 0.019), and increased geometric mean maternal total IgG (50.4 v 28.9 g/l; p<0.001). Placental infection was not significantly associated with geometric mean maternal measles antibody titres (65.8 v 50.4 ELISA units/l). The relation between cord and maternal antibody titre and placental malaria infection was defined under linear regression (R² = 0.46; p<0.001) and is illustrated in fig 1. Placental histological classification slightly improved the model (R² = 0.49; p<0.001) in multivariate analysis. Other confounding variables were insignificant and were excluded. The expected cord titre in active placental malaria infection was 70.5% (95% CI, 52.0% to 95.5%) of that expected with no placental infection, and in past infection, 68.7% (49.5% to 95.5%). The relation between antimalarial treatment and the transformed cord:maternal measles antibody transfer ratio is illustrated in fig 2. Among non-infected mothers, those who received antimalarial drugs during pregnancy transferred significantly more measles antibody than those who did not (geometric mean transfer ratios: 1.33 v 0.98 respectively; p = 0.046).

DISCUSSION

Placental malaria was associated with impaired transplacental transfer of measles antibody in this study. Antenatal antimalarial drug exposure was associated with improved transfer in women uninfected at delivery. Such women were likely to have been infected earlier in pregnancy but cleared
the parasites more effectively, limiting placental pathiology and improving the transfer capacity of the syncytiotrophoblast. Antimalarial drug exposure may have represented demographic confounding but no evidence for this was detected in the variables examined, and exposure was irrelevant in women infected at delivery. Potential interactions between placental malaria and HIV co-infection were avoided in this HIV seronegative sample.

Reduced concentration of measles antibody at birth is critical in determining early susceptibility and severity of measles infection in infants, as well as the timing of effective measles vaccination. In Malawi between 1996 and 1998, 51% of infants with measles were less than 9 months of age and 17% less than 6 months. Improved malaria control in pregnancy has substantial benefits for the mother and the baby, which may include a reduced risk of measles in early infancy. Studies of infant measles susceptibility in relation to placental malaria and maternal antibody transfer are warranted.

ACKNOWLEDGEMENTS
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