The Impact of Malaria in Pregnancy on Changes in Blood Pressure in Children During Their First Year of Life

Omolola O. Ayoola, Olayemi O. Omotade, Isla Gemmell, Peter E. Clayton,* J. Kennedy Cruickshank*

Abstract—We established a maternal birth cohort in Ibadan, Nigeria, where malaria is hyperendemic, to assess how intrauterine exposure to malaria affected infant blood pressure (BP) development. In a local maternity hospital, healthy pregnant women had regular blood films for malaria parasites from booking to delivery. Growth and BP were measured on 318 babies, all followed from birth to 3 and 12 months. Main outcomes were standardized measures of anthropometry and change in BP to 1 year. Babies exposed to maternal malaria were globally smaller at birth, and boys remained smaller at 3 months and 1 year. Change in systolic BP (SBP) during the year was greater in boys than in girls (20.9 versus 15.7 mm Hg; P=0.002) but greater in girls exposed to maternal malaria (18.7 versus 12.7 mm Hg; 95% confidence interval, 1–11 mm Hg; P=0.02). Eleven percent of boys (greater than twice than expected) had a SBP ≥95th percentile (hypertensive, US criteria), of whom 68% had maternal malaria exposure. On regression analysis (β coefficients, mm Hg), sex (boys>girls; β=4.4; 95% confidence interval, 1.1–7.7; P=0.01), maternal malaria exposure (3.64; 0.3–6.9; P=0.03), and weight change (2.4; 0.98–3.8; 1 standard deviation score; P=0.001) all independently increased SBP change to 1 year, whereas increase in length decreased SBP (−1.98; −3.6 to −0.40). In conclusion, malaria-exposed boys had excess hypertension, whereas malaria-exposed girls a greater increase in SBP. Intrauterine exposure to malaria had sex-dependent effects on BP, independent of infant growth. Because infant–child–adult BP tracking is powerful, a malarial effect may contribute to the African burden of hypertension. (Hypertension. 2014;63:167-172.)

Key Words: child development ■ malaria ■ pregnancy

In Nigeria, as for much of sub-Saharan Africa, increasing noncommunicable diseases coexist with traditional infections. The steady rise in hypertension prevalence at younger ages than in developed countries leads to earlier complications and premature death from hypertensive heart disease, stroke, and end-stage renal failure.

Malarial infection is hyperendemic in Nigeria, particularly in pregnancy, leading to maternal anemia and intrauterine growth restriction. Up to 24% of newborns are born small weight (<2500 g), of which malaria in pregnancy may cause 5% to 12%, 35% preventable, so contributing to 75 000 to 200 000 infant deaths each year in Africa.

Globally, low birth weight is associated with increased risks of hypertension and diabetes mellitus in later life. Based in part on the developmental origins hypothesis, intrauterine and early experience seems to program anatomic, physiological, and endocrine pathways resulting in excess adult disease. There are arguments that postnatal catch-up growth rather than prenatal development is more critical because the association between birth weight and blood pressure (BP) is strengthened by adjustment for later size. Weight gain in the first 3 months is a driver of BP at 1 year. In sub-Saharan Africa, to our knowledge, there are no studies on the role that maternal malarial infection may play on the relationships between infant growth and development of BP. In Nigerian infants, we tested the hypothesis that malaria in pregnancy, with its effects on size at birth and early growth, would be independently related to BP change by 12 months of age.

Methods

Study Site and Participants

Families came from a range of socioeconomic backgrounds, including those with improving lifestyles, in the community of Yemetu-Adeoyo, Ibadan in Southwest Nigeria, where malaria transmission is perennial. Healthy women were eligible if aged 18 to 45 years, presenting before 36 weeks’ gestation and subsequently delivering at ≥37 weeks’ gestation at Adeoyo Maternity Hospital. Exclusions included HIV infection, sexually transmitted infections, or multiple pregnancies. Chronic maternal disease (eg, hypertension, diabetes mellitus) and babies with known syndromes, metabolic defects, major congenital abnormalities, or severe birth trauma were also exclusions.

During 1 year to cover wet and dry seasons, 624 women were recruited, of whom 161 did not deliver at Adeoyo hospital. Of 463 mother–baby pairs, 27 were excluded because of 4 (0.9%) maternal deaths, 11 (2.4%) still births, 5 (1.1%) miscarriages, and 7 (1.5%)

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neonatal deaths, leaving 436 pairs at birth. At 3 months, 384 babies were measured, and at 12 months of age, 380 babies were measured. There had been a further maternal and 10 infant deaths from febrile illnesses, or relocation or refusal (87% response rate overall). Data from infants measured at all time points (birth, 3, and 12 months; n=318; 173 boys and 145 girls) were analyzed (Figure).

Study procedures included informed consent at booking with sociodemographic, obstetric, family, and health history, including malaria and use of antimalarial drugs. All women were issued prescriptions for sulfadoxine-pyrimethamine for Intermittent Preventive Therapy for malaria according to standard hospital practice. The University of Ibadan/University College Hospital and University of Manchester’s Ethics committees approved this study.

Blood Measurements
Two milliliters of blood was collected at booking in EDTA tubes for full blood count. Thick and thin blood films were stained with 3% Giemsa at pH 7.2 and examined for malaria parasites under light microscopy with repeat films at subsequent visits, delivery, and from cord blood. Thick smears were recorded as negative only after scanning 200 high-powered microscope fields. In those with malaria, absolute parasite counts were determined11 by counting the number of parasites (np) among 200 leucocytes on thick film using the equation: absolute parasite counts (number per microliter of blood)=(np/200)×total leucocyte count. For quality control, 40% of negative and positive samples were re-examined by 2 different trained microscopists.

Malaria was defined as asexual blood stages of Plasmodium falciparum during any pregnancy visit or at delivery, in the placenta or cord blood. Women were grouped into 2 categories: (1) no malaria=no parasites detected throughout pregnancy or delivery; and (2) malaria present=parasites present at least once during pregnancy or at delivery.

Measurements
Three nurses, proficient in pediatric venepuncture, were trained in anthropometry and BP measures from the World Health Organization (WHO) manual (1995) and standard operating procedures, using the same equipment throughout. They had 3 monthly refresher training sessions with procedures and training videos to minimize inter- and within-observer errors.

Within 72 hours of birth, babies were weighed naked to the nearest 0.1 kg and crown-heel length measured on an infant stadiometer. Other measures included occipitofrontal circumference (widest circumference of the head using a nonstretchable tape), mid-upper arm circumference (halfway between the scapula’s acromion process and the olecranon with the infant’s arm bent), and left-sided skin-fold thicknesses (triceps, biceps, subcapular, and suprailiac) using Holtain calipers. All were obtained in duplicate or triplicate if disagreeing by >15%.

Before performing BP readings, the baby was lying comfortably on the mother’s lap for >5 minutes; many times they were asleep. Measurements were done with the Datascope BP monitor, specifically validated for infants, using appropriate newborn cuffs on the left arm and repeated 3 times with the mean of the last 2 readings analyzed. The cuff bladder width covered at least two thirds of the upper arm.

Statistical Analyses
Anthropometric data were transformed into standard deviation scores (SDSs) with WHO child growth standards (version 3.1). t tests were used to test for differences in anthropometry and BP associated with maternal malaria status. Actual change in SDSs and SDS change predicted by regression to the mean, for which the effect of malaria on growth was adjusted, were calculated.12 BP percentiles at 1 year were calculated using tables developed by the National High BP Education Program Working Group, using the mean sex-specific heights at 1 year of the infants.13 Multiple regression models were used to examine the relationship of BP to maternal malaria status, sex, and anthropometry at birth, 3, and 12 months. Data were analyzed using SPSS version 14 (SPSS Inc, Chicago, IL). Other method details are in our previous neonatal report.14

Results
Malaria parasitemia occurred ≥1 in pregnancy or delivery in 160 (50%) of 318 mothers (hereafter, exposed), but its respective prevalence in 3- and 12-month-old babies was only 2.6% and 5.3%.

Anthropometry, Growth, and BP by Sex and Effect of Maternal Malaria
All infants were breastfed, ≈97% for >12 months, and had average weight and length for age SDSs <0 (Table 1). Weight SDS ≤−1 occurred in 42% and 53%, and length SDS ≤−1 in 36% and 37% at birth and 12 months, respectively. Mean birth anthropometry and SDSs of all malaria-exposed infants, sexes combined, were globally and significantly smaller than those not exposed (as detailed previously)14 but differed...
between boys and girls. At birth, boys were longer by 0.6 cm (95% confidence interval, 0.07–1.06; P = 0.04) and had greater head circumference by 0.3 cm (0.06–0.60; P = 0.017) but lower systolic BP (SBP, −3.3 mm Hg; P = 0.023) and diastolic BP (−2.2 mm Hg; P = 0.034). At 3 months, anthropometric indices were greater in boys than in girls (all P < 0.01), but BPs were not different. At 12 months, boys were heavier and taller than girls with larger head and arm circumferences (all P < 0.01), but had similar BPs.

At 3 months, babies with maternal malaria exposure remained shorter by 0.6 cm (0.01–1.11; P = 0.04), lighter by 0.2 kg (0.04–0.40; P = 0.019), and had smaller circumferences (head, 0.3 cm [0.01–0.65; P = 0.04]; arm, 0.3 cm [0.04–0.56; P = 0.02]) than those without malaria, attributable to effects on boys (Table 1). At 12 months, these effects persisted in boys.

Changes in weight/length SDSs in exposed boys (−0.3, −0.2) were significantly smaller than the changes in exposed girls (−0.08, −0.1) after adjusting for regression to the mean (weight β=0.352, P = 0.043; length β=0.331, P = 0.036). There were no relationships between maternal weight at booking, nor BPs nor blood glucose (at any time point), and birth weight [mean glucose for those with weight SDS <-2; 4.20 [0.4]; and weight SDS ≥2; mean, 4.22 [0.7] mmol/L; t <0.23; P = 0.82], nor with infant BPs at any time (not shown).

### Effect of Maternal Malaria on Infant BP and Its Early Changes in Boys Versus Girls

These anthropometric effects of malaria in pregnancy had important influences on infant BP. At birth, mean SBPs of exposed babies were lower than those not (69.4 versus 73.1 mm Hg; P = 0.01; significant in girls, Table 1). At 3 and 12 months, mean SBP and diastolic BP were similar in exposed boys and girls (Table 1). Although changes in BP were overall greater in boys than in girls, mean changes in SBP from birth to 3 and to 12 months were greater in both sexes exposed to malaria (SBP change from birth to 3 months, 19.4 versus 13.9; difference, 5.5 mm Hg; 0.3–10.7 mm Hg; P = 0.04; and to 12 months, 18.7 versus 12.7; difference, 6.0 mm Hg; 1.1–10.9 mm Hg; P = 0.02) with and without maternal malaria, respectively (Table 1).
during the first 3 months, SBP was lower by 1.98 mm Hg. A sex×malaria status interaction was tested, as was an effect of maternal weight at booking, maternal BP, and blood glucose at varying time points, but none of these were significant. For change in diastolic BP from birth to 12 months, change in weight SDSs from birth to 3 months was the only significant determinant.

Discussion
To our knowledge, this is the first report on the effect of maternal malaria on BP in an infant cohort all followed during infancy. At birth, infants with maternal malaria were smaller, as expected, and had lower BPs.15,16 Exposed babies had a greater change in SBP from birth to 3 and 12 months, notably in girls, but maternal malaria had a continued effect on SBP. The majority of these Nigerian babies fell below WHO standards for weight and length at birth, features which persisted until 1 year of age, when arm and skinfold measures were still well below standards. These results corroborate many previous reports,17 recently redocumented in rural Nigeria,18 but none of those measured BP. Few studies have examined longitudinal growth of West African infants in early life; most were cross-sectional.19,20 Here, in the first year, maternal malaria continued to exaggerate reduced size and exposed boys fared worse than girls (Table 3). The impact of malaria on growth here, as elsewhere,21,22 seems related to chronic placental infection and its insufficiency leading to proportionate fetal growth restriction.23,24 Apart from length SDSs from birth to 3 months, the babies showed no evidence of catch-up growth; in fact, growth was less than that predicted by regression to the mean. Similar results occurred in Malawian children in whom maternal malaria at delivery was associated with reduced weight for age and thinness at 12 months.25 Both fetal and early postnatal growth have been related to BP in adolescents and adults.26,27 Children who are thin at birth and rapidly increase in size, particularly adiposity, in their first 6 months develop higher SBP at 3 years of age.28 Here, we find similar results by 1 year, which may set the scene for higher BP later. In Gambian children, there was no relation between BP and birth weight in children aged 1 to 8 years, but there was an inverse relation in those aged >8 years.29 In children in Jamaica aged 6 to 16 years, in Zimbabwe aged 6 years, and in South Africa aged 5 years, there were inverse relations between birth weight and BP after adjustment for current weight.30–32 In the Gambia and Zimbabwean studies, children would have been exposed to malaria but any effects from it were not assessed.

Strengths and Limitations of the Study
The strengths of the study are the sizeable cohort of mothers participating, with excellent retention of the women and infants to 1 year, so that genuinely longitudinal follow-up was possible. The size of the sample of women infected with malaria in pregnancy and of those not infected was similar, and BP measurement was by a validated semiautomatic device, hence nearly operator independent. The increased BP change in infants exposed to maternal (but here not infant) malaria became apparent as a significant independent effect after adjustment in regression analysis for their previous smaller body size, alongside an independent, positive effect from increase in weight but also a protective effect from increasing growth in length. That together with difficulties in measurement from previous, observer-dependent sphygmomanometry

Table 3. Regression Analyses for Determinants of Change in Infant Blood Pressure From Birth to 1 Year of Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>ΔSBP</th>
<th>ΔDBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>0–12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (boy/girl)</td>
<td>−4.4</td>
<td>−7.72 to −1.08</td>
</tr>
<tr>
<td>Malaria status</td>
<td>3.64</td>
<td>0.32 to 6.95</td>
</tr>
<tr>
<td>Length SDS 0–3</td>
<td>−1.98</td>
<td>−3.56 to −0.40</td>
</tr>
<tr>
<td>Weight SDS 0–3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight SDS 0–12</td>
<td>2.41</td>
<td>0.98 to 3.84</td>
</tr>
<tr>
<td>Baby’s malarial status at 3 mo</td>
<td>−6.39</td>
<td>−15.6 to 2.81</td>
</tr>
<tr>
<td>Baby’s malarial status at 12 mo</td>
<td>−0.720</td>
<td>−7.38 to 5.94</td>
</tr>
</tbody>
</table>

Malarial status: coding 0 = no malaria; 1 = malaria present. CI indicates confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; and SDS, standard deviation score.

Table 2. Comparison of Infant BP by Maternal Malaria With US BP Percentiles at 1 Year of Age

<table>
<thead>
<tr>
<th>BP Percentile</th>
<th>Boys (n=173)</th>
<th>Girls (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MP No (n=86)</td>
<td>%</td>
</tr>
<tr>
<td>&lt;90th</td>
<td>70</td>
<td>81.4</td>
</tr>
<tr>
<td>90th–94th</td>
<td>10</td>
<td>11.6</td>
</tr>
<tr>
<td>≥95th</td>
<td>6</td>
<td>7.0</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; and MP, maternal malarial parasites detected.
perhaps explains how malarial exposure has not previously been considered an influence for elevating BP. The potential impact of such an effect is seen from comparison with US BP centiles: 19% of these generally small babies had BP >90th centile (ie, nearly twice that expected), despite differing but controlled measurement and generally much warmer conditions (which would lower BP) than for the US readings. Hence, 10% were hypertensive (295th centile) on these standardized readings, with 68% exposed to maternal malaria. This distortion of the expected distribution was more prominent in boys than in girls. US BP centiles are unavailable at birth or 3 months but our 1 year results indicate that the BP in Nigerian infants was relatively high.

The US BP tables are based on auscultation for BP measurement. Some oscillometric devices, including the device used here, were developed with tailored algorithms for young children to improve accuracy and are validated at this age group. When so validated and calibrated, oscillometric devices reduce observer error and are convenient and preferred for BP measurement in newborns and young infants, in whom auscultation is difficult.33,34

Limitations include the limited facilities available and the related issue of not screening for a variety of rarer potential infections (cytomegalovirus, etc) despite exclusion of HIV-positive infants. Some may consider results at year 1 to be too early but BP tracking from early life35 has become established enough to lead authors of a systematic review to conclude: “evidence for BP tracking from childhood into adult life is strong. Childhood BP is associated with BP in later life, and early intervention is important.”36

Areas for Future Research

We are unaware of previous work on intrauterine exposure to malaria and its impact on infant BP. Clearly, confirmation in other cohorts or other malarial areas (eg, South-East Asia) would be useful.

Clarifying what measureable cytokines indicate malarial placental sequestration and significant placental infarction and whether this extends to and limits growth of the fetal arterial tree are mechanisms to explore for how and when malaria in pregnancy affects later BP. We suggest the hypothesis that because of maternal malaria and resultant smaller birth size, there is general growth restriction and, consequently, a smaller vascular tree and possibly aortic size not measured here, manifested as progressively higher BPs, leading to excess risk of later hypertension. Whether such mechanisms affect SBP more than diastolic BP, as found and not accounted for here, and whether this is detectable because increased arterial stiffness in malaria-exposed children is also of great interest. As the child grows, the more restricted aorta and vascular tree of smaller infants may not itself grow adequately to meet end-organ demands without higher BPs. The later BP profiles of this and other such cohorts would also be key further results.

Perspectives

Nigerian babies were smaller, shorter, and thinner than WHO standards at birth and failed to catch up during their first year. The findings were more pronounced in babies with maternal malaria, particularly boys. Changes in BP were overall greater in boys than in girls, but mean change in SBP during infancy was higher in children with maternal malaria, particularly girls. At 1 year of age, 8% to 11% had BPs already in the hypertensive range and more than half had had maternal malaria, suggesting a potentially important role for intrauterine exposure to malaria in influencing early BP changes. Because malaria continues to be a major cause of early mortality,37 for those children who survive and then put on excess weight, notably in urban settings, a maternal malarial influence on BP may be related to the higher risk of hypertension in later life in Nigeria, sub-Saharan Africa, and perhaps elsewhere. That would be a substantial development in understanding.

Acknowledgments

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Disclosures

None.

References

Novelty and Significance

What Is New?

- Studying a fully longitudinal infant cohort for blood pressure (BP) as well as growth in relation to maternal malaria exposure in a sub-Saharan country with a high prevalence of hypertension.
- Finding that for babies born to mothers having malaria in pregnancy (who as expected were smaller in every dimension than control babies of uninfected mothers), malaria had a greater effect on the change in the pumping (systolic) BP than in controls, independent of size differences.

What Is Relevant?

- Because malaria remains a key cause of mortality and in pregnancy leaves a size deficit on surviving children, such exposure may compromise the affected child’s blood vessel development and at least in part account for some of the excess hypertension experienced by sub-Saharan and other African-origin adults.

Summary

At 1 year of age, independent of sex, growth in weight and height, exposure to malaria in pregnancy had an independent effect on change in infants’ pumping (systolic) BP. Ten percent of infants had BP already in the hypertensive range on US tables, and two thirds (65%) had been exposed to maternal malaria, suggesting a potentially important role for intrauterine exposure to malaria in influencing early BP changes. These BP patterns may be related to Nigeria and sub-Saharan Africa’s high risk of hypertension in later life.
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