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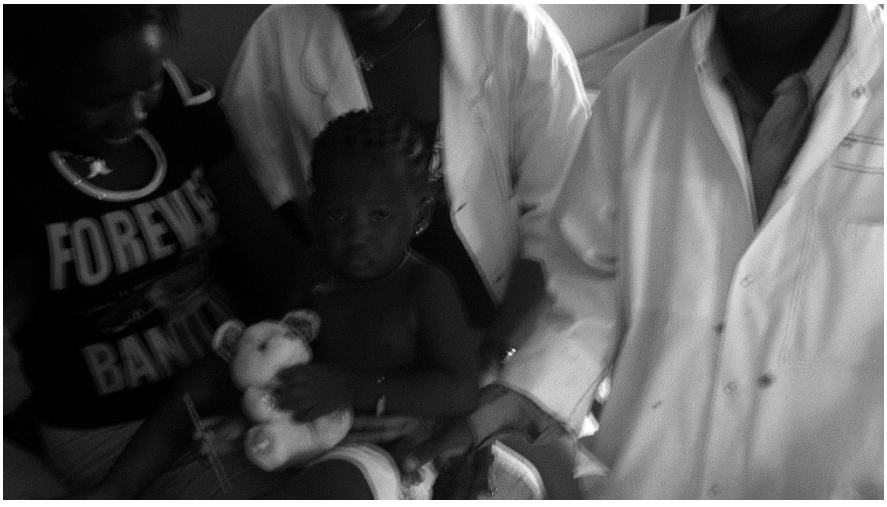

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# CHAPTER 2

## Young Adolescent Girls are at High Risk for Adverse Pregnancy outcomes in Sub-Saharan Africa: an Observational Multi-Country Study

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## Abstract

***Objectives***: One of Africa's most important challenges is to improve maternal and neonatal health. The identification of groups at highest risk for adverse pregnancy outcomes is important for developing and implementing targeted prevention programs. This study assessed whether young adolescent girls constitute a group at increased risk for adverse birth outcomes among pregnant women in sub-Saharan Africa.

***Setting***: Data were collected prospectively as part of a large randomized controlled clinical trial evaluating intermittent preventive treatment of malaria in pregnancy (NCT00811421 - Clinical Trials.gov), conducted between September 2009 and December 2013 in Benin, Gabon, Mozambique, and Tanzania.

***Participants***: Out of 4749 participants, pregnancy outcomes were collected for 4388 deliveries with 4183 live births including 83 multiple gestations. Of 4100 mothers with a singleton live birth delivery, 24% (975/4100) were adolescents (≤19 years of age) and 6% (248/4100) were aged ≤ 16 years.

***Primary and secondary outcome measures***: Primary outcomes of this pre-defined analysis were preterm delivery and low birth weight.

***Results***: The overall prevalence of low birth weight infants and preterm delivery was 10% (371/3851) and 4% (159/3862), respectively. Mothers aged ≤16 years showed higher risk for the delivery of a low birth weight infant (OR: 1.96; 95% CI: 1.35 to 2.83). Similarly, preterm delivery was associated with young maternal age (≤16 years; OR: 2.62; 95% CI: 1.59 to 4.30). In a sub-analysis restricted to primiparous women, preterm delivery: OR 4.28; 95% CI: 2.05 to 8.93; low birth weight: OR: 1.29; 95% CI: 0.82 to 2.01.

***Conclusions***: Young maternal age increases risk for adverse pregnancy outcomes and it is a stronger predictor for low birth weight and preterm delivery than other established risk factors in sub-Saharan Africa. This finding highlights the need to improve adolescent reproductive health in sub-Saharan Africa.

Trial registration: NCT00811421 - Clinical Trials.gov


Keywords: adolescent pregnancy; sub-Saharan Africa; low birth weight; preterm birth

## Introduction

Improving maternal and neonatal health is among Africa's most urgent challenges in public health (1,2). The excess rate of maternal and neonatal morbidity and mortality derives from multiple causes in sub-Saharan Africa including endemic infectious diseases, malnutrition and micronutrient deficiencies, gynaecologic and obstetric complications with sub-optimal ante- and perinatal as well as often inadequate postnatal care caused by a lack of adequate financial and logistic resources (2–4). Targeted public health interventions such as intermittent preventive treatment of malaria in pregnancy (IPTp), vitamin and micronutrient supplementation, provision of long-lasting insecticide-treated nets (LLITNs), the prevention of mother-to-child HIV transmission (PMTC) and improved frequency and quality of gynaeco-obstetric health care are the cornerstones of current strategies to reduce adverse pregnancy outcomes in Africa (5–8).

It is well known that the risk for adverse pregnancy outcomes is distributed highly unevenly within populations. Further reductions of maternal and neonatal morbidity and mortality can therefore be achieved most efficiently by the identification of those individuals most at risk (9).

With 44% of its population aged below 15 years, sub-Saharan Africa is the youngest region of the world (10). However, from a medical and public health perspective adolescence is a largely neglected period of life. Few epidemiological studies in Africa focus on this period of life and targeted public health programs addressing the most important challenges for adolescent health and well-being are lacking.

Sexual and reproductive health is arguably among the most vital health challenges for adolescents in sub-Saharan Africa (11). Although some regions in sub-Saharan Africa are characterized by a high proportion of very young pregnant women, it is currently unclear whether these young girls benefit equally from established routine antenatal care programs or whether more targeted programs would be necessary to address specific needs of this vulnerable group of pregnant women.

Based on previous retrospective studies this study was designed to evaluate prospectively whether young maternal age may serve as an easily recognisable predictor for adverse pregnancy outcome in sub-Saharan African. This hypothesis was assessed in the context of a clinical trial with access to a package of free and high quality routine antenatal care, effective preventive treatment of malaria in pregnancy, and provision of LLITNs.

## Materials and Methods

Pregnant women and their offspring participated in a randomised controlled trial assessing alternative drugs for intermittent preventive treatment of malaria in pregnancy (MiPPAD; NCT00811421 - Clinical Trials.gov) (12). This study was conducted in four African countries between September 2009 and December 2013, involving regions from Western, Eastern, Central and Southern sub-Saharan Africa. Pregnant women were recruited at their first antenatal visit if they were HIV-negative, presented with a gestational age below 28 weeks of gestation at their first antenatal care visit, were willing to participate in the study and to give birth in the study health facility. Exclusion criteria were a history of allergy to any of the study drugs or any other ongoing serious condition. All women received LLITNs and randomly allocated to either standard sulfadoxine-pyrimethamine or mefloquine preventive treatment for malaria. Women were followed up until one month after delivery and infants were followed up until their first anniversary. All costs for antenatal and postnatal care and transport to respective health facilities were free of charge for participants.

Participants' baseline information were recorded at recruitment including maternal age, weight, height, mid-upper arm circumference (MUAC), date of last menstruation and gestational age by bimanual palpation, obstetrical history, syphilis test (RPR testing), haemoglobin level, literacy as ability to read and/or write. Body mass index (BMI) was categorized for further statistical analysis using predefined threshold levels by World Health Organization (WHO) (underweight: BMI<18.5; normal weight: BMI 18.5-24.9; overweight: BMI 25.0-29.9; obese: BMI>=30.0). The cut-off for the MUAC was defined by 240mm according to UNICEF recommendations (13).

Gestational age, birth outcome and characteristics of delivery were recorded at delivery and haemoglobin levels were assessed from finger-prick or venous blood using the HemoCue device (www.eurotrol.com). Infection with *P. falciparum* at delivery was defined as the detection of malaria parasites in peripheral blood or placental samples collected at delivery. Parasitological assessments were performed from peripheral, cord blood, and placenta by thick and thin smears and impression smears, respectively.

Maternal age was calculated from the date of birth recorded in official health booklet at enrolment or in case of lack of documentation by self-reported date of birth. Adolescence was defined as per WHO, "young individuals between the ages of 10 and 19 years" (14). Maternal age was divided into four categories including young adolescents aged $\leq$16 years, adolescents aged 17 to 19 years, adults aged 20 to 30 years and those aged 31 years and above. The sample size of the dataset supported the use of such stratification in all analyses.

The main delivery endpoints for this analysis were the proportions of low birth weight infants and preterm delivery and secondarily the proportion of maternal anaemia at delivery. Low birth weight was defined as less than 2500g and was measured within the 24 hours after birth using digital infant scales. Scales were calibrated weekly and quality controlled. In case of home deliveries or other reasons for delayed measurement of birth weight, data were imputed using a previously published regression model (15). Premature delivery was defined as delivery before 37 weeks of gestation. Gestational age at recruitment was determined from the measure of the symphysis-fundus height by bimanual palpation at the first antenatal visit. At delivery gestational age was assessed by Ballard Score (16). Anaemia was defined as haemoglobin level <11g/dL.

***Statistical analysis, Conceptual framework, and Causal diagram***

Several factors including socio-economic disadvantage, low BMI and MUAC, primiparity, and non-attendance of antenatal care visits have been described as risk factors associated with poor birth outcomes. These factors could therefore potentially confound any observed association between young adolescent pregnancy and adverse pregnancy outcome and were therefore included in statistical analysis. A simplified illustration of the conceptual framework built up to guide this analysis is shown in Figure 1.

Statistical analyses were restricted to singleton births and were conducted using Stata IC/13.1 for Windows (StataCorpLp, College station TX). The distribution of baseline characteristics was described and compared according to maternal age groups. Univariate analysis was performed to assess the crude association between maternal age and low birth weight or preterm delivery. In addition other variables associated with higher odds for low birth weight, prematurity, and maternal anaemia were identified. Variables associated with both adverse birth outcomes and maternal age were considered potential confounders. In a further step logistic regression models adjusting for potential confounders or other covariables were constructed according to their effect on the point estimate rather than providing p-values. As a guide the change in the point estimate was considered significant if equal or above 10% - an arbitrary cut-off level. We performed stepwise removal of variables in the absence of evidence for an effect on the point estimate (17). However, forced variables (country, treatment arm) were defined and were kept in the final model whatever their effect on the point estimate was as these were inherent to the study design.The final model evaluated the adjusted odds ratios of adverse birth outcome in the different age groups. For the analysis of preterm delivery data from Tanzania were excluded because of a systematic error in the assessment of gestational age by Ballard score at this study site.

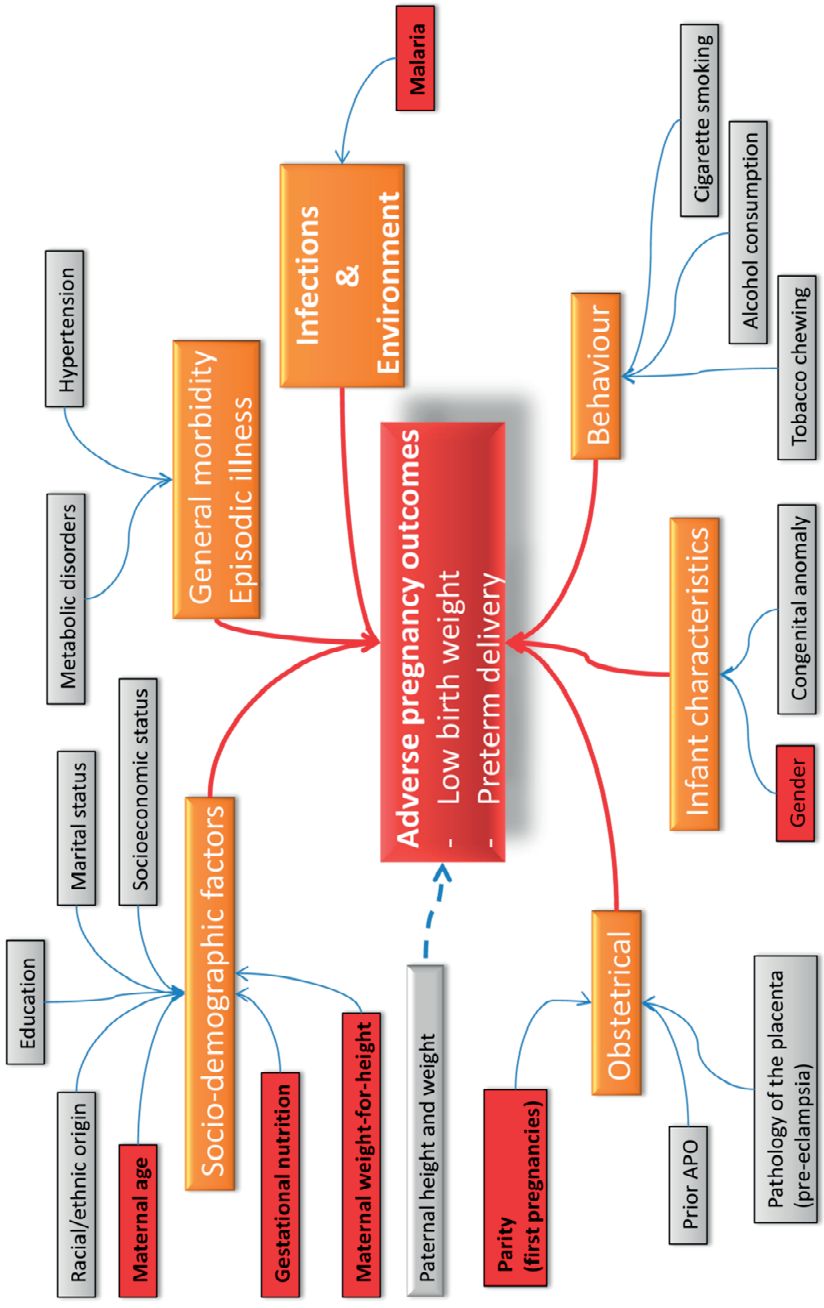


Figure 1: **Conceptual framework of risk factors of adverse pregnancy outcome (APO)** Risk factors of Adverse Pregnancy Outcome (APO) have been categorized (orange boxes). The red boxes are the risk factors discussed throughout this paper. The grey boxes represent known risk factors of APO which were not addressed in this paper.

***Ethical considerations***

The MiPPAD study protocol and study materials received ethical approvals from the University Hospital of Barcelona Institutional Review Board and from national ethics committees of each African site. All women participating in the study had signed a written informed consent form before any study related procedure was performed. The study was conducted according to the ICH-GCP principles and the Declaration of Helsinki.

## Results

A total of 14,179 pregnant women attending antenatal clinics in Benin, Gabon, Mozambique, and Tanzania were screened between September 2009 and December 2012 for recruitment to the MiPPAD trial and 4,749 were randomised at the four study sites. Among those 361 (7.6%) were lost or withdrawn before delivery, with 79 (22%) adolescents, 237 (66%) women aged between 20 and 30 years and 45 (12%) women aged 31 year or more. There was no significant difference observed in baseline characteristics between the women lost or withdrawn from the study and those considered in the analysis for this study (supplementary Figure 1). Of the 4,388 recorded deliveries, 4,183 were living births including 83 multiple gestations. Mother-child pairs of 4,100 singleton infants constitute the population of the primary analysis of this report. Details of the participant flow are depicted in Figure 2.

Among 4,100 pregnant participants with a singleton live birth, 24% (975/4100) were adolescents with 6% (248/4100) aged $\leq$ 16 years. There was a significant difference in the proportion of adolescent mothers between countries (Table 1).

Significant differences between maternal age groups were identified according to the period of first antenatal visit as adolescent women attended earlier compared to other age groups. Differences were also apparent for parity, nutritional status, literacy, baseline anaemia, and syphilis infection at first presentation to antenatal care clinics (Table 1). Due to the randomization there was no difference in the allocation to respective intermittent preventive treatment groups (Table1).

Among singleton live births the overall proportion of low birth weight infants and preterm delivery was 10% (371/3851) and 4% (159/3862), respectively. The proportion of women with maternal anaemia at delivery was 41% (1586/3884).

At delivery very young maternal age ($\leq$16 years) was the variable with the highest risk for the delivery of a low birth weight infant, 16% (39/248) compared to adult mothers aged 20 to 30 years, 9% (207/2376) (crude OR: 1.96; 95% CI: 1.35-2.83) (Table 2). Other factors significantly associated with increased risk for low birth weight were country, trimester of first antenatal

visit, parity, BMI, and MUAC (Table 2). Similarly, preterm birth was most closely associated with very young maternal age ≤ 16 years (OR: 2.62; 95% CI: 1.59 to 2.13). Other factors significantly associated with preterm birth were country, BMI, and literacy (Table 2).

Multivariable risk factors analysis was performed to assess confounding and potential causal relationships of co-variables. After controlling for country, trimester of first antenatal visit, treatment group, and infant gender, there remained strong evidence for increased odds for low birth weight in very young adolescent mothers (≤16 years), OR 2.06 (1.37 to 3.12). However this association was weaker when controlling for BMI, parity, literacy, plasmodium infection, and MUAC (Table 3). Conversely, preterm delivery remained significantly associated with young maternal age in multivariate analysis, OR 2.16 (1.10 to 4.24) (Table 3). Maternal anaemia was not associated with respective age groups (Supplementary Tables 1 and 2).

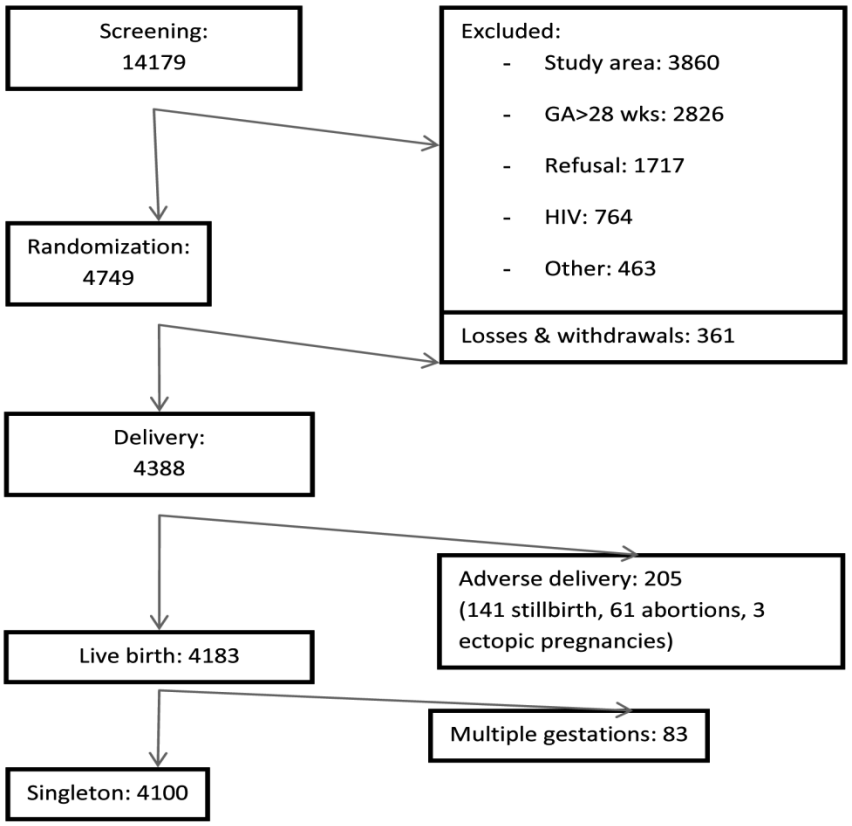


Figure 2: **Participants flow**

Abbreviations: GA: gestational age; HIV: Human Immunodeficiency Virus·

Table 1: **Distribution of baseline characteristics by maternal age group**

| | | Overall | maternal age (years) | | | | *P* value* |
|---|---|---|---|---|---|---|---|
| | | N=4100 | 14-16 (n=248) | 17-19 (n=727) | 20-30 (n=2400) | 31+ (n=725) | |
| *Country* | *Benin* | 1027 | 5 (0.5) | 98 (9.5) | 754 (73.4) | 170 (16.6) | <0.001 |
| | *Gabon* | 953 | 79 (8.3) | 221 (23.2) | 462 (48.5) | 191 (20.0) | |
| | *Mozambique* | 1098 | 157 (14.3) | 277 (25.2) | 489 (44.5) | 175 (15.9) | |
| | *Tanzania* | 1022 | 7 (0.7) | 131 (12.8) | 695 (68.0) | 189 (18.5) | |
| *First ANC visit* | *1st trimester* | 298 | 22 (8.9) | 66 (9.1) | 161 (6.7) | 49 (6.8) | 0.005 |
| | *2nd trimester* | 2899 | 186 (75.0) | 522 (71.9) | 1667 (69.5) | 524 (72.2) | |
| | *3rd trimester* | 902 | 40 (16.1) | 138 (19.0) | 572 (23.8) | 152 (21.0) | |
| *Parity* | *Nulliparous* | 1328 | 239 (96.4) | 548 (75.4) | 522 (21.7) | 19 (2.6) | <0.001 |
| | *Multiparous* | 2772 | 9 (3.6) | 179 (24.6) | 1878 (78.2) | 706 (97.4) | |
| *BMI* | *Underweight* | 493 | 30 (12.1) | 101 (13.9) | 306 (12.8) | 56 (7.7) | <0.001 |
| | *Normal* | 2689 | 184 (74.2) | 548 (75.6) | 1572 (65.5) | 385 (53.1) | |
| | *Overweight/Obese* | 915 | 34 (13.7) | 76 (10.5) | 521 (21.7) | 284 (39.2) | |
| *MUAC* | *≥240mm* | 3312 | 171 (68.9) | 524 (72.4) | 1964 (82.1) | 653 (90.1) | <0.001 |
| | *<240mm* | 776 | 77 (31.1) | 200 (27.6) | 427 (17.9) | 72 (9.9) | |
| *Literacy* | *Literate* | 2846 | 220 (88.7) | 626 (86.1) | 1527 (63.6) | 473 (65.2) | <0.001 |
| | *Illiterate* | 1254 | 28 (11.3) | 101 (13.9) | 873 (36.4) | 252 (34.8) | |
| *Baseline Anaemia* | *No* | 1656 | 94 (37.9) | 261 (36.0) | 985 (41.2) | 316 (43.8) | 0.001 |
| | *Yes* | 2430 | 154 (62.0) | 463 (64.0) | 1408 (58.8) | 405 (56.2) | |
| *Syphilis test* | *Negative* | 3961 | 246 (100) | 705 (98.7) | 2319 (98.8) | 691 (97.2) | 0.001 |
| | *Positive* | 57 | 0 (0) | 9 (1.3) | 28 (1.2) | 20 (2.8) | |
| *IPTp* | *MQ* | 2720 | 166 (66.9) | 479 (65.9) | 1599 (66.6) | 476 (65.7) | 0.95 |
| | *SP* | 1380 | 82 (33.1) | 248 (34.1) | 801 (33.4) | 249 (34.3) | |

ANC: antenatal clinic; BMI: body mass index; MUAC: mid-upper arm circumference; IPTp: intermittent preventive treatment of malaria in pregnancy; SP: sulfadoxine-pyrimethamine; MQ: mefloquine
*$\chi^2$ test

Table 2: **Incidence of low birth weight and preterm birth and univariate analysis of the risk factors**

| *Parameters* | | *Birth weight* | | | | *Preterm birth* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Singleton live births, N | LBW, n (%) | Unadjusted OR (95% CI) | *P* value* | Singleton live births, N | Preterm, n (%) | Unadjusted OR (95% CI) | *P* value* |
| *Maternal age* | *14-16 years* | 248 | 39 (15.7) | 1.96 (1.35-2.83) | | 214 | 20 (9.4) | 1.82 (1.09-3.03) | |
| | *17-19 years* | 714 | 98 (13.7) | 1.67 (1.29-2.15) | <0.001 | 543 | 35 (6.4) | 1.22 (0.81-1.83) | 0.15 |
| | *20-30 years* | 2376 | 207 (8.7) | 1 | | 1548 | 83 (5.4) | 1 | |
| | *≥ 31 years* | 718 | 47 (6.6) | 0.73 (0.53-1.02) | | 486 | 26 (5.4) | 1.00 (0.63-1.57) | |
| *Country* | *Benin* | 1019 | 108 (10.6) | 1.37 (1-01-1.84) | | 923 | 50 (5.4) | 1 | |
| | *Gabon* | 929 | 119 (12.8) | 1.70 (1.27-2.27) | 0.0002 | 886 | 50 (5.6) | 1.04 (0.70-1.56) | 0.56 |
| | *Mozambique* | 1092 | 87 (8.0) | 1 | | 982 | 64 (6.5) | 1.21 (0.83-1.78) | |
| | *Tanzania* | 1016 | 77 (7.6) | 0.95 (0.69-1.30) | | n.a | n.a | n.a | |
| *First ANC visit* | *first trimester* | 292 | 35 (12.0) | 1.66 (1.08-2.55) | | 224 | 16 (7.1) | 1.51 (0.82-2.79) | |
| | *second trimester* | 2868 | 288 (10.0) | 1.36 (1.03-1.79) | 0.03 | 1865 | 114 (6.1) | 1.28 (0.86-1.89) | 0.33 |
| | *third trimester* | 895 | 68 (7.6) | 1 | | 701 | 34 (4.8) | 1 | |
| *Parity* | *Nulliparous* | 1314 | 182 (13.8) | 1.95 (1.58-2.40) | <0.0001 | 835 | 54 (6.5) | 1.16 (0.83-1.62) | 0.39 |
| | *Multiparous* | 2742 | 209 (7.6) | 1 | | 1956 | 110 (5.6) | 1 | |
| *BMI* | *Normal* | 2663 | 264 (9.9) | 1 | | 1620 | 117 (6.1) | 1 | |
| | *Underweight* | 488 | 80 (16.4) | 1.78 (1.35-2.33) | <0.0001 | 372 | 24 (6.4) | 1.06 (0.67-1.67) | 0.39 |
| | *Overweight / Obese* | 902 | 47 (5.2) | 0.50 (0.36-0.69) | | 496 | 23 (4.6) | 0.75 (0.47-1.18) | |
| *MUAC* | *≥240mm* | 3277 | 272 (8.3) | 1 | | 2199 | 128 (5.8) | 1 | |
| | *<240mm* | 767 | 119 (15.5) | 2.03 (1.61-2.56) | <0.0001 | 586 | 36 (6.1) | 1.06 (0.72-1.55) | 0.77 |
| *Literacy* | *Literate* | 2811 | 262 (9.3) | 1 | | 1725 | 96 (5.6) | 1 | |
| | *illiterate* | 1245 | 129 (10.4) | 1.12 (0.90-1.40) | 0.33 | 1066 | 68 (6.4) | 1.16 (0.84-1.59) | 0.38 |
| *Plasmodial infection at delivery* | *No* | 3682 | 344 (9.3) | 1 | | 2580 | 1449 (5.8) | 1 | |
| | *Yes* | 197 | 27 (13.7) | 1.54 (1.01-2.35) | 0.05 | 174 | 9 (5.2) | 0.89 (0.44-1.78) | 0.74 |
| *IPTP* | *MQ* | 2686 | 260 (9.7) | 1 | | 1845 | 111 (6.0) | 1 | |
| | *SP* | 1370 | 131 (9.6) | 0.99 (0.79-1.23) | 0.9 | 946 | 53 (5.6) | 0.93 (0.66-1.30) | 0.66 |
| *Baseline anaemia* | *No* | 1646 | 149 (9.0) | 1 | | 1016 | 69 (6·8) | 1 | |
| | *Yes* | 2396 | 242 (10.1) | 1.13 (0.91-1.40) | 0.4 | 1764 | 95 (5.4) | 0.78 (0.57-1.08) | 0.13 |
| *Syphilis test* | *Negative* | 3921 | 379 (9.7) | 1 | | 2723 | 156 (5.7) | 1 | |
| | *Positive* | 55 | 5 (9.1) | 0.93 (0.37-2.36) | 0.88 | 39 | 5 (12.8) | 2.42 (0.93-6.27) | 0.1 |

Note Table 2: OR: odds ratio; 95%CI: 95% confidence interval; ANC: antenatal clinic; BMI: body mass index; MUAC: mid-upper arm circumference; IPTp: intermittent preventive treatment of malaria in pregnancy; SP: sulfadoxine-pyrimethamine; MQ: mefloquine;

A sub-analysis restricted to primiparous women was performed to control for parity, which is a well-established risk factor for adverse pregnancy outcome and which inherently is associated with maternal age. This restricted analysis demonstrated that very young maternal age was associated with higher risk for adverse pregnancy outcome (preterm delivery: OR 4.28; 95% CI: 2.05-8.93; low birth weight: OR: 1.29; 95% CI: 0.82-2.01) (supplementary Table 3).

**Table 3: Multivariate analysis of risk factors associated with low birth weight and preterm delivery**

| *Parameters* | | *Birth weight* | | | | *Preterm birth* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Adjusted Model 1* OR (95% CI) | P value (LRT) | Adjusted final Model OR (95% CI) | P value (LRT) | Adjusted Model 1** OR (95% CI) | P value (LRT) | Adjusted final Model OR (95% CI) | P value (LRT) |
| *Maternal age* | *14-16 years* | 2.06 (1.37-3.12) | | 1.29 (0.81-2.06) | | 1.73 (1.01-2.98) | | 2.16 (1.10-4.24) | |
| | *17-19 years* | 1.74 (1.33-2.30) | <0.0001 | 1.28 (0.93-1.75) | 0.48 | 1.18 (0.77-1.81) | 0.19 | 1.41 (0.85-2.35) | 0.18 |
| | *20-30 years* | 1 | | 1 | | 1 | | 1 | |
| | *≥31 years* | 0.73 (0.52-1.03) | | 0.85 (0.60-1.20) | | 0.92 (0.57-1.49) | | 0.88 (0.51-1.36) | |
| *BMI* | *Normal* | 1 | | 1 | | | | | |
| | *Underweight* | 1.72 (1.29-2.29) | <0.0001 | 1.49 (1.09-2.03) | 0.001 | | | | |
| | *Overweight/Obese* | 0.52 (0.28-0.67) | | 0.65 (0.46-0.92) | | | | | |
| *Literacy* | *Literate* | 1 | 0.8 | 1 | 0.17 | 1 | 0.14 | 1 | 0.11 |
| | *Illiterate* | 1.04 (0.78-1.38) | | 1.23 (0.91-1.66) | | 1.35 (0.91-2.01) | | 1.43 (0.94-2.16) | |
| *Baseline anaemia* | *No* | | | | | 1 | 0.18 | 1 | 0.14 |
| | *Yes* | | | | | 0.80 (0.57-1.11) | | 0.79 (0.56-1.10) | |
| *Plasmodial infection at delivery* | *Negative* | 1 | 0.07 | 1 | 0.4 | 1 | 0.89 | 1 | 0.81 |
| | *Positive* | 1.38 (0.89-2.12) | | 1.21 (0.78-1.88) | | 0.95 (0.47-1.92) | | 0.93 (0.46-1.88) | |
| *Parity* | *Nulliparous* | 2.03 (1.62-2.53) | <0.0001 | 1.64 (1.23-2.19) | 0.001 | 1.10 (0.77-1.56) | 0.6 | 0.83 (0.51-1.36) | 0.47 |
| | *Multiparous* | 1 | | 1 | | 1 | | 1 | |
| *MUAC* | *>240mm* | 1 | <0.0001 | 1 | 0.05 | | | | |
| | *<240mm* | 1.84 (1.44-2.36) | | 1.32 (1.00-1.74) | | | | | |

*adjusted for country, antenatal clinic; BMI: body mass index; MUAC: mid-upper arm circumference

**adjusted for country, first antenatal clinic visit, treatment group, and infant gender

OR: odds ratio; 95%CI: 95% confidence interval; LRT: likelihood ratio; ANC: antenatal clinic; BMI: body mass index; MUAC: mid-upper arm circumference; IPTp: intermittent preventive treatment of malaria in pregnancy; SP: sulfadoxine-pyrimethamine; MQ: mefloquine

## Discussion

The identification of high risk groups among pregnant women is of high priority to develop cost-effective interventions to further reduce maternal and neonatal mortality in sub-Saharan Africa. In this prospective multinational cohort of pregnant women in sub-Saharan Africa, young maternal age was the strongest predictor for adverse pregnancy outcome. Very young mothers were more likely than their older peers to deliver prematurely or a low-birth weight infant – two of the key surrogate markers for adverse pregnancy outcome and infant mortality (9,18,19).

Our finding is supported by previous reports from other geographical and socioeconomic settings demonstrating a higher than normal risk for teenagers in pregnancy (20,21). Several hypotheses have been previously proposed to explain the higher risk for adverse pregnancy outcomes in this group of pregnant women including social and economic disadvantage, behavioural factors increasing the risk for adverse pregnancy outcome and biological immaturity of the mother (22). In this analysis there was no difference in literacy, nutritional status, or syphilis prevalence between young and older pregnant women. In addition antenatal care was provided uniformly during the conduct of the clinical trial excluding differences in healthcare related effects. Importantly, this study was not designed to investigate underlying causes for adverse pregnancy outcome. Conversely, the aim of this study was to assess whether young maternal age may be used as a simple predictive marker for a population at high risk for adverse pregnancy outcome in sub-Saharan Africa and to allow for future targeted interventions in this at risk group.

Interestingly, young maternal age showed a stronger association with adverse pregnancy outcome than other established risk factors including parity or malaria infection in univariate analysis. In regions of high malaria transmission it is estimated that plasmodial infections may cause about 19% of low birth weight deliveries (23). Malaria infection was highly prevalent in this study in Gabon and Benin and these two countries concordantly had the highest incidence of low birth weight. It is also well established that the impact of malaria in pregnancy is highest in primigravid women (24). Whereas this was similarly observed in this cohort of pregnant women, an analysis restricted to primigravid women still demonstrated an excess risk for low birth weight and preterm delivery in young adolescent mothers stressing the importance of young maternal age as risk factor. In addition multivariable analysis indicated that young maternal age is significantly associated with premature delivery. These data unequivocally demonstrate that young maternal age constitutes a risk factor for adverse birth outcome. Based on these data it is evident that

young adolescent girls are a readily identifiable at risk population in sub-Saharan Africa.

Young adolescent pregnancy rates differ considerably between countries. In this study high rates were observed in Gabon and Mozambique and lower rates were found in Benin and Tanzania. This difference is mainly explained by sociocultural and religious determinants of societies. This fact also highlights that young adolescent pregnancies may not be of similar public health importance in all sub-Saharan African countries. In countries with high proportions of young adolescent pregnancies the establishment of dedicated antenatal care programs may therefore be of comparatively higher public health importance to improve maternal, neonatal and adolescent health.

Major strengths of this study were its prospective design and the highly standardized data collection and follow up of participants in diverse African sub-regions. In addition, the setting of a randomized controlled trial ensured high coverage of standard antenatal care including vitamin and micronutrient supplementation, insecticide treated bednets and availability of healthcare without access barriers. However, this analysis is not without limitations. Importantly this study only included HIV negative pregnant women willing to participate in the main clinical trial constituting a limitation for the external validity of this study. Furthermore the interplay between risk factors for adverse pregnancy outcome is complex and residual confounding may not be completely ruled out. To minimize this risk multivariable analysis and restricted analysis of data have been performed supporting the univariate findings.

In summary, this large prospective clinical trial provides conclusive evidence that young adolescent girls are at considerably higher risk for premature and low birth weight deliveries in sub-Saharan Africa. From a public health perspective young adolescent pregnant women constitute an easily identifiable patient population amenable to targeted antenatal care programs. Development of tailored antenatal care and facilitation of early attendance of antenatal care by young adolescent girls should therefore become a priority to improve adolescent health in sub-Saharan Africa.

**Authors' contribution**

GMN and MR conceived the study; GMN analysed the data and drafted the manuscript; MC, RG, PK, MY, AAA, JJA, CM, and MR reviewed all the aspects of the study design and analysis and contributed to drafting of the manuscript; JRM, RZM, AB, PBM, SO, AM, EM, RG, AM, SA, and GMN collected the data and contributed to data analysis and drafting of the manuscript. All authors approved the final version of the manuscript

**Conflict of interest**

Authors declare no conflict of interest

**Data sharing statement**

No additional data available

**Financial disclosure**

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