Assessing the Relationship Between Gravidity and Placental Malaria Among Pregnant Women in a High Transmission Area in Ghana

Ayodele Akinnawo (ayodele.a@hotmail.co.uk)
      London School of Hygiene & Tropical Medicine https://orcid.org/0000-0003-2458-6272

Kaali Seyram
      Kintampo Health Research Centre

Ellen Boamah Kaali
      Kintampo Health Research Centre

Samuel Harrison
      Kintampo Health Research Centre

David Dosoo
      Kintampo Health Research Centre

Matthew Caims
      London School of Hygiene & Tropical Medicine

Kwaku Poku Asante
      Kintampo Health Research Centre

---

Research Article

Keywords: Placental malaria, gravidity, primigravidae, secundigravidae, multigravidae, transmission, regression model

Posted Date: December 14th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1158506/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background

Malaria infection during pregnancy can cause significant morbidity and mortality to a pregnant woman, her foetus and newborn. In areas of high endemic transmission, gravidity is an important risk factor for infection, but there is a complex relationship with other exposure-related factors, and use of protective measures. This study investigated the association between gravidity and placental malaria (PM), among pregnant women aged 14-49 in Kintampo, a high transmission area of Ghana.

Methods

Between 2008-2011, as part of a study investigating the association between PM and malaria in infancy, pregnant women attending antenatal care (ANC) clinics in the study area were enrolled and followed up until delivery. The outcome of PM was assessed at delivery by placental histopathology. Multivariable logistic regression analyses were used to investigate the association between gravidity and PM, identify other key risk factors, and control for potential confounders. Pre-specified effect modifiers including area of residence, socio-economic score (SES), ITN use and IPTp-SP use were explored.

Results

The prevalence of PM was 65.9% in primigravidae, and 26.5% in multigravidae. After adjusting for age, SES and relationship status, primigravidae were shown to have over three times the odds of PM compared to multigravidae, defined as women with 2 or more previous pregnancies (adjusted OR=3.36 (95% CI 2.39-4.71), N=1808, P<0.001). The association appeared stronger in rural areas (OR for PG vs. MG was 3.79 (95% CI: 3.61-5.51) in rural areas; 2.09 (95% CI: 1.17- 3.71) in urban areas; P for interaction =0.07), and among women with lower socio-economic scores (OR for PG vs. MG was 4.73 (95% CI 3.08-7.25) amongst women with lower SES; OR=2.14 (95% CI 1.38-3.35) among women with higher SES; P for interaction =0.008. There was also evidence of lower risk among primigravidae with better use of the current preventive measures IPTp and LLIN.

Conclusions

The burden of PM is most heavily focused on primigravidae of low SES living in rural areas of high transmission. Programmes should prioritize primigravidae and young women of child-bearing age for interventions such as LLIN distribution, educational initiatives and treatment to reduce the burden of malaria in first pregnancy.

Background
Malaria infection during pregnancy can cause significant morbidity and mortality to a pregnant woman, her foetus and newborn (1). A common complication is placental malaria (PM), in which *P. falciparum* infects erythrocytes and cause them to sequester within the placental intervillous space (2). Mothers infected with PM are at risk of adverse perinatal outcomes including miscarriages, pulmonary oedema, hypoglycaemia and maternal anaemia (3). Adverse birth outcomes for the foetus include spontaneous abortion, still birth, intra uterine growth retardation, preterm delivery and low birth weight (4)(5).

Globally, malaria infection affects approximately 11 million pregnancies—predominantly in the sub-Saharan African region, and up to 100,000 infant deaths are attributed to PM every year (6). In regions of low-transmission, levels of acquired immunity to malaria tend to be low, and all pregnant women are vulnerable to malaria, which is often symptomatic (1). In contrast, in regions of endemic transmission, levels of acquired immunity tend to be high and *P. falciparum* infection tends to be asymptomatic during pregnancy (1)(7). WHO recommends women in high-transmission areas be given long-lasting insecticide treated nets (LLINs), at least three doses of intermittent preventative therapy with sulfadoxine-pyrimethamine (IPTp-SP) and prompt diagnosis and treatment (1)(8).

Susceptibility to malaria increases during pregnancy (9). In high-transmission areas, primigravidae, are at substantially greater risk of PM than secundigravidae or multigravidae, due to a parity-specific immune mechanism acquired through successive pregnancies (9)(10). Current understanding is that placental *P. falciparum* parasites express surface antigens on the surface of infected erythrocytes, which facilitate sequestration in the placenta via adhesion to placental chondroitin sulphate A. Primigravidae lack antibodies to block this adhesion, however, over repeated exposure and successive pregnancies, the antibodies increase, making secundigravidae and multigravidae less susceptible to infection (11). Primigravid women are also at elevated risk from infections acquired prior to conception, because use of protective measures is much lower among adolescents and women of child-bearing age prior to first pregnancy than among women who have been pregnant and received LLIN through ANC (12)(13).

The extra risk of PM in primigravidae, compared to other gravidities is not well characterized in the literature, nor how this risk reduces over successive pregnancies in a specific setting, or the effect of malaria-specific interventions on this risk. Moreover, some effect modifiers are still controversial, with very few studies investigating the effect of factors such as area of residence, doses of IPTp-SP, ITN use and socio-economic grouping on the relationship between gravidity and PM. This study aims to add to the available literature by quantifying the strength of these associations, and characterising the changing profile of risk with gravidity in a high-transmission area of Ghana.

Although the elevated risk in primigravidae is well known, how this elevated risk varies within a particular context, and how risk is influenced by other factors is less well described. It is also challenging to disentangle the risk from low gravidity itself (i.e. naivety to pregnancy-specific antigenic variants of *P. falciparum*) and from factors associated with gravidity (maternal age, use of protective measures, etc.) which might also affect malaria risk. To investigate these issues, the association between gravidity and placental malaria was investigated using data from a large cohort study in Ghana, in which placental
malaria status was determined using the gold standard of placental histology, and in which a wide range of factors related to exposure were carefully documented.

**Methods**

This secondary data analysis uses data collected during a prospective cohort study which investigated PM as a risk factor for malaria infection in infants. The study was conducted in the Bono East Region of Ghana (14). Between 2008-2011, forty-two communities were selected from the Kintampo Health and Demographic Surveillance System (KHDSS). All pregnant women residing in the regions were identified via vital registers collated by community key informants or Kintampo Health and Demographic Surveillance System staff who made twice yearly home visits, recording demographic events such as pregnancy, births, deaths, and migration (15) (16). The only maternal exclusion criteria applied to the above study was that women were required to stay in the study region for one year post delivery. Of the 2160 pregnant women contacted, 337 (15.6%) were excluded due to refused consent, unsuccessful placental tissue collection or still birth, resulting in a final cohort of 1823 pregnant women. The final cohort for this secondary analysis included all 1823 women.

Surveys were administered by interviewers at enrolment (i.e. while the woman was still pregnant) and information on demographic, socioeconomic and obstetric characteristics and the PM infection status of women were collected. (15). Upon delivery, a placental biopsy was taken and assessed by histopathologists for the outcome of placental malaria, as described below (15). Ethical approval for the original study was obtained from the ethics committees of Kintampo Health Research Centre, Ghana Health Service, LSHTM, and Noguchi Memorial Institute for Medical Research. Written informed consent was obtained from all study participants.

**Classification of outcome and primary exposure**

Mothers responded to a questionnaire on enrolment, which captured their obstetric history, including the number of all living, deceased, aborted or ectopic babies born to the mother. The total number was calculated (minus the current pregnancy) to give the gravidity number, confirmed after cross-checking with the woman. To ascertain the PM status, women were followed-up until delivery, at which time a placental biopsy was taken. A histopathologist then categorized each sample as no infection, acute infection (presence of parasites only), chronic infection (presence of both parasites and hemozoin pigment), or past infection (presence of hemozoin pigment only), using the classification system described by Bulmer et al. (17). Acute, chronic and past infections were considered as ‘placental malaria’. A second histopathologist checked 28% of randomly selected samples and the pairwise correlation coefficient between the two readings was 0.92, indicating a high degree of correlation.

**Statistical analysis**
Cleaned data were analysed using STATA 16 (StataCorp, College Station, Texas). Socio-economic quintiles (SES) were derived for the study population using principal component analysis, which aggregated information on women’s household amenities, household construction and durable assets (Additional file 1). The crude association between gravidity and placental malaria was determined, and the effect of adjusting for potential confounders (i.e. factors related to both gravidity and malaria risk) on this association was explored, firstly using Mantel-Haenszel stratification and then multivariable logistic regression, to derive adjusted odds ratios. Potential effect modifiers pre-specified for investigation \textit{a priori} were, area of residence (rural vs. urban), SES, IPTp use and ITN use. Evidence for effect modification was assessed using the Likelihood Ratio Test (LRT).

\textbf{Results}

All 1823 participants were aged between 14-49, with a mean age of 26.6 years. At delivery, 37.4\% (683/1823) of women had the outcome of placental malaria (PM). Of these, 9.4\% (64/683) had acute infection, 10.4\% (71/683) had chronic infection and 80.2\% (548/683) had past infection.

The number of previous pregnancies women had in the study ranged from zero to four. Three hundred and fifty two (19.3\%) women were primigravidae and 341 (18.7\%) were secundigravidae. Of the 1130 multigravidae, 325 (17.8\%) women had experienced two prior pregnancies, 251 (13.8\%) women had experienced three prior pregnancies and 554 (30.4\%) women had experienced 4 prior pregnancies (figure 1). The risk of developing PM in the full sample of women was 37.5\% (683/1823), however the risk was higher in PG, 65.9\% (232/352), than SG, 44.6\% (152/341), or MG, 26.5\% (299/1130).

As gravidity increased, the prevalence of PM decreased sharply over the first three pregnancies (i.e. gravidity 0 to 2), but was similar between women with 3 or 4 previous pregnancies (Figure 2a). The univariate analysis (Additional file 2) showed that gravidity was strongly associated with odds of PM (global p-value from LRT <0.001), with evidence that the association was non-linear (p-value for departure from linearity P=0.0017). The decrease in prevalence with increasing gravidity was less marked among women living in urban areas than among women living in rural areas (Figure 2b).

For multivariable analysis, to avoid data sparsity, gravidity was grouped into three levels: primigravidae (PG), secundigravidae (SG) and multigravidae (2 or more pregnancies, MG). Comparing PG to MG, the crude odds ratio for PM was OR=5.37 95\%, CI 4.08-7.07, P<0.001, and for SG was OR=2.24 95\%, CI 1.73-2.88, P<0.001 (Table 1). The final multivariable logistic regression model (Table 1) included PM, gravidity, and the confounding variables age, wealth index and relationship status. After adjusting for all confounding variables, the magnitude of the association diminished, however, there remained strong evidence that primigravidae were at increased odds of developing PM, adjusted OR=3.36 (95\% CI 2.39-4.71), N=1808, P<0.001.

\textbf{Table 1.} Crude and adjusted odds ratios for the effect of gravidity as a multi-level variable, age, wealth index and relationship status on placental malaria, adjusted for confounders, estimated by logistic regression in Ghanaian women aged 14-49 (N=1,808)
| Variable       | Category             | Crude model |          | Fully adjusted model |          |
|---------------|----------------------|-------------|----------|----------------------|----------|
|               |                      | OR (95% CI) | p-value  | OR (95% CI)          | p-value  |
|               |                      |             | (LRT)    |                      | (LRT)    |
| Gravidity     | MG                   | (REF)       |          | (REF)                |          |
|               | SG                   | 2.24 (1.73-2.88) | <0.001  | 1.67 (1.24-2.25)    | <0.001  |
|               | PG                   | 5.37 (4.08-7.07) |          | 3.36 (2.39-4.71)    |          |
| Age           | <18                  | (REF)       |          | (REF)                |          |
|               | 18-25                | 0.36 (0.26-0.51) |          | 0.66 (0.45-0.96)    |          |
|               | 25-49                | 0.14 (0.10-0.21) |          | 0.43 (0.27-0.67)    |          |
| Wealth index  | Least poor           | (REF)       |          | (REF)                |          |
|               | Less poor            | 1.12 (0.82-1.53) |          | 1.10 (0.78-1.54)    |          |
|               | Poor                 | 1.40 (1.02-1.90) |          | 1.48 (1.06-2.07)    |          |
|               | More poor            | 2.08 (1.53-2.84) |          | 2.14 (1.53-2.98)    |          |
|               | Extremely poor       | 1.59 (1.17-2.17) |          | 1.93 (1.38-2.69)    |          |
| Relationship  | Married              | (REF)       |          | (REF)                |          |
| Status        | Living together      | 1.97 (1.60-2.42) |          | 1.25 (0.99-1.59)    |          |
|               | Widowed/ Divorced/ Separated | 1.90 (0.98-3.71) |          | 0.91 (0.44-1.87)    |          |
|               | Single               | 3.40 (2.36-4.88) |          | 1.38 (0.91-2.09)    |          |

LRT: Likelihood ratio test

Abbreviations: MG, multigravidae; PG, primigravidae

1 Model adjusted for age group, wealth index and relationship status.

Effect modification (interaction) was explored in the adjusted model (Table 2). The association between primigravidity and PM was stronger in rural areas (adjusted OR= 3.79, 95% CI 3.61-5.51), compared to urban areas (adjusted OR=2.09, 95% CI 1.17-3.71), LRT p-value P=0.07. The five category wealth index was collapsed into two categories (grouping women in the upper 2 quintiles and lower 3 quintiles) when assessing effect modification, in order to increase the power of the test for interaction. The OR comparing
PG to MG was 4.73 (95% CI 3.08-7.25) among women in the lower three quintiles, and 2.14 (95% CI 1.38-3.35) among women in the upper two quintiles, LRT P=0.008.

Comparing PG to MG within strata of bednet use, the association with placental malaria was stronger among non-users of ITNs, OR= 4.22, (95% CI 2.68-6.67, P=0.10) than among primigravidae who did use ITNs (adjusted OR=2.36, 95%CI 1.54-3.60), LRT P=0.01. Finally, there was some suggestion that the increased odds of PM in PG, relative to MG, was greatest in primigravidae who took no IPTp-SP (OR=7.13, 95% CI 1.76-28.81), and smallest in primigravidae who took at least 3 IPTp-SP (OR=1.86, 95% CI 2.38 (1.59-3.57), although the confidence intervals around the ORs in the strata of IPTp uptake overlapped LRT p-value, P= 0.12).

Table 2. Stratum-specific odds ratios of effect modifiers to the association of gravidity as a multi-level variable and placental malaria, among Ghanaian mothers aged 14-49, estimated by logistic regression fitted with interaction parameters after adjustment\(^1\)\(^2\) for confounders

| LRT; Likelihood ratio test |
|---------------------------|
| 1 Adjusted for age, wealth and relationship status |
| 2 Adjusted for age relationship |

**Discussion**

**Summary of results**

This study aimed to explore the relationship between gravidity and PM among women in a high transmission area of Ghana, and explore how this risk was modified by other characteristics of the pregnant women. After adjustment for age, wealth index and relationship status through a multivariable logistic regression model, there was strong evidence that, primigravidae were at markedly higher risk of developing PM than multigravidae. Importantly, evidence was found that the extent to which primigravidae were at an elevated risk was influenced by area of residence and relative wealth, with approximately 75% of primigravid women in rural areas experiencing PM, compared to 30% of multigravidae living in urban areas. Use of protective measures such as ITNs and IPTp-SP may mitigate this risk.

The strong overall association between gravidity and PM was expected given the biological mechanism behind acquired immunity. From the analyses of gravidity as a multi-level variable, it can be seen that the excess risk in PG declines rapidly with successive pregnancies. In a higher-transmission area like Kintampo North Municipality, this is likely to occur more quickly than in a lower transmission area, because immunity to PM should be acquired over a smaller number of pregnancies (10) (18) (19). However, few studies have investigated how the effect of gravidity on PM varies according to level of exposure (assessed here through the proxies of place of residence and SES) and use of protective
| Variable                          | Category                  | Gravidity group | % PM (pm/N)          | Stratum specific OR (95% CI) | p-value (LRT) |
|---------------------------------|---------------------------|-----------------|----------------------|-----------------------------|---------------|
| Stratified by Area (N=1823)     | Urban                     | Multigravidae   | 29.5% (59/200)       | 1                           | 0.07          |
|                                 |                           | Secundigravidae | 35.9% (33/92)        | 1.04 (0.60-1.81)            |               |
|                                 |                           | Primigravidae   | 57.7% (52/90)        | 2.09 (1.17-3.71)            |               |
|                                 | Rural                     | Multigravidae   | 25.8% (240/930)      | 1                           |               |
|                                 |                           | Secundigravidae | 47.8% (119/249)      | 1.87 (1.34-2.62)            |               |
|                                 |                           | Primigravidae   | 68.7% (180/262)      | 3.79 (3.61-5.51)            |               |
| Stratified by Wealth index      | Higher                    | Multigravidae   | 23.1% (98/424)       | 1                           | 0.008         |
| (N=1823)                        |                           | Secundigravidae | 32.9% (51/155)       | 1.21 (0.79-1.86)            |               |
|                                 |                           | Primigravidae   | 52.0% (78/150)       | 2.14 (1.38-3.35)            |               |
|                                 | Lower                     | Multigravidae   | 28.5% (201/706)      | 1                           |               |
|                                 |                           | Secundigravidae | 54.3% (101/186)      | 2.05 (1.41-2.98)            |               |
|                                 |                           | Primigravidae   | 76.2% (154/202)      | 4.73 (3.08-7.25)            |               |
| Stratified by ITN use (N=1782)  | Don’t use                 | Multigravidae   | 23.9% (137/573)      | 1                           | 0.10          |
|                                 |                           | Secundigravidae | 43.3% (62/143)       | 1.83 (1.20-2.79)            |               |
|                                 |                           | Primigravidae   | 70.0% (100/145)      | 4.22 (2.68-6.67)            |               |
|                                 | Use                       | Multigravidae   | 29.6% (158/532)      | 1                           |               |
|                                 |                           | Secundigravidae | 45.6% (87/191)       | 1.39 (0.95-2.04)            |               |
|                                 |                           | Primigravidae   | 62.6% (124/198)      | 2.36 (1.54-3.60)            |               |
| Doses of Fansidar (IPTp) | 0 | Multigravidae | 16.1% (10/62) | 1 | 0.12 |
|--------------------------|---|--------------|---------------|---|------|
|                         |   | Secundigravidae | 38.1% (8/21) |   | 2.00 (0.63-6.27) |
|                         |   | Primigravidae | 69.2% (9/13) |   | 7.13 (1.76-28.81) |
| (N=1820)                | 1 | Multigravidae | 26.6 % (37/139) | 1 |   |
|                         |   | Secundigravidae | 38.6% (17/44) |   | 1.28 (0.61-2.69) |
|                         |   | Primigravidae | 78.4% (40/51) |   | 5.50 (2.46-12.32) |
|                         | 2 | Multigravidae | 25.5% (72/282) | 1 |   |
|                         |   | Secundigravidae | 48.3% (42/87) |   | 2.09 (1.22-3.56) |
|                         |   | Primigravidae | 71.0% (64/90) |   | 4.86 (2.71-8.73) |
|                         | 3 | Multigravidae | 27.8% (179/645) | 1 |   |
|                         |   | Secundigravidae | 45.0% (85/189) |   | 1.56 (1.07-2.28) |
|                         |   | Primigravidae | 60.4% (119/197) |   | 2.38 (1.59-3.57) |

measures. Comparable results to those presented were obtained treating gravidity as a binary variable (grouping SG with MG), in order to increase power (Additional file 3).

Relative to multigravidae, the increase in risk in primigravidae was greater in rural locations, and in women of lower SES, than in urban locations and women of higher SES. These result are consistent with both rural residence and poverty being strongly associated with elevated malaria risk (e.g. (20) (10)), and could potentially lead to very large differences in individual risk within a small geographic area. For example, 75.6% of primigravidae in the lowest SES stratum, living in rural areas had PM, compared to 30.6% of multigravidae in urban areas, in the highest SES group. Exposure to higher infection rates will lead to faster acquisition of immunity over successive pregnancies and a sharper drop in infection rates with increasing gravidity. A further contributing factor, (although this was not investigated in our study) is that there may be higher prevalence of infection prior to first pregnancy in adolescents and young women of low SES in rural areas. Although our data reflect the situation around 10 years ago, the differences in transmission between rural and urban areas, and the different relationship between gravidity and prevalence in areas with different levels of transmission provide insights into the potential changes that may arise from future reductions in transmission in rural areas. If the finding of effect modification is
true, then acquisition of immunity may occur more slowly as transmission is brought under control, and the excess risk in PG compared to MG may become smaller. This is a positive change, but will mean that women of higher gravidities may bear a larger share of the burden of PM, and prioritisation of women of all gravidities may need to become the focus.

The finding that current preventive interventions for malaria in pregnancy (ITN use and uptake of IPTp-SP) appear to mitigate the excess risk in primigravidae is consistent with the demonstrated effectiveness of these interventions (1). PG using an ITN were still at increased odds of PM compared to MG who used an ITN, but the odds ratio was much smaller than PG without ITN use compared to MG without ITN use (21). The ORs comparing PG to MG were progressively smaller with increasing doses of IPTp-SP, i.e. a dose-response relationship, although the confidence intervals were wide in each stratum. Assuming this finding is robust, it would support the effectiveness of IPTp-SP in reducing the risk among primigravid women. In Ghana, a minimum of 3 doses, up to a maximum of five doses of IPTp-SP are recommended (one at each ANC visit from the second trimester until delivery), and coverage of three doses is reasonably high at 60% (8) (22). Although these findings are plausible, evidence for effect modification was less strong than for areas of residence and SES, and there is potential for residual confounding through better access to these interventions likely being a proxy for lower malaria risk.

Strengths of the study include collection of data on a wide range of potential exposures, with a high degree of data completeness. The outcome of PM infection and infection type was objective and diagnosed by histology, which has a high specificity. Key limitations are the potential inaccuracy of self-reported measures such as maternal ITN use, uptake of IPTp-SP (through social-desirability bias) and to a lesser extent education status. There could also be residual confounding either from imperfect measurement of confounders that were included, or from other factors unaccounted for in the analysis, which are related to both gravidity and PM. However, residual confounding would need to be strong to negate the effects observed, which is unlikely.

**Conclusion**

This study provides evidence that the risk of PM in women in a high transmission area of Ghana is markedly higher among primigravidae than multigravidae. This risk is not shared equally – primigravidae from rural areas, and those with lower relative wealth, who typically have lower access to health services, are likely to be at highest risk. Programmes distributing ITN should ensure that primigravidae in these high risk groups are prioritized for interventions such as ITN distribution, and encouraged to attend ANC as early as possible in their pregnancy to receive IPTp-SP. Given the likelihood that risks among primigravid women reflect risks among the population from which these pregnancies arose, control programmes should also prioritize young women of child bearing age to try to protect first pregnancies from PM.

**Abbreviations**
Declarations

Ethics approval and consent to participate

Ethical approval for the original study was obtained from the ethics committees of Kintampo Health Research Centre, Ghana Health Service, LSHTM, and Noguchi Memorial Institute for Medical Research. Written informed consent was obtained from all study participants. The current study was approved by LSHTM (Ref: 22142).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from Kwaku Poku Asante (kwakupoku.asante@kintampo-hrc.org) on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding
Financial support for the original Kintampo Birth Cohort Study was provided by the Division of Microbiology and Infectious Disease, National Institute of Allergy and Infectious Diseases, National Institute of Health, United States of America [Contract no: HHSN266200400016C]. The Gates Malaria Partnership, London School of Hygiene & Tropical Medicine provided support for placental tissue histology. The Malaria Capacity Development Consortium (MCDC), supported by the Wellcome Trust (grant number 084289/Z/07/Z), supported laboratory and field personnel costs for the Kintampo Birth Cohort study. MC is supported by a ‘Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (Grant Number 220658/Z/20/Z).

Authors’ contributions

AA, MC and KPA conceived the idea and designed the secondary analyses. KPA, EBK and DD conducted the original Kintampo Birth Cohort study. AA performed statistical analysis with support from MC. AA wrote the first draft of the manuscript with support from MC. KPA, KS, SH edited the first draft of the manuscript. All authors contributed to the data interpretation and manuscript writing. All authors read and approved the final version of the manuscript.

Acknowledgements

We are grateful to the community leaders in the study area, study parents and their infants; staff and management of Kintampo Health Research Centre and the other Ghana Health Service facilities in the study area and the Pathology Department of University of Ghana Medical School, which supported the Kintampo Birth Cohort study and the team of investigators of the Kintampo Birth Cohort Study

References

1. WHO. WHO | Malaria in pregnant women. Who [Internet]. 2018 [cited 2020 Jul 1]; Available from: http://www.who.int/malaria/areas/high_risk_groups/pregnancy/en/

2. Mockenhaupt FP, Ulmen U, Von Gaertner C, Bedu-Addo G, Bienzle U. Diagnosis of placental malaria. J Clin Microbiol [Internet]. 2002 [cited 2020 Jul 1];40(1):306–8. Available from: /pmc/articles/PMC120131/?report=abstract

3. Liu Y, Griffin JB, Muehlenbachs A, Rogerson SJ, Bailis AJ, Sharma R, et al. Diagnosis of placental malaria in poorly fixed and processed placental tissue. Malar J [Internet]. 2016 May 10 [cited 2020 Jul 1];15(1):272. Available from: https://malariajournal.biomedcentral.com/articles/10.1186/s12936-016-1314-6

4. Uneke CJ. Impact of placental Plasmodium falciparum malaria on pregnancy and perinatal outcome in sub-Saharan Africa. II: Effects of placental malaria on perinatal outcome; malaria and HIV [Internet]. Vol. 80, Yale Journal of Biology and Medicine. Yale Journal of Biology and Medicine; 2007 [cited 2020 Jul 14]. p. 95–103. Available from: /PMC/2248298/?report=abstract

5. Omer SA, Idress HE, Adam I, Abdelrahim M, Noureldine AN, Abdelrazig AM, et al. Placental malaria and its effect on pregnancy outcomes in Sudanese women from Blue Nile State. Malar J [Internet].
6. Tran EE, Cheeks ML, Kakuru A, Muhindo MK, Natureeba P, Nakalembe M, et al. The impact of gravidity, symptomatology and timing of infection on placental malaria. Malar J [Internet]. 2020 Dec 24 [cited 2020 Jul 1];19(1):227. Available from: https://malariajournal.biomedcentral.com/articles/10.1186/s12936-020-03297-3

7. Agudelo O, Arango E, Maestre A, Carmona-Fonseca J. Prevalence of gestational, placental and congenital malaria in north-west Colombia. Malar J [Internet]. 2013 Sep 23 [cited 2020 Jul 14];12(1):341. Available from: http://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-12-341

8. Agyeman YN, Newton S, Annor RB, Owusu-Dabo E. Intermittent preventive treatment comparing two versus three doses of sulphadoxine pyrimethamine (IPTp-SP) in the prevention of anaemia in pregnancy in Ghana: A cross-sectional study. Luty AJF, editor. PLoS One [Internet]. 2021 Apr 20 [cited 2021 Apr 26];16(4):e0250350. Available from: https://dx.plos.org/10.1371/journal.pone.0250350

9. Fried M, Duffy PE. Malaria during pregnancy. Cold Spring Harb Perspect Med [Internet]. 2017 Jun 1 [cited 2020 Aug 24];7(6). Available from: /pmc/articles/PMC5453384/?report=abstract

10. Okiring J, Olwoch P, Kakuru A, Okou J, Ochokoru H, Ochieng TA, et al. Household and maternal risk factors for malaria in pregnancy in a highly endemic area of Uganda: A prospective cohort study. Malar J [Internet]. 2019 Apr 23 [cited 2020 Aug 16];18(1):144. Available from: /pmc/articles/PMC6480498/?report=abstract

11. Mayor A, Rovira-Vallbona E, Machevo S, Bassat Q, Aguilar R, Quintó L, et al. Parity and placental infection affect antibody responses against Plasmodium falciparum during pregnancy. Infect Immun [Internet]. 2011 Apr 1 [cited 2020 Aug 14];79(4):1654–9. Available from: https://iai.asm.org/content/79/4/1654

12. Berry I, Walker P, Tagbor H, Bojang K, Coulibaly SQ, Kayentao K, et al. Seasonal dynamics of malaria in pregnancy in West Africa: Evidence for carriage of infections acquired before pregnancy until first contact with antenatal care. Am J Trop Med Hyg [Internet]. 2018 Dec 4 [cited 2021 Mar 28];98(2):534–42. Available from: www.ajtmh.org.

13. Walker PGT, Griffin JT, Cairns M, Rogerson SJ, Van Eijk AM, Ter Kuile F, et al. A model of parity-dependent immunity to placental malaria. Nat Commun [Internet]. 2013 [cited 2020 Jul 15];4. Available from: https://pubmed.ncbi.nlm.nih.gov/23511473/

14. Dery DB, Brown C, Asante KP, Adams M, Dosoo D, Amenga-Etego S, et al. Patterns and seasonality of malaria transmission in the forest-savannah transitional zones of Ghana. Malar J [Internet]. 2010 Nov 7 [cited 2020 Aug 18];9(1):314. Available from: http://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-9-314

15. Asante KP, Owusu-Agyei S, Cairns M, Dodoo D, Boamah EA, Gyasi R, et al. Placental Malaria and the Risk of Malaria in Infants in a High Malaria Transmission Area in Ghana: A Prospective Cohort Study. 2013;
Figures

Figure 1

Flowchart to summarize final study participants. Abbreviations: MG, multigravidae; SG, secundigravidae; PG, primigravidae

Figure 2

Graphs to show the prevalence of placental malaria infection, and associated confidence intervals in each gravidity group.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx
- Additionalfile3.docx
- Additionalfile2.docx
- Additionalfile4.docx