BMJ Open

Weekly miscarriage rates in a community-based prospective cohort study in rural western Kenya

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011088
Article Type:	Research
Date Submitted by the Author:	11-Jan-2016
Complete List of Authors:	Dellicour, stephanie; Liverpool School of Tropical Medicine, Clinical Sciences Aol, George; Kenya Medical Research Institute Centre for Global Health Research Ouma, Peter; Kenya Medical Research Institute Centre for Global Health Research Yan, Nicole; Liverpool School of Tropical Medicine Bigogo, Godfrey; Kenya Medical Research Institute Centre for Global Health Research Hamel, Mary; Centers for Disease Control and Prevention Office of Infectious Diseases Burton, Deron; Centers for Disease Control and Prevention Oneko, Martina; Kenya Medical Research Institute Centre for Global Health Research Breiman, Robert; Emory University , Global Health Institute Slutsker, Laurence; Centers for Disease Control and Prevention Feikin, Daniel; Centers for Disease Control and Prevention Kariuki, Simon; Kenya Medical Research Institute Centre for Global Health Research Odhiambo, Frank; Kenya Medical Research Institute Centre for Global Health Research Calip, Gregory; University of Illinois at Chicago Stergachis, Andreas; University of Washington School of Public Health Laserson, Kayla; Centers for Disease Control and Prevention ter Kuile, Feiko; Liverpool School of Tropical Medicine Desai, Meghna; Centers for Disease Control and Prevention
Primary Subject Heading:	Public health
Secondary Subject Heading:	Obstetrics and gynaecology, Epidemiology
Keywords:	Miscarriage, rate, prospective cohort, Kenya, sub-Saharan Africa

SCHOLARONE™ Manuscripts

Weekly miscarriage rates in a community-based prospective cohort study in rural western Kenya

Authors

Stephanie Dellicour*, Liverpool School of Tropical Medicine, Liverpool, UK, email: stephanie.dellicour@lstmed.ac.uk

George Aol, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: gaol@kemricdc.org

Peter Ouma, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: pouma@kemricdc.org

Nicole Yan, Liverpool School of Tropical Medicine, Liverpool, UK, email: nicole.yan@lstmed.ac.uk

Godfrey Bigogo, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: gbigogo@kemricdc.org

Mary J. Hamel, Centers for Disease Control and Prevention, Atlanta GA, USA, email: mlh8@cdc.gov

Deron C. Burton, Centers for Disease Control and Prevention, Atlanta GA, USA, email: akq7@cdc.gov

Martina Oneko, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: moneko@kemricdc.org

Robert F. Breiman, Global Health Institute, Emory University, Atlanta GA, USA, email: rfbreiman@emory.edu

Laurence Slutsker, Centers for Disease Control and Prevention, Atlanta GA, USA, email: lms5@cdc.gov

Daniel Feikin, Centers for Disease Control and Prevention, Atlanta GA, USA, email: drf0@cdc.gov

Simon Kariuki, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: skariuki@kemricdc.org

Frank Odhiambo, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: fodhiambo@kemricdc.org

Greg Calip, Pharmacy Systems, Outcomes and Policy Department, University of Illinois at Chicago, USA, email: gcalip@uic.edu

Andy Stergachis, Departments of Pharmacy and Global Health, Schools of Pharmacy and Public Health, University of Washington, Seattle, USA, email: stergach@uw.edu

Kayla F. Laserson, Centers for Disease Control and Prevention, Atlanta GA, USA and India, email: kel4@cdc.gov

Feiko O. ter Kuile, Liverpool School of Tropical Medicine, Liverpool, UK, email:
Feiko.TerKuile@lstmed.ac.uk

Meghna Desai, Centers for Disease Control and Prevention, Atlanta GA, USA, email: mud8@cdc.gov

*Corresponding author

Dr Stephanie Dellicour

Liverpool School of Tropical Medicine

Pembroke Place

Liverpool L3 5QA, UK

Tel: +44(0)151 705 3346

E-mail: stephanie.dellicour@lstmed.ac.uk

Abstract

Objective: Information on adverse pregnancy outcomes is important to monitor the impact of public health interventions. Miscarriage is a challenging endpoint to ascertain and there is scarce information on its rate in low income countries. The objective was to estimate the background rate and cumulative probability of miscarriage in rural western Kenya.

Design: This was a population-based prospective cohort

Participants and Setting: Women of childbearing age were followed prospectively to identify pregnancies and ascertain their outcomes in Siaya County, western Kenya. The cohort study was carried out in 33 adjacent villages under health and demographic surveillance.

Outcome measure: Miscarriage

Results: Between 2011 and 2013, among 5,536 women of childbearing age, 1,453 pregnancies were detected and 1,134 were included in the analysis. The rate of miscarriage over the first 28 weeks of gestation was 16.4 per 100 pregnancies (95% CI: 13.3- 20.4) and the cumulative probability was 18.9%. The weekly miscarriage rate declined steadily with increasing gestation until approximately 20 weeks. Known risk factors for miscarriage were confirmed such as maternal age, gravidity, occupation, household wealth and HIV infection.

Conclusion: This is the first report of weekly miscarriage rates in a rural African setting in the context of high HIV and malaria prevalence. Future studies should consider the involvement of community health workers to identify pregnancy cohort of early gestation for better data on the actual number of pregnancies and the assessment of miscarriage.

Key words

Miscarriage, rate, prospective cohort, Kenya, sub-Saharan Africa

Strengths and limitations of this study

- This study identified pregnancies early from the general population in a rural setting in western Kenya and refusal rate was low (6%).
- The study is strengthened by the use of survival analysis with left truncation and the life table method to estimate background rate and cumulative probability of miscarriage respectively.
- Misclassification between spontaneous and induced abortion cannot be ruled out, which is a limitation of the present study. Given estimates were within the expected range and that known risk factors for miscarriages could be confirmed, this is unlikely to have had substantial effect on the estimates.
- Estimates for the rate of miscarriage in early week of gestation were less precise due to the low numbers of pregnancies detected <6 weeks gestation.

Background

Miscarriage is a critical indicator of embryotoxicity and an important outcome for the study of embryotoxic effects of environmental, occupational and medication risks [1-3]. Furthermore it is a relevant endpoint to track the progress of reproductive health programs and their impact on maternal health. Without accounting for miscarriage, maternal and reproductive health related indicators miss a significant number of unreported pregnancies that are often not seen by the health system and are not recorded. For instance, indicators for antenatal care coverage is based on the total number of women who had a live birth in a specific time period not accounting for up to 30% of pregnancies that are lost either to miscarriage or stillbirth [4, 5]. This may lead to unrepresentative estimates of access and utilization of health care for high risk pregnancies ending in miscarriage or stillbirth. Despite this being a significant reproductive health outcome, data on miscarriage rates in low and middle income countries is scarce. Studies from industrialised countries report rates of miscarriage in clinically recognised pregnancies (i.e. from five gestational weeks following the last menstrual period (LMP)) that vary between 11% and 22% [6-9].

Miscarriage is a challenging endpoint to ascertain and accurate rates of miscarriage difficult to estimate. Crude rate estimates (i.e. dividing the number of miscarriages by the total number of pregnancies under study) are appropriate when it is possible to detect and enroll pregnancies from the time of conception from a representative sample of the population. Most miscarriages occur early in pregnancy prior to clinical detection of pregnancy [10]; the rapidly decreasing risk of miscarriage across the first trimester of pregnancy highlights the influence of gestational weeks at time of pregnancy detection in study or program settings on the estimated miscarriage rates. Therefore rate estimates should account for left truncation and estimates should account, as far as it is possible, for the actual number of pregnancies under observation at each specific gestational week [11-13]. Few studies have ascertained pregnancies close to the time of conception by enrolling participants that are planning to conceive and consent to regular pregnancy tests [7, 8, 14]. Since a significant proportion of pregnancies are unplanned[15], data from such population may have limited generalizability. Other studies recruiting women from antenatal clinics miss pregnancy loss occurring before initiation of antenatal care (ANC) and may also be prone to selection bias as women presenting early for antenatal care may represent higher risk pregnancies than women presenting later[11]. A low proportion of women initiate ANC in their first trimester in sub-Saharan Africa, recent estimates varied between 11%-54% [16-18]. The methodological constraints for measuring this outcome require early pregnancy detection and prospective follow up from a population-based representative sample of all women of childbearing age (WOCBA) to minimise selection bias. There are no published data on such studies in low income countries. The study presented here describes the rate of miscarriage and associated risk factors in a community based prospective cohort study of WOCBA in rural western Kenya.

Methods

Overview of study design

A prospective cohort of pregnant women was enrolled within a pharmacovigilance study to assess the risk of inadvertent first trimester exposures to artemisinin combination therapy (being reported elsewhere[19]) between February 2011 and February 2012. Pregnancies were identified as early as possible through health facility and community-based strategies (described below), and followed prospectively (i.e. before the pregnancy outcome was known) to document pregnancy outcome.

Study site

The study area was located in Siaya County, lying northeast of Lake Victoria in Nyanza Province, western Kenya. The cohort study was carried out in 33 adjacent villages under the Kenya Medical Research Institute-Centers for Disease Control and Prevention (KEMRI-CDC) health and demographic surveillance system area (KEMRI-CDC HDSS [20]). Nyanza Province has a high burden of disease and health indicators that are worse than overall Kenyan national statistics.[21] Malaria transmission is perennial and holo-endemic with peaks following the two rainy seasons. An annual cross-sectional survey in this area showed parasitaemia of 42% in under-5 years old, 60% in 5-14 years old and 20% in over 14 year old (unpublished KEMRI/CDC data for 2010). Whereas the national HIV prevalence is 6.3% (4% for men and 8% for women), the prevalence for Nyanza Province is close to double, around 14% (11% for men and 16% for women).[22]

Community mobilization and formative research

The acceptability of community-based pregnancy testing was unknown but important for this study. Community mobilisation activities included a series of meetings over several months with the District Medical Officer for Health, village chiefs, district officers and counsellors, the community advisory board was set up by KEMRI-CDC, and community members to introduce and get feedback on the proposed study plans. "Baraza" (community meetings) were held in all 33 villages within the study area. Study brochures were also distributed through the community meetings and at the central health facility. Formative research involving ten focus group discussions was carried out with the aim to explore the socio-cultural context around pregnancy and to investigate acceptability of proposed study procedures (reported elsewhere [23, 24]).

Recruitment of WOCBA and pregnancy detection

Following community mobilisation, door-to-door enrolment was carried out to inform eligible WOCBA. All women age 15-49 years resident in households within the defined HDSS catchment area and participating in a population-based disease surveillance project (PBIDS) [25, 26] were eligible for enrolment. Women were excluded if they refused to participate, were unable to provide informed consent due to mental, physical or social inability or if they refused to be followed up to the end of pregnancy. Enrolment was active throughout the study period whereby newly eligible women (who turned 15 years of age during the study period or in-migrant joining PBIDS) were invited to join the study.

WOCBA who consented to participate were asked if they might be pregnant and offered a pregnancy test at the time of enrolment and again approximately every three months thereafter by village-based community interviewers. Any participant with a detected pregnancy was referred to the antenatal clinic at the referral health facility, Lwak Hospital, where trained study nurses confirmed the pregnancy and offered free ANC. Additionally, all pregnant patients presenting at Lwak Hospital were assessed for study eligibility by a study nurse and enrolled if all selection criteria were met.

Gestational age assessment

Gestational age was assessed using multiple methods, including ultrasound scans at the first antenatal visit at Lwak ANC (for participants presenting before 24 weeks); reported first day of LMP; reported gestational age at the time of pregnancy loss; Ballard scoring for live-births captured within

3 days of delivery [27] ; and, fundal height measurements recorded at ANC. Not all methods were available for all pregnancies since some were not seen at ANC (no fundal height or ultrasound measurement available) or were seen at ANC but beyond 24 weeks. The Ballard score was only available for live-births seen within three days of delivery. Furthermore, some participants could not recall their LMP or, in some instances, had not resumed their menses since their previous pregnancy. For this analysis, gestational age was determined using the most accurate measurement available for each participant. Methods in order of decreasing accuracy were: ultrasound scan taken before 24 weeks gestation, Ballard estimates, LMP or reported gestation at time of pregnancy loss and lastly gestational age derived from fundal height assessment.

Risk factors

Obstetric history and ANC laboratory information collected routinely at antenatal booking (haemoglobin level, HIV and syphilis testing, and malaria microscopy) were extracted from the ANC records at Lwak Hospital or antenatal cards by study nurses. Demographic characteristics and medical history, including illnesses and drug used during the current pregnancy was collected through interviews at each study visit at ANC and at the time of pregnancy outcome follow up. Household level wealth quintiles were obtained from data collected routinely through the HDSS (such as occupation of household head, primary source of drinking water, use of cooking fuel, in-house assets [e.g. radio and television] and livestock) which were calculated as a weighted average using multiple correspondence analysis [28].

Pregnancy outcome

Pregnancy outcomes were assessed using a combination of health facility and home-based follow-ups. The latter is particularly relevant for miscarriages, because the vast majority of these events occur in the community and not in the health facilities. Village-based staff received monthly lists of participants with estimated delivery dates in their respective catchment area. Study nurses were notified of pregnancy outcomes by village-based staff and follow ups were done either at home or at the health facility. A detailed structured questionnaire about the delivery and outcome was administered face-to-face. Pregnancy outcomes captured included: pregnancy losses (miscarriages, induced abortions and stillbirths), live-births, and major congenital malformations detectable at birth by surface examination. We defined miscarriage, also called spontaneous abortion, as a pregnancy that ends spontaneously before 28 weeks gestation as per the World Health Organization definition of fetus viability [29]. A fetal death after viable gestational age is defined as a stillbirth.

Data analysis

Analyses were performed using Stata v12.1 (StataCorp LP, College Station, Texas). Survival analysis with left truncation was used to estimate the miscarriage rate by gestational week to account for delayed pregnancy detection and the range in gestational ages at the time of pregnancy detection. Left truncation was used to account for survival bias as the average gestational age that pregnancies were detected was around 13 weeks and only pregnancies that survived the early weeks of gestation (the highest risk of miscarriage) were followed prospectively[12, 30]. The life table methods were used to calculate the cumulative probability of survival and cumulative probability of miscarriage. Standard methods were used to calculate probability of miscarriage by gestational week [6]. In brief, the miscarriage rate during the specific week of gestation was converted to probability using the formula: (Miscarriage Rate)/(1+ (Miscarriage Rate x 0.5)). The remaining risk of miscarriage by gestational week was calculated by subtracting the probability of surviving the remaining weeks from 1. The probability of fetal survival during the remaining weeks was the product of the probability of survival for week x and the probability of survival for week x+1.

Ethical review and consent

The study was reviewed and approved by the institutional review boards of CDC (No. 5889), KEMRI (No. 1752) and the Liverpool School of Tropical Medicine (No. 09.70). Written informed consent or assent was obtained from each participant including consent to linking individual data to PBIDS and HDSS data.

Results

Participant enrolment and study uptake

Between February 15th 2011 and February 15th 2013, 5,536 (94% of 5911 WOCBA approached) consented to participate and 1,453 pregnancies among these women were detected; about 10% of participants were detected as pregnant at the time of enrolment. Refusal to take part in the study was low at 6% of screened participants, as were refusals to take pregnancy tests during follow up home visits (2%). Out of the 1,453 identified pregnancies, 1,134 (78%) were included in the data analysis for miscarriage; 319 were excluded because pregnancy detection occurred beyond 28 weeks gestation (219) or at the time of pregnancy outcome (33), lack of information on gestational age of exposure (21), loss to follow up immediately after pregnancy detection (41), or inconsistent pregnancy end dates (5) (figure 1). The 1,134 pregnancies involved a total of 1,079 women, 55 of whom had two pregnancies and 1,024 who had one pregnancy during the study period.

Overall, 62% of deliveries took place at a health facility, and 25% of identified miscarriages were cared for at a health facility. Sixty seven percent of pregnancy outcomes were captured less than one week after the end of pregnancy; however, for miscarriage this proportion was only 20%. The median number of days between outcome and follow up was 3 overall (range: 0-755) and 24 (range: 0-602) for miscarriage. This reflects the fact that follow ups were arranged at the convenience of participants and to ensure suitable amount of time between the event and home visit by study staff.

Participant characteristics and risk factors for miscarriage

The mean gestational age at time of pregnancy detection was 13.3 weeks (standard deviation [sd] 6.9) and median was 12.1 weeks. The mean maternal age was 26.1 years with women who miscarried being slightly older (29.5 [sd=8] years mean age vs 25.8 years [sd=7]) (Table 1). Overall the vast majority were married (79%) and about half of the women had completed primary education, but few had completed secondary school, with no significant difference between the groups. Farming was the main income generating activity for a higher proportion of women who miscarried compared to those with other pregnancy outcomes. There was a statistically significant difference in wealth between groups, with women who miscarried generally poorer than those with other pregnancy outcomes (Table 1). A higher proportion of miscarriage cases occurred in multigravid women with four or more pregnancies and about 25% of cases reported having a previous miscarriage (compared to 13% for other pregnancy outcomes). Only 26% of women who miscarried had any history of antenatal care (compared to 98% in the other group) which may reflect the fact that most miscarriages occur before the average gestational age (21 weeks) when women initiate ANC in this area. Consequently very few received any intermittent preventive treatment of malaria in pregnancy and an HIV test result was not available for over half of the miscarriage cases (since HIV tests are offered during first ANC visit). However, among those with known HIV status (44), 30% were HIV positive compared to 23% among those with other pregnancy outcomes.

Cumulative probability of miscarriage and rate per gestational week

There were 89 (7.9%) miscarriages among the 1,134 pregnancies included in the analysis. The mean gestational age at the time of miscarriage was 14.4 weeks (SD: 5.7) and the median was 13 weeks (range: 4.3-28); 75% of miscarriages occurred by 18 weeks. Overall the rate of miscarriage was 0.59 per 100 pregnancy-weeks (95%CI: 0.47- 0.73) calculated by survival analysis with left truncation and the rate of miscarriage over the first 28 weeks of pregnancy estimated at 16.4 per 100 pregnancy (95% CI: 13.3- 20.4). The cumulative probability of miscarriage was 18.9%. The weekly miscarriage rate declined steadily with increasing gestation (see Figure 2 and Table 2 for miscarriage weekly rates and probabilities) until approximately 16 to 20 weeks, after which it remained steady at approximately 0.3 per 100 pregnancy-weeks. Figure 3 shows the cumulative pregnancy survival probabilities per gestation week.

Discussion

This study provides the first description of the miscarriage rate in this rural Kenyan population in the context of high malaria and HIV prevalence; there are very little data on miscarriage background rate for sub-Saharan Africa in general. The cumulative probability of miscarriages by 28 weeks gestation accounting for staggered pregnancy detection in our study population was 18.9%, and the probability by week declined from 16 weeks onward. The true rate is likely to be higher as information from very early pregnancies (e.g. < 6 weeks gestation) was not captured and the average gestational age of pregnancy detection was 13.3 weeks, which meant that only 57% of pregnancies were detected during the highest risk period for miscarriage (the 1st trimester). However, the rate of 19% is similar to that reported by McGready *et al.* from the Thai-Burmese border (20%) [31] and consistent with that observed in other prospective studies in non-malarious areas, which ranges from 10% to 22% [6, 7, 9, 14]. Known risk factors for miscarriages were confirmed in this population, including older maternal age [32], more than three previous pregnancies[33], having a previous pregnancy loss [34], HIV infection [35, 36], occupation [2, 3] and lower household wealth[37].

Acceptability of pregnancy testing was surprisingly high and refusal to take a pregnancy test following enrolment remained around 2% throughout the home-based surveys. In this community, engaging trained village based staff to offer pregnancy tests through regular home-visits worked well as reflected by the high acceptance rate (94%) and low loss to follow up (8%). Since initiation of this study, other studies have used trained fieldworkers (both male and female) to do pregnancy detection and reported similar success. For future studies of miscarriage, we recommend working with the community to identify the most suitable approach to identify early pregnancy. Particular attention should be given to adolescent girls, and adequate youth-friendly referral services should be identified. Community health workers now being deployed in many sub-Saharan African countries [38] could play a key role in early pregnancy detection, thus providing better data on the actual number of pregnancies for programmatic planning and monitoring as well as referring pregnant women to initiate ANC in the first trimester.

A few limitations should be noted. Despite our best effort to capture pregnancy early, the relatively low numbers of pregnancy detected before 12 weeks gestation (508) generate moderately imprecise estimates and wide confidence intervals particularly in early weeks (<6 weeks gestation). Depending on the gestational age ascertainment method used there could have been more or less measurement error leading to misclassification of time at entry and exit in the cohort, and therefore miscarriage rate in a specific gestation week. Lastly, there is risk that induced abortions were misclassified as miscarriage or as lost to follow up. Kenya has strict laws on induced abortion, and it is only permitted if, according to a trained health professional, there is a need for emergency treatment, or the life or health of the mother is in danger, or if permitted by any other written law. Due to restrictive laws and stigmatization, underreporting is common. Nine induced abortions (<1%) were reported in this study which is much lower than a reported expected ratio of 30 abortions per 100 births for Kenya [39]. However it is probable that women consenting to participate in the study would be at lower risk of seeking induced abortion by accepting to be followed up through pregnancy. This could lead to selection bias but the refusal rate was low at 5% and therefore this is unlikely to affect estimates substantially.

Conclusion

This prospective cohort study in WOCBA provides the first estimates of weekly miscarriage rates in a rural African setting in the context of high HIV and malaria prevalence. This information should be valuable to researchers and program managers for resource planning, to monitor trends and impact of interventions as well as to clinicians in gauging miscarriage rates at a given gestational week. We have demonstrated the feasibility of conducting a community based pregnancy cohort in a resource-constrained setting for analysing the outcome of pregnancies with respect to miscarriage risk.

List of Abbreviations

ANC, antenatal care; CDC, US Centers for Disease Control and Prevention; HDSS, health and demographic surveillance system; KEMRI, Kenya Medical Research Institute; LMP, last menstrual period; PBIDS, population-based infectious disease surveillance

Competing interest

The authors declare that they have no competing interests.

Acknowledgements

The work presented in this paper was performed under the KEMRI and CDC Collaboration in western Kenya. We are very grateful to all participants for taking part in the study. We wish to thank the EMEP study team for their perseverance and hard work. Furthermore we wish to thank the Asembo District health and medical team and the Lwak Mission Hospital Board for their support. We also wish to thank Dr. John Williamson and Jane Bruce for the statistical support and advice. KEMRI-CDC HDSS is a member of the INDEPTH Network. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention. This paper is published with the permission of the KEMRI Director.

Authors contribution

Conceived and designed the experiments: SD FtK AS LS MJH. Conducted field work: SD GA PO MO GB. Analyzed the data: SD GC. Contributed data/analysis tools: GB DF RFB SK DB NY FO FtK. Interpreted the data: SD, DB, RFB, MJH, LS, DF, SK, KL, AS, MD, FtK. Wrote the first draft of the manuscript: SD FtK MD. All authors reviewed, revised and approved the final version of the manuscript.

Funding

This work was partly supported by the Malaria in Pregnancy (MiP) Consortium, which is funded through a grant from the Bill and Melinda Gates Foundation to the Liverpool School of Tropical Medicine, UK and partly by the US Centers for Disease Control and Prevention (CDC), Division of Parasitic Diseases and Malaria through a cooperative agreement with Kenya Medical Research Institute (KEMRI), Center for Global Health Research (CGHR), Kisumu, Kenya. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data sharing statement

Additional data are available by emailing the KEMRI/CDC Malaria Branch data manager: vwere@kemricdc.org.

References

1. Goldstein DJ, Sundell KL, DeBrota DJ, Offen WW: **Determination of pregnancy outcome risk rates after exposure to an intervention**. *Clinical pharmacology and therapeutics* 2001, **69**(1):7-13.
2. Kline JK: **Maternal occupation: effects on spontaneous abortions and malformations**. *Occup Med* 1986, **1**(3):381-403.
3. Kumar S: **Occupational, environmental and lifestyle factors associated with spontaneous abortion**. *Reproductive sciences* 2011, **18**(10):915-930.
4. **Millennium Development Goals Indicators** [http://mdgs.un.org/unsd/mdg/Metadata.aspx?IndicatorId=0&SeriesId=762]
5. World Health Organization: **Reproductive Health Indicators: Guidelines for their generation, interpretation and analysis for global monitoring.** . In. Geneva: World Health Organization; 2006.
6. Avalos LA, Galindo C, Li D-K: **A Systematic Review to Calculate Background Miscarriage Rates using Life Table Analysis**. *Birth Defects Research (Part A)* 2012, **94**(417).
7. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC: **Incidence of early loss of pregnancy**. *N Engl J Med* 1988, **319**(4):189-194.
8. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG: **Estimates of human fertility and pregnancy loss**. *Fertil Steril* 1996, **65**(3):503-509.
9. Ellish NJ, Saboda K, O'Connor J, Nasca PC, Stanek EJ, Boyle C: **A prospective study of early pregnancy loss**. *Hum Reprod* 1996, **11**(2):406-412.
10. Regan L, Rai R: **Epidemiology and the medical causes of miscarriage**. *Bailliere's best practice & research Clinical obstetrics & gynaecology* 2000, **14**(5):839-854.
11. Goldhaber MK, Fireman BH: **The fetal life table revisited: spontaneous abortion rates in three Kaiser Permanente cohorts**. *Epidemiology* 1991, **2**(1):33-39.
12. Howards PP, Hertz-Picciotto I, Poole C: **Conditions for bias from differential left truncation**. *Am J Epidemiol* 2007, **165**(4):444-452.
13. Margulis AV, Mittleman MA, Glynn RJ, Holmes LB, Hernandez-Diaz S: **Effects of gestational age at enrollment in pregnancy exposure registries**. *Pharmacoepidemiol Drug Saf* 2015, **24**(4):343-352.
14. Wang X, Chen C, Wang L, Chen D, Guang W, French J: **Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study**. *Fertil Steril* 2003, **79**(3):577-584.
15. Singh S, Sedgh G, Hussain R: **Unintended pregnancy: worldwide levels, trends, and outcomes**. *Studies in family planning* 2010, **41**(4):241-250.
16. Central Statistical Agency [Ethiopia], ICF International: **Ethiopia Demographic and Health Survey 2011**. In. Addis Ababa, Ethiopia and Calverton, Maryland, USA: Central Statistical Agency and ICF International; 2012.

17. Ghana Statistical Service (GSS), Ghana Health Service (GHS), ICF Macro: **Ghana Demographic and Health Survey 2008**. In. Accra, Ghana: GSS, GHS, and ICF Macro; 2009.
18. Pell C, Menaca A, Were F, Afrah NA, Chatio S, Manda-Taylor L, Hamel MJ, Hodgson A, Tagbor H, Kalilani L *et al*: **Factors affecting antenatal care attendance: results from qualitative studies in Ghana, Kenya and Malawi**. *PLoS One* 2013, **8**(1):e53747.
19. Dellicour S, Desai M, Aol G, Oneko M, Ouma P, Bigogo G, Burton D, Breiman RF, Hamel M, Slutsker L *et al*: **Risks of miscarriage and inadvertent exposure to artemisinin derivatives in the first trimester of pregnancy: a prospective study in western Kenya**. *In preparation*.
20. Odhiambo FO, Laserson KF, Sewe M, Hamel MJ, Feikin DR, Adazu K, Ogwang S, Obor D, Amek N, Bayoh N *et al*: **Profile: the KEMRI/CDC Health and Demographic Surveillance System--Western Kenya**. *Int J Epidemiol* 2012, **41**(4):977-987.
21. Kenya National Bureau of Statistics (KNBS) and ICF Macro: **Kenya Demographic and Health Survey 2008-09**. Calverton, Maryland, USA. http://www.measuredhs.com/pubs/pdf/FR229/FR229.pdf; 2011.
22. Kenya National Bureau of Statistics (KNBS), Macro I: **Kenya Demographic and Health Survey 2008-09**. In. Edited by Macro KaI. Calverton, Maryland; 2010.
23. Dellicour S, Desai M, Mason L, Odidi B, Aol G, Phillips-Howard PA, Laserson KF, Ter Kuile FO: **Exploring risk perception and attitudes to miscarriage and congenital anomaly in rural Western kenya**. *PLoS One* 2013, **8**(11):e80551.
24. Mason L., Dellicour S., Ter Kuile F., Ouma P., Phillips-Howard P., Were F., K. L, M. D: **Barriers and facilitators to antenatal and delivery care in western Kenya: a qualitative study**. *BMC Pregnancy and Childbirth* 2015, **15**(26).
25. Bigogo G, Audi A, Aura B, Aol G, Breiman RF, Feikin DR: **Health-seeking patterns among participants of population-based morbidity surveillance in rural western Kenya: implications for calculating disease rates**. *Int J Infect Dis* 2010, **14**(11):e967-973.
26. Feikin DR, Audi A, Olack B, Bigogo GM, Polyak C, Burke H, Williamson J, Breiman RF: **Evaluation of the optimal recall period for disease symptoms in home-based morbidity surveillance in rural and urban Kenya**. *Int J Epidemiol* 2010, **39**(2):450-458.
27. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R: **New Ballard Score, expanded to include extremely premature infants**. *The Journal of pediatrics* 1991, **119**(3):417-423.
28. McKenzie D: **Measuring inequality with asset indicators**. *Journal of Population Economics* 2005, **18**(2):229.
29. World Health Organization: **Spontaneous and Induced Abortion: Report of a WHO scientific group**. In: *WHO Technical Report Series.* vol. 461. Geneva; 1970.
30. Meister R, Schaefer C: **Statistical methods for estimating the probability of spontaneous abortion in observational studies--analyzing pregnancies exposed to coumarin derivatives**. *Reprod Toxicol* 2008, **26**(1):31-35.
31. McGready R, Lee SJ, Wiladphaingern J, Ashley EA, Rijken MJ, Boel M, Simpson JA, Paw MK, Pimanpanarak M, Mu O *et al*: **Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study**. *Lancet Infect Dis* 2012, **12**(5):388-396.
32. Smith KE, Buyalos RP: **The profound impact of patient age on pregnancy outcome after early detection of fetal cardiac activity**. *Fertil Steril* 1996, **65**(1):35-40.
33. Kline J: **I. An epidemiological review of the role of gravidity in spontaneous abortion**. *Early Hum Dev* 1978, **1**(4):337-344.
34. Regan L, Braude PR, Trembath PL: **Influence of past reproductive performance on risk of spontaneous abortion**. *BMJ* 1989, **299**(6698):541-545.
35. Brocklehurst P, French R: **The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis**. *Br J Obstet Gynaecol* 1998, **105**(8):836-848.

36. Temmerman M, Lopita MI, Sanghvi HC, Sinei SK, Plummer FA, Piot P: **The role of maternal syphilis, gonorrhoea and HIV-1 infections in spontaneous abortion**. *International journal of STD & AIDS* 1992, **3**(6):418-422.
37. Norsker FN, Espenhain L, S AR, Morgen CS, Andersen PK, Nybo Andersen AM: **Socioeconomic position and the risk of spontaneous abortion: a study within the Danish National Birth Cohort**. *BMJ open* 2012, **2**(3).
38. McCord GC, Liu A, Singh P: **Deployment of community health workers across rural sub-Saharan Africa: financial considerations and operational assumptions**. *Bulletin of the World Health Organization* 2013, **91**(4):244-253B.
39. African Population and Health Research Center, Ministry of Health Kenya, Ipas, Guttmacher Institute: **Incidence and Complications of Unsafe Abortion in Kenya: Key Findings of a National Study**. In. Nairobi, Kenya; 2013.

Table 1. Participant characteristics according to pregnancy outcomes (number and percentage in brackets or otherwise specified).

	Overall (N=1134)	Miscarriage (N=89)	Other Pregnancy Outcomes (n=1045)	P-values*	Rate of Miscarriage per 1000 pregnancy-weeks (95%CI)
Gestational age at detection in weeks (mean (SD))	13.3 (6.9; 0-27.9)	7.8 (4.4)	13.7 (6.9)	P=0.094	
Age in years (mean (SD))	26.1 (6.8)	29.5 (7.9)	25.8 (6.6)	**P<0.001**	
Age categories				**P<0.001**	
15-20	285 (25.1)	14 (15.7)	271 (25.9)		3.77 (2.28- 6.71)
21-25	287 (25.3)	14 (15.7)	273 (26.1)		3.47 (2.02- 6.47)
26-30	255 (22.5)	16 (18.0)	239 (22.9)		4.52 (2.81- 7.71)
31-35	179 (15.8)	21 (23.6)	158 (15.1)		8.81 (5.87-13.79)
>35	128 (11.3)	24 (27.0)	104 (10.0)		15.47 (10.26- 24.18)
Education level	*Missing n= 18*	*Missing n= 2*	*Missing n= 16*	P=0.634	
None/ Primary not completed	495 (44.4)	38 (43.7)	457 (44.4)		5.66 (4.10- 8.04)
Primary completed	533 (47.8)	44 (50.6)	489 (47.5)		6.26 (4.70- 8.51)
Secondary completed	88 (7.9)	5 (5.8)	83 (8.1)		4.11 (1.39- 17.15)
Occupation	*Missing n= 31*	*Missing n= 3*	*Missing n=28*	**P<0.001**	
Not working	379 (34.4)	22 (25.6)	357 (35.1)		4.70 (3.15- 7.32)
Farming	369 (33.5)	39 (45.4)	330 (32.5)		7.39 (5.37- 10.42)
Small business/Skilled Labour/Salaried	335 (30.4)	19 (22.1)	316 (31.1)		4.16 (2.69- 6.79)
Other	20 (1.8)	6 (7.0)	14 (1.4)		27.38 (11.81- 70.63)
Marital Status	*Missing n= 18*	*Missing n= 2*	*Missing n=16*	P=0.224	
Single	240 (21.5)	22 (25.3)	218 (21.2)		7.33 (4.81- 11.67)
Married	876 (78.51)	65 (74.7)	811 (78.8)		5.44 (4.26- 7.05)
Household wealth quintiles	*Missing n= 54*	*Missing n= 1*	*Missing n=53*	P=0.011	
poorest	105 (9.7)	18 (20.5)	87 (8.8)		13.55 (8.25- 23.39)
very poor	158 (14.6)	9 (10.2)	149 (15.0)		4.30 (2.28- 9.05)
poor	220 (20.4)	16 (18.2)	204 (25.6)		5.34 (3.24- 9.40)
less poor	269 (24.9)	22 (25.0)	247 (24.9)		6.04 (4.06- 9.37)
least poor	328 (30.4)	23 (26.1)	305 (30.8)		5.14 (3.40- 8.11)
Gravidity	*Missing n= 16*	*Missing n= 0*	*Missing n= 16*	**P<0.001**	
Primigravid	219 (19.6)	17 (19.3)	202 (19.6)		6.24 (3.93- 10.47)
1-3 pregnancies	525 (47.0)	23 (26.1)	502 (48.8)		3.10 (2.09- 4.81)
4+ pregnancies	374 (33.5)	49 (55.1)	325 (31.6)		10.20 (7.72- 13.70)
Previous pregnancy loss	160 (14.3), *Missing n=17*	22 (25.0), *Missing n= 1*	138 (13.4) , *Missing n= 16*	**P=0.001**	11.07 (7.38- 17.25)

	Overall (N=1134)	Miscarriage (N=89)	Other Pregnancy Outcomes (n=1045)	P-values*	Rate of Miscarriage per 1000 pregnancy-weeks (95%CI)
Antenatal Care Summary					
Gestational age at 1st ANC visit in weeks (mean (SD))*	20.8 (7.8) Range: 1.7-41.0	10.4 (4.9), missing n=71	21.0 (7.7), missing n=227	**P<0.001**	
Number of ANC visit	*Missing n=39*	*Missing n= 0*	*Missing n=39*	**P<0.001**	
none	89 (8.1)	66 (74.2)	23 (2.3)		110 (86.47-140)
1	90 (8.2)	18 (20.2)	72 (7.2)		16.58 (10.48-27.36)
2	155 (14.2)	1 (1.1)	154 (15.3)		0.46 **
3	244 (22.3)	3 (3.4)	241 (24.0)		0.91 (0.29-4.41)
4+	517 (47.2)	1 (1.1)	516 (51.3)		0.13 **
IPTp doses (HIV negative)	*Missing n= 280*	*Missing n= 18*	*Missing n= 265*	**P<0.001**	24.38 (19.25- 31.14)
none	242 (28.3)	73 (98.7)	169 (21.7)		0.85**
1	95 (11.1)	1 (1.4)	94 (12.1)		0.00
2	175 (20.5)	0	175 (22.4)		0.00
3	222 (26.0)	0	222 (28.5)		0.00
4	120 (14.1)	0	120 (15.4)		
Vaginal Bleeding	*Missing n= 298*	*Missing n= 71*	*Missing n= 227*	**P<0.001**	1.24 (0.75- 2.22)
No	813 (97.3)	14 (77.8)	799 (97.7)		13.96 (5.28- 46.69)
Yes	23 (2.8)	4 (22.2)	19 (2.3)		24.38 (19.25- 31.14)
ANC Profile at 1st ANC visit					
HIV positive				**P<0.001**	
Negative	771 (68.0)	17 (19.0)	754 (72.2)		1.57 (0.99- 2.64)
Positive	262 (23.1)	27 (30.3)	235 (22.5)		7.77 (5.27- 11.88)
Unknown	101 (8.9)	45 (50.6)	56 (5.4)		48.91 (35.79- 67.20)
Haemoglobin (mean (SD; range))	11.2 (1.9; 4.3-17.2) Missing n=309	12.4 (1.9) *missing n=72*	11.2 (1.9) *missing n=237*	**P=0.017**	
Anaemia (Hb<11g/dl)	*Missing n=309*	*Missing n=72*	*Missing n=237*	P=0.171	
No	476 (57.7)	13 (76.5)	463 (57.3)		1.91 (1.13- 3.49)
Yes	349 (42.3)	4 (23.5)	345 (42.7)		0.87 (0.33- 3.11)
Syphilis reactive test	*Missing n=226*	*Missing n=68*	*Missing n=158*	P=0.651	
Negative	838 (92.3)	20 (95.2)	818 (92.2)		1.70 (1.11- 2.73)
Positive	70 (7.7)	1 (4.8)	69 (7.8)		1.05 **
Malaria slide positive at 1st ANC visit	*Missing n=306*	*Missing n=71*	*Missing n=235*	P=0.747	
Negative	712 (86.0)	16 (88.9)	696 (85.9)		1.62 (1.01- 2.78)
Positive	116 (14.0)	2 (11.1)	114 (14.1)		1.24 (0.27-12.24)

*P value refers to log-rank test for categorical variables and to univariate Cox proportional hazard regression for continuous variables

**Confidence intervals are missing because of an insufficient number of failures

Table 2. Table of weekly miscarriage rate, cumulative probabilities of survival and of miscarriage and remaining risk of miscarriage at each gestation week.

Gestational week	Pregnancies Detected during week	Pregnancy-Weeks at Risk	Miscarriage	Induced abortion	Loss to follow up & withdrawals	Weekly miscarriage rate per 1000 pregnancy-weeks (95%CI)	Probability of miscarriage per gestational week	Probability of survival per gestational week	Cumulative probability of survival	Cumulative probability of miscarriage	Remaining probability of miscarriage
<4	48	32.3	0	1	1	0	0.000	1.000	1.000	0.000	0.189
4	42	67.4	2	0	0	29.66 (7.42- 120)	0.029	0.971	0.971	0.029	0.189
5	77	127.6	2	0	0	15.68 (3.92- 62.69)	0.016	0.984	0.956	0.044	0.165
6	79	200.1	5	0	0	24.98 (10.4- 60.02)	0.025	0.975	0.932	0.068	0.152
7	69	276.9	2	3	0	7.22 (1.81- 28.88)	0.007	0.993	0.925	0.075	0.130
8	71	334.1	3	1	1	8.98 (2.9- 27.84)	0.009	0.991	0.917	0.083	0.124
9	63	397.7	6	0	0	15.09 (6.78- 33.58)	0.015	0.985	0.903	0.097	0.116
10	59	451	7	0	0	15.52 (7.4- 32.56)	0.015	0.985	0.889	0.111	0.103
11	57	502.6	6	1	1	11.94 (5.36- 26.57)	0.012	0.988	0.879	0.121	0.088
12	52	548.3	12	1	1	21.89 (12.43- 38.54)	0.022	0.978	0.860	0.140	0.078
13	41	583.4	3	1	0	5.14 (1.66- 15.94)	0.005	0.995	0.855	0.145	0.057
14	52	626.6	4	0	1	6.38 (2.4- 17.01)	0.006	0.994	0.850	0.150	0.052
15	40	667.9	9	0	0	13.47 (7.01- 25.9)	0.013	0.987	0.839	0.161	0.046
16	43	703.1	2	0	0	2.84 (0.71- 11.37)	0.003	0.997	0.836	0.164	0.033
17	44	739.9	5	1	0	6.76 (2.81- 16.24)	0.007	0.993	0.831	0.169	0.030
18	30	769.1	5	0	0	6.5 (2.71- 15.62)	0.006	0.994	0.825	0.175	0.024
19	33	796.4	2	0	0	2.51 (0.63- 10.04)	0.003	0.997	0.823	0.177	0.018
20	26	823.9	4	0	1	4.86 (1.82- 12.94)	0.005	0.995	0.819	0.181	0.015
21	33	852.1	1	0	1	1.17 (0.17- 8.33)	0.001	0.999	0.818	0.182	0.010
22	23	873.4	0	0	1	0	0.000	1.000	0.818	0.182	0.009
23	36	905.6	1	0	0	1.1 (0.16- 7.84)	0.001	0.999	0.817	0.183	0.009
24	30	937.3	0	0	0	0	0.000	1.000	0.817	0.183	0.008
25	20	960.1	2	0	0	2.08 (0.52- 8.33)	0.002	0.998	0.816	0.184	0.008
26	38	994.4	4	0	0	4.02 (1.51- 10.72)	0.004	0.996	0.812	0.188	0.006
27	28	1016.9	2	0	12	1.97 (0.49- 7.86)	0.002	0.998	0.811	0.189	0.002

Figures

Figure 1. Study participant flow diagram from screening to inclusion in data analysis for miscarriage.

Figure 2. Miscarriage rate per 1000 pregnancy-week by week of gestation with upper and lower estimates of 95% confidence interval.

Figure 3. Miscarriage Kaplan Meier survival curve by gestational week.

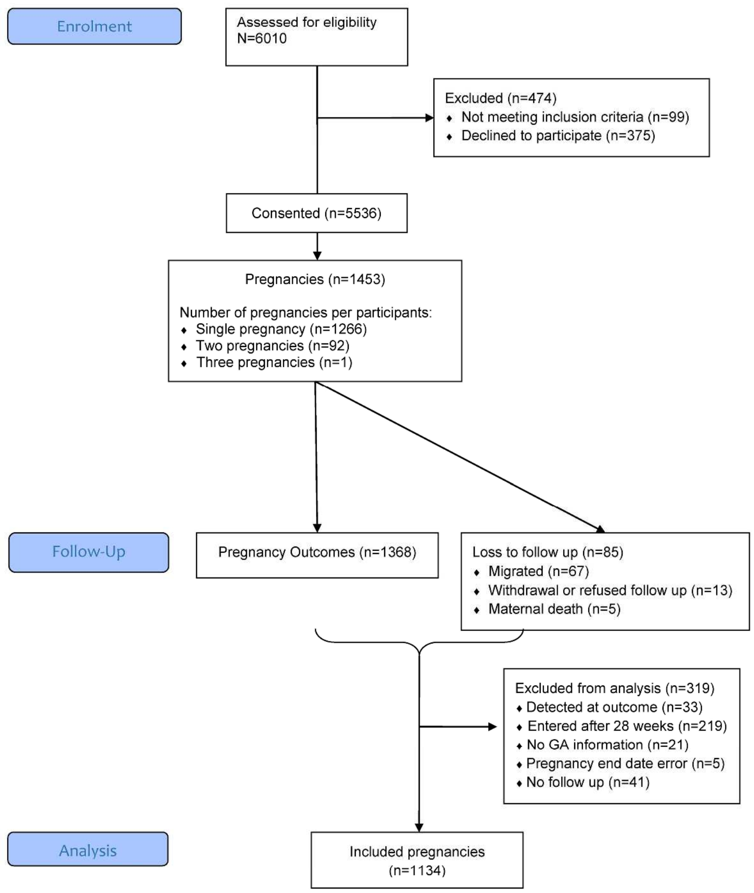


Figure 1. Study participant flow diagram from screening to inclusion in data analysis for miscarriage.
297x420mm (300 x 300 DPI)

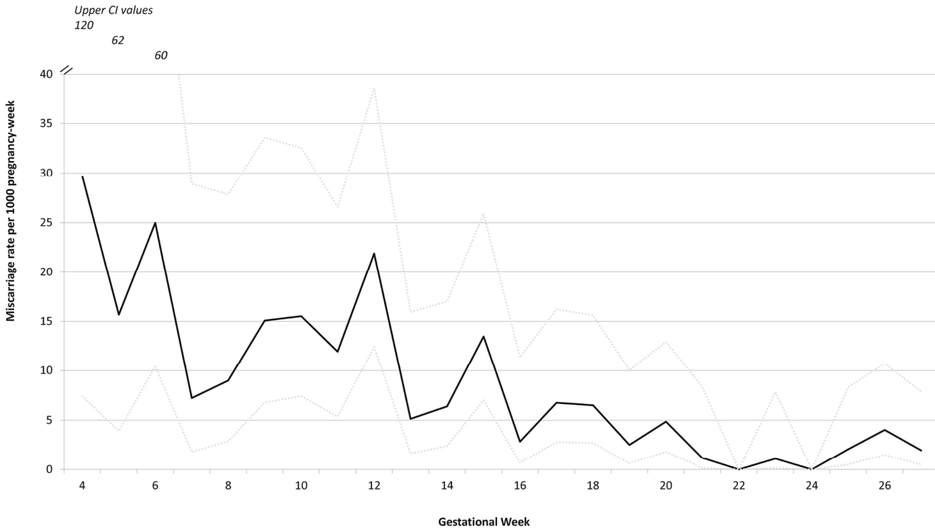


Figure 2. Miscarriage rate per 1000 pregnancy-week by week of gestation with upper and lower estimates of 95% confidence interval.
190x107mm (300 x 300 DPI)

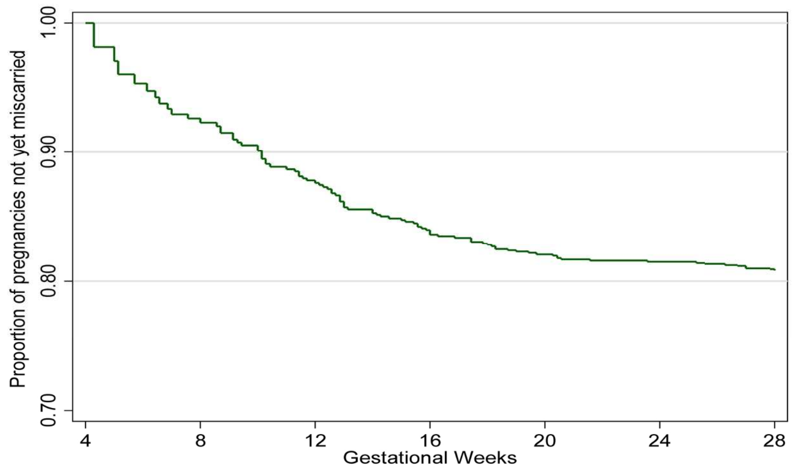


Figure 3. Miscarriage Kaplan Meier survival curve by gestational week.
190x107mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	√ p.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	√ p.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√ p.4
Objectives	3	State specific objectives, including any prespecified hypotheses	NA
Methods			
Study design	4	Present key elements of study design early in the paper	√ p.4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	√ p.5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	√ p.5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√ p.6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√ p.6
Bias	9	Describe any efforts to address potential sources of bias	√ p.6
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	√ p.6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	√ p.6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	√ p.6
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	√ p.7
		(b) Give reasons for non-participation at each stage	√ p.7
		(c) Consider use of a flow diagram	√ Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	√ p.7 & table 1
		(b) Indicate number of participants with missing data for each variable of interest	√ table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	√ p.8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	√ p.8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	√ p.8-9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	√ p.8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	√ p.8-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	√ p.9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Weekly miscarriage rates in a community-based prospective cohort study in rural western Kenya

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011088.R1
Article Type:	Research
Date Submitted by the Author:	08-Mar-2016
Complete List of Authors:	Dellicour, stephanie; Liverpool School of Tropical Medicine, Clinical Sciences Aol, George; Kenya Medical Research Institute Centre for Global Health Research Ouma, Peter; Kenya Medical Research Institute Centre for Global Health Research Yan, Nicole; Liverpool School of Tropical Medicine Bigogo, Godfrey; Kenya Medical Research Institute Centre for Global Health Research Hamel, Mary; Centers for Disease Control and Prevention Office of Infectious Diseases Burton, Deron; Centers for Disease Control and Prevention Oneko, Martina; Kenya Medical Research Institute Centre for Global Health Research Breiman, Robert; Emory University , Global Health Institute Slutsker, Laurence; Centers for Disease Control and Prevention Feikin, Daniel; Centers for Disease Control and Prevention Kariuki, Simon; Kenya Medical Research Institute Centre for Global Health Research Odhiambo, Frank; Kenya Medical Research Institute Centre for Global Health Research Calip, Gregory; University of Illinois at Chicago Stergachis, Andreas; University of Washington School of Public Health Laserson, Kayla; Centers for Disease Control and Prevention ter Kuile, Feiko; Liverpool School of Tropical Medicine Desai, Meghna; Centers for Disease Control and Prevention
Primary Subject Heading:	Public health
Secondary Subject Heading:	Obstetrics and gynaecology, Epidemiology
Keywords:	Miscarriage, rate, prospective cohort, Kenya, sub-Saharan Africa

SCHOLARONE™ Manuscripts

Weekly miscarriage rates in a community-based prospective cohort study in rural western Kenya

Authors

Stephanie Dellicour*, Liverpool School of Tropical Medicine, Liverpool, UK, email: stephanie.dellicour@lstmed.ac.uk

George Aol, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: gaol@kemricdc.org

Peter Ouma, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: pouma@kemricdc.org

Nicole Yan, Liverpool School of Tropical Medicine, Liverpool, UK, email: nicole.yan@lstmed.ac.uk

Godfrey Bigogo, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: gbigogo@kemricdc.org

Mary J. Hamel, Centers for Disease Control and Prevention, Atlanta GA, USA, email: mlh8@cdc.gov

Deron C. Burton, Centers for Disease Control and Prevention, Atlanta GA, USA, email: akq7@cdc.gov

Martina Oneko, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: moneko@kemricdc.org

Robert F. Breiman, Global Health Institute, Emory University, Atlanta GA, USA, email: rfbreiman@emory.edu

Laurence Slutsker, Centers for Disease Control and Prevention, Atlanta GA, USA, email: lms5@cdc.gov

Daniel Feikin, Centers for Disease Control and Prevention, Atlanta GA, USA, email: drf0@cdc.gov

Simon Kariuki, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: skariuki@kemricdc.org

Frank Odhiambo, Kenya Medical Research Institute Centre for Global Health Research, Kisumu, Kenya, email: fodhiambo@kemricdc.org

Greg Calip, Pharmacy Systems, Outcomes and Policy Department, University of Illinois at Chicago, USA, email: gcalip@uic.edu

Andy Stergachis, Departments of Pharmacy and Global Health, Schools of Pharmacy and Public Health, University of Washington, Seattle, USA, email: stergach@uw.edu

Kayla F. Laserson, Centers for Disease Control and Prevention, Atlanta GA, USA and India, email: kel4@cdc.gov

Feiko O. ter Kuile, Liverpool School of Tropical Medicine, Liverpool, UK, email:
Feiko.TerKuile@lstmed.ac.uk

Meghna Desai, Centers for Disease Control and Prevention, Atlanta GA, USA, email: mud8@cdc.gov

*Corresponding author

Dr Stephanie Dellicour

Liverpool School of Tropical Medicine

Pembroke Place

Liverpool L3 5QA, UK

Tel: +44(0)151 705 3346

E-mail: stephanie.dellicour@lstmed.ac.uk

Abstract

Objective: Information on adverse pregnancy outcomes is important to monitor the impact of public health interventions. Miscarriage is a challenging endpoint to ascertain and there is scarce information on its rate in low income countries. The objective was to estimate the background rate and cumulative probability of miscarriage in rural western Kenya.

Design: This was a population-based prospective cohort

Participants and Setting: Women of childbearing age were followed prospectively to identify pregnancies and ascertain their outcomes in Siaya County, western Kenya. The cohort study was carried out in 33 adjacent villages under health and demographic surveillance.

Outcome measure: Miscarriage

Results: Between 2011 and 2013, among 5,536 women of childbearing age, 1,453 pregnancies were detected and 1,134 were included in the analysis. The cumulative probability was 18.9%. The weekly miscarriage rate declined steadily with increasing gestation until approximately 20 weeks. Known risk factors for miscarriage such as maternal age, gravidity, occupation, household wealth and HIV infection were confirmed.

Conclusion: This is the first report of weekly miscarriage rates in a rural African setting in the context of high HIV and malaria prevalence. Future studies should consider the involvement of community health workers to identify pregnancy cohort of early gestation for better data on the actual number of pregnancies and the assessment of miscarriage.

Key words

Miscarriage, rate, prospective cohort, Kenya, sub-Saharan Africa

Strengths and limitations of this study

- This study identified pregnancies early from the general population in a rural setting in western Kenya and refusal rate was low (6%).
- The study is strengthened by the use of survival analysis with left truncation and the life table method to estimate weekly background rates and cumulative probability of miscarriage respectively.
- Misclassification between spontaneous and induced abortion cannot be ruled out, which is a limitation of the present study. Given estimates were within the expected range and that known risk factors for miscarriages could be confirmed, this is unlikely to have had substantial effect on the estimates.
- Estimates for the rate of miscarriage in early week of gestation were less precise due to the low numbers of pregnancies detected <6 weeks gestation.

Background

Miscarriage is the most common adverse pregnancy outcome with aggravating emotional consequences for affected individuals and families. It is also a critical indicator of embryotoxicity and an important outcome for the study of embryotoxic effects of environmental, occupational and medication risks [1-3]. Furthermore it is a relevant endpoint to track the progress of reproductive health programs and their impact on maternal health. Without accounting for miscarriage, maternal and reproductive health related indicators miss a significant number of unreported pregnancies that are often not seen by the health system and are not recorded. For instance, indicators for antenatal care coverage is based on the total number of women who had a live birth in a specific time period not accounting for up to 30% of pregnancies that are lost either to miscarriage or stillbirth [4, 5]. This may lead to unrepresentative estimates of access and utilization of health care for high risk pregnancies ending in miscarriage or stillbirth. Despite this being a significant reproductive health outcome, data on miscarriage rates in low and middle income countries is scarce. Studies from industrialised countries report rates of miscarriage in clinically recognised pregnancies (i.e. from five-six gestational weeks following the last menstrual period (LMP), the common gestational age for pregnancy recognition) that vary between 11% and 22% [6-9]. When taking into account early miscarriage for pregnancies diagnosed by human chorionic gonadotropin (HCG) or ultrasound before the appearance of fetal heart activity, reported rates are closer to 30% [7].

Miscarriage is a challenging endpoint to ascertain and accurate rates of miscarriage difficult to estimate. There are methodological complexities of conducting studies to assess miscarriage rate [10] which relate to the difficulties in identifying a representative sample of pregnancies at time of conception; the confirmation of suspected pregnancy and the determination of the exact timing of pregnancy loss. To accurately capture all pregnancy losses in a population, a study needs to be able to identify pregnancies from the time of conception and follow them prospectively. Early pregnancy losses, which occur before a pregnancy is usually recognised (i.e. <5-6 weeks gestation), can only be detected by frequently repeated highly sensitive pregnancy tests.

Few studies have been designed to detect such early pregnancy loss and ascertained pregnancies close to the time of conception by enrolling participants that are planning to conceive and consent to regular pregnancy tests [7-9, 11-13]. Since a significant proportion of pregnancies are unplanned[14], data from these studies may have limited generalizability. Other studies recruiting women from antenatal clinics miss pregnancy loss occurring before initiation of antenatal care (ANC) and may also be prone to selection bias as women presenting early for antenatal care may represent higher risk pregnancies than women presenting later[15]. The assigned timing of miscarriage is usually based on the time of clinical recognition of pregnancy loss however fetal death may have occurred weeks before [16].

Studies of miscarriage in low and middle income countries face additional challenges as most miscarriages occur without any contact with the formal healthcare system and are not registered. As pregnant women usually present for antenatal care late in pregnancy (with an estimated 11%-54% of women initiating ANC in the first trimester [17-19] and most presenting late in the second trimester), health facility based recruitment and data collection strategies are inappropriate. In such settings the study of miscarriage requires a community based approach taking into account the different cultural and superstitious beliefs that may affect pregnancy disclosure and detection [19-

21]. Furthermore reliable data on gestational age is difficult to obtain as ultrasound scans are rarely available and date of last menstrual period may not be reliable in settings with limited literacy [22, 23]. There is also a higher risk of misclassification of induced abortions as spontaneous abortions as the former are illegal in most of these settings. The methodological constraints for measuring this outcome require early pregnancy detection and prospective follow up from a population-based representative sample of all women of childbearing age (WOCBA) to minimise selection bias. There are no published data on such studies in low income countries. The study presented here describes the rate of miscarriage and associated risk factors in a community based prospective cohort study of WOCBA in rural western Kenya.

Methods

Overview of study design

A prospective cohort of pregnant women was enrolled within a pharmacovigilance study to assess the risk of inadvertent first trimester exposures to artemisinin combination therapy (being reported elsewhere[24]) between February 2011 and February 2013. Pregnancies were identified as early as possible through health facility and community-based strategies (described below), and followed prospectively (i.e. before the pregnancy outcome was known) to document pregnancy outcome.

Study site

The study area was located in Siaya County, lying northeast of Lake Victoria in Nyanza Province, western Kenya. The cohort study was carried out in 33 adjacent villages under the Kenya Medical Research Institute-Centers for Disease Control and Prevention (KEMRI-CDC) health and demographic surveillance system area (KEMRI-CDC HDSS [25]). Nyanza Province has a high burden of disease and health indicators that are worse than overall Kenyan national statistics.[26] Malaria transmission is high with parasitaemia of 20% in over 14 year old (unpublished KEMRI/CDC data for 2010). Whereas the national HIV prevalence is 6.3% (4% for men and 8% for women), the prevalence for Nyanza Province is close to double, around 14% (11% for men and 16% for women).[27] The total fertility rate in the area was 5.4 and around a third of currently married women age 15-49 used a modern contraceptive method according to a health and demographic survey in 2008-9[26].

Community mobilization and formative research

The acceptability of community-based pregnancy testing was unknown but important for this study. Community mobilisation activities included a series of meetings over several months with the District Medical Officer for Health, village chiefs, district officers and counsellors, the community advisory board was set up by KEMRI-CDC, and community members to introduce and get feedback on the proposed study plans. "Baraza" (community meetings) were held in all 33 villages within the study area. Study brochures were also distributed through the community meetings and at the central health facility. Formative research involving ten focus group discussions was carried out with the aim to explore the socio-cultural context around pregnancy and to investigate acceptability of proposed study procedures (reported elsewhere [28, 29]).

Recruitment of WOCBA and pregnancy detection

Following community mobilisation, door-to-door enrolment was carried out to inform eligible WOCBA. All women age 15-49 years resident in households within the defined HDSS catchment area and participating in a population-based disease surveillance project (PBIDS) [30, 31] were eligible for enrolment. Women were excluded if they refused to participate, were unable to provide informed consent due to mental, physical or social inability or if they refused to be followed up to the end of pregnancy. Enrolment was active throughout the study period whereby newly eligible women (who turned 15 years of age during the study period or in-migrant joining PBIDS) were invited to join the study.

WOCBA who consented to participate were asked if they might be pregnant and offered a pregnancy test at the time of enrolment if they were not visibly pregnant and again approximately every three months from October 2011 onwards by village-based community interviewers. Any participant with a detected pregnancy was referred to the antenatal clinic at the referral health facility, Lwak Hospital, where trained study nurses confirmed the pregnancy through ultrasound or examination and auscultation for gestations >24 weeks and offered free ANC. Additionally, all pregnant patients presenting at Lwak Hospital ANC were assessed for study eligibility by a study nurse and enrolled if all selection criteria were met.

Gestational age assessment

Gestational age was assessed using multiple methods, including ultrasound scans at the first antenatal visit at Lwak ANC (for participants presenting before 24 weeks); reported first day of LMP; reported gestational age at the time of pregnancy loss; Ballard scoring for live-births captured within 3 days of delivery [32] ; and, fundal height measurements recorded at ANC. Not all methods were available for all pregnancies since some were not seen at ANC (no fundal height or ultrasound measurement available) or were seen at ANC but beyond 24 weeks. The Ballard score was only available for live-births seen within three days of delivery. Furthermore, some participants could not recall their LMP or, in some instances, had not resumed their menses since their previous pregnancy. For this analysis, gestational age was determined using the most accurate measurement available for each participant. Methods in order of decreasing accuracy were: ultrasound scan taken before 24 weeks gestation, Ballard estimates, LMP or reported gestation at time of pregnancy loss and lastly gestational age derived from fundal height assessment.

Risk factors

Obstetric history and ANC laboratory information collected routinely at antenatal booking (haemoglobin level, HIV and syphilis testing, and malaria microscopy) were extracted from the ANC records at Lwak Hospital or antenatal cards by study nurses. Demographic characteristics was collected through interviews at ANC or at the time of pregnancy outcome follow up if the participant was not seen at ANC. Household level wealth quintiles were obtained from data collected routinely through the HDSS (such as occupation of household head, primary source of drinking water, use of cooking fuel, in-house assets [e.g. radio and television] and livestock) which were calculated as a weighted average using multiple correspondence analysis [33].

Pregnancy outcome

Pregnancy outcomes were assessed using a combination of health facility and home-based follow-ups. The latter is particularly relevant for miscarriages, because the vast majority of these events occur in the community and not in the health facilities. Village-based staff received monthly lists of participants with estimated delivery dates in their respective catchment area. Study nurses were notified of pregnancy outcomes by village-based staff and follow ups were done either at home or at the health facility. A detailed structured questionnaire about the delivery and outcome was administered face-to-face. Pregnancy outcomes captured included: pregnancy losses (miscarriages, induced abortions and stillbirths), live-births, and major congenital malformations detectable at birth by surface examination. We defined miscarriage, also called spontaneous abortion, as a pregnancy that ends spontaneously before 28 weeks gestation as per the World Health Organization definition of fetus viability [34]. A fetal death after viable gestational age is defined as a stillbirth.

Data analysis

Analyses were performed using Stata v12.1 (StataCorp LP, College Station, Texas). Survival analysis with left truncation was used to estimate the miscarriage rate by gestational week to account for delayed pregnancy detection and the range in gestational ages at the time of pregnancy detection. Crude rate estimates (i.e. dividing the number of miscarriages by the total number of pregnancies under study) are appropriate when it is possible to detect and enrol pregnancies from the time of conception. Most miscarriages occur early in pregnancy prior to clinical detection of pregnancy [35]; the rapidly decreasing risk of miscarriage across the first trimester of pregnancy highlights the influence of gestational weeks at time of pregnancy detection in study or program settings on the estimated miscarriage rates. Therefore rate estimates should account for left truncation (early pregnancy) and, as far as it is possible, for the actual number of pregnancies under observation at each specific gestational week [15, 36, 37]. Left truncation was used to account for survival bias as the average gestational age that pregnancies were detected was around 13 weeks and only pregnancies that survived the early weeks of gestation (the highest risk of miscarriage) were followed prospectively[36, 38]. The life table methods were used to calculate the cumulative probability of survival and cumulative probability of miscarriage. Standard methods were used to calculate probability of miscarriage by gestational week [6]. In brief, the miscarriage rate during the specific week of gestation was converted to probability using the formula: (Miscarriage Rate)/(1+ (Miscarriage Rate x 0.5)). The remaining risk of miscarriage by gestational week was calculated by subtracting the probability of surviving the remaining weeks from 1. The probability of fetal survival during the remaining weeks was the product of the probability of survival for week x and the probability of survival for week x+1. Cox proportional hazard regression models with left truncation were fitted to estimate the effect of risk factors on miscarriage.[36].

Ethical review and consent

The study was reviewed and approved by the institutional review boards of CDC (No. 5889), KEMRI (No. 1752) and the Liverpool School of Tropical Medicine (No. 09.70). Written informed consent or assent was obtained from each participant including consent to linking individual data to PBIDS and HDSS data.

Results

Participant enrolment and study uptake

Between February 15th 2011 and February 15th 2013, 5,536 (94% of 5911 WOCBA approached) consented to participate and 1,453 pregnancies among these women were detected; about 10% of participants were detected as pregnant at the time of enrolment. Refusal to take part in the study was low at 6% of screened participants, as were refusals to take pregnancy tests during follow up home visits (2%). Out of the 1,453 identified pregnancies, 1,134 (78%) were included in the data analysis for miscarriage; 319 were excluded because pregnancy detection occurred beyond 28 weeks gestation (219) or at the time of pregnancy outcome (33), lack of information on gestational age

(21), loss to follow up immediately after pregnancy detection (41), or inconsistent pregnancy end dates (5) (figure 1). The 1,134 pregnancies involved a total of 1,079 women, 55 of whom had two pregnancies and 1,024 who had one pregnancy during the study period. Figure 2 depicts the number of pregnancies detected by the different strategies.

Overall, 62% of deliveries took place at a health facility, and 25% of identified miscarriages were cared for at a health facility. Sixty seven percent of pregnancy outcomes were captured less than one week after the end of pregnancy; however, for miscarriage this proportion was only 20%. The median number of days between outcome and follow up was 3 overall (range: 0-755) and 24 (range: 0-602) for miscarriage. This reflects the fact that follow ups were arranged at the convenience of participants and to ensure suitable amount of time between the event and home visit by study staff.

Participant characteristics and risk factors for miscarriage

The mean gestational age at time of pregnancy detection was 13.3 weeks (standard deviation [sd] 6.9) and median was 12.1 weeks. The mean gestational age at time of detection decreased over the study period with the introduction of 3 monthly home visits (Figure 2). The mean maternal age was 26.1 years with women who miscarried being slightly older (29.5 [sd=8] years mean age vs 25.8 years [sd=7]) (Table 1). Overall the vast majority were married (79%) and about half of the women had completed primary education, but few had completed secondary school, with no significant difference between the groups. Farming was the main income generating activity for a higher proportion of women who miscarried compared to those with other pregnancy outcomes. There was a statistically significant difference in wealth between groups, with women who miscarried generally poorer than those with other pregnancy outcomes (Table 1). A higher proportion of miscarriage cases occurred in multigravid women with four or more pregnancies and about 25% of cases reported having a previous miscarriage (compared to 13% for other pregnancy outcomes). Only 26% of women who miscarried had any history of antenatal care (compared to 98% in the other group) which may reflect the fact that most miscarriages occur before the average gestational age (21 weeks) when women initiate ANC in this area. Consequently very few received any intermittent preventive treatment of malaria in pregnancy and an HIV test result was not available for over half of the miscarriage cases (since HIV tests are offered during first ANC visit). However, among those with known HIV status (44), 30% of those who miscarried were HIV positive compared to 23% among those with other pregnancy outcomes.

Cumulative probability of miscarriage and rate per gestational week

There were 89 (7.9%) miscarriages among the 1,134 pregnancies included in the analysis. The mean gestational age at the time of miscarriage was 14.4 weeks (SD: 5.7) and the median was 13 weeks (range: 4.3-28); 75% of miscarriages occurred by 18 weeks. The cumulative probability of miscarriage calculated through the life-table method was 18.9%.Overall the rate of miscarriage was 0.59 per 100 pregnancy-weeks (95%CI: 0.47- 0.73) calculated by survival analysis with left truncation. The weekly miscarriage rate declined steadily with increasing gestation (see Figure 3 and Table 2 for miscarriage weekly rates and probabilities) until approximately 16 to 20 weeks, after which it remained steady at approximately 0.3 per 100 pregnancy-weeks. Figure 4 shows the cumulative pregnancy survival probabilities per gestation week.

Discussion

This study provides the first description of the miscarriage rate in this rural Kenyan population in the context of high malaria and HIV prevalence; there are very little data on miscarriage background rate for sub-Saharan Africa in general. The cumulative probability of miscarriages by 28 weeks gestation accounting for staggered pregnancy detection in our study population was 18.9%, and the probability by week declined from 16 weeks onward. The true rate is likely to be higher as information from very early pregnancies (e.g. < 6 weeks gestation) was not captured and the average gestational age of pregnancy detection was 13.3 weeks, which meant that only 57% of pregnancies were detected during the highest risk period for miscarriage (the 1st trimester). However, this represents a more accurate estimate of the risk of miscarriage than the crude prevalence of 7.9% as pregnancies were not observed from the time of conception and entered the study at different gestational ages[6, 10, 15]. The rate of 19% is similar to that reported by McGready *et al.* from the Thai-Burmese border (20%) [39] and consistent with that observed in other prospective studies in non-malarious areas, which ranges from 10% to 22%. Known risk factors for miscarriages were confirmed in this population, including older maternal age [40], more than three previous pregnancies[41], having a previous pregnancy loss [42], HIV infection [43, 44], occupation [2, 3] and lower household wealth[45].

Acceptability of pregnancy testing was surprisingly high and refusal to take a pregnancy test following enrolment remained around 2% throughout the home-based surveys. Women in this setting are usually reluctant to disclose their pregnancy status due to cultural and superstitious beliefs about pregnancy disclosure. This has been recognised as one of the reasons for delay in seeking antenatal care[19, 21]. Women are worried about gossip, witchcraft particularly in the early stage of pregnancy, being accused of boastfulness and embarrassment in case of later pregnancy loss. For unmarried and/or young girls, pregnancy is not disclosed due to fear of social repercussions. Before initiation of the study, no information was available on the acceptability of pregnancy tests in a similar rural community; our formative research indicated very few women were even aware such tests existed. In this community, engaging trained village based staff to offer pregnancy tests through regular home-visits worked well as reflected by the high acceptance rate (94%) and low loss to follow up (8%). Since initiation of this study, other studies have used trained fieldworkers (both male and female) to do pregnancy detection and reported similar success. For future studies of miscarriage, we recommend working with the community to identify the most suitable approach to identify early pregnancy. Community health workers now being deployed in many sub-Saharan African countries [46] could play a key role in early pregnancy detection, thus providing better data on the actual number of pregnancies for programmatic planning and monitoring as well as referring pregnant women to initiate ANC in the first trimester.

A few limitations should be noted. Despite our best effort to capture pregnancy early, the relatively low numbers of pregnancy detected before 12 weeks gestation (508) generate moderately imprecise estimates and wide confidence intervals particularly in early (<6 weeks) gestation. Depending on the gestational age ascertainment method used there could have been more or less measurement error leading to misclassification of time at entry and exit in the cohort, and therefore miscarriage rate in a specific gestation week. There could have been error in the estimation of gestation at the time of miscarriage since this was largely self-reported sometimes months after the event. There is risk that induced abortions were misclassified as miscarriage or as lost to follow up. Kenya has strict laws on induced abortion, and it is only permitted if, according to a trained health professional, there is a need for emergency treatment, or the life or health of the mother is in danger, or if permitted by any other written law. Due to restrictive laws and stigmatization, underreporting is common. Nine induced abortions (<1%) were reported in this study which is much lower than a reported expected ratio of 30 abortions per 100 births for Kenya [47]. However it is probable that women consenting to participate in the study would be at lower risk of seeking induced abortion by accepting to be followed up through pregnancy. This could lead to selection bias but the refusal rate was low at 5% and therefore this is unlikely to affect estimates substantially. Lastly, as HIV and malaria are known risk factors for miscarriage [39, 43, 44, 48] and are highly prevalent in this area, this may influence generalizability of study findings to areas with differing disease burden.

Conclusion

This prospective cohort study in WOCBA provides the first estimates of weekly miscarriage rates in a rural African setting in the context of high HIV and malaria prevalence. This information should be valuable to researchers and program managers for resource planning, to monitor trends and impact of interventions as well as to clinicians in gauging miscarriage rates at a given gestational week. We have demonstrated the feasibility of conducting a community based pregnancy cohort in a resource-constrained setting for analysing the outcome of pregnancies with respect to miscarriage risk.

List of Abbreviations

ANC, antenatal care; CDC, US Centers for Disease Control and Prevention; HDSS, health and demographic surveillance system; KEMRI, Kenya Medical Research Institute; LMP, last menstrual period; PBIDS, population-based infectious disease surveillance

Competing interest

The authors declare that they have no competing interests.

Acknowledgements

The work presented in this paper was performed under the KEMRI and CDC Collaboration in western Kenya. We are very grateful to all participants for taking part in the study. We wish to thank the EMEP study team for their perseverance and hard work, particularly: Jane Oiro, Teresa Aluoch, Elizabeth Aballa, Emily Ayanga, Everlyne Oteyo, Everline Ochola, Faith Samo, Eric Onyango and Joshua Auko. Furthermore we wish to thank the Asembo District health and medical team and the Lwak Mission Hospital Board for their support. We also wish to thank Dr. John Williamson and Jane Bruce for the statistical support and advice. KEMRI-CDC HDSS is a member of the INDEPTH Network. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention. This paper is published with the permission of the KEMRI Director.

Authors contribution

Conceived and designed the experiments: SD FtK AS LS MJH. Conducted field work: SD GA PO MO GB. Analyzed the data: SD GC. Contributed data/analysis tools: GB DF RFB SK DB NY FO FtK. Interpreted the data: SD, DB, RFB, MJH, LS, DF, SK, KL, AS, MD, FtK. Wrote the first draft of the manuscript: SD FtK MD. All authors reviewed, revised and approved the final version of the manuscript.

Funding

This work was partly supported by the Malaria in Pregnancy (MiP) Consortium, which is funded through a grant from the Bill and Melinda Gates Foundation to the Liverpool School of Tropical Medicine, UK and partly by the US Centers for Disease Control and Prevention (CDC), Division of Parasitic Diseases and Malaria through a cooperative agreement with Kenya Medical Research Institute (KEMRI), Center for Global Health Research (CGHR), Kisumu, Kenya. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data sharing statement

The anonymised dataset will be available upon request from the data manager at KEMRI: vwere@kemricdc.org

References

1. Goldstein DJ, Sundell KL, DeBrota DJ, Offen WW: **Determination of pregnancy outcome risk rates after exposure to an intervention**. *Clinical pharmacology and therapeutics* 2001, **69**(1):7-13.
2. Kline JK: **Maternal occupation: effects on spontaneous abortions and malformations**. *Occup Med* 1986, **1**(3):381-403.
3. Kumar S: **Occupational, environmental and lifestyle factors associated with spontaneous abortion**. *Reproductive sciences* 2011, **18**(10):915-930.
4. **Millennium Development Goals Indicators** [http://mdgs.un.org/unsd/mdg/Metadata.aspx?IndicatorId=0&SeriesId=762]
5. World Health Organization: **Reproductive Health Indicators: Guidelines for their generation, interpretation and analysis for global monitoring.** . In. Geneva: World Health Organization; 2006.
6. Avalos LA, Galindo C, Li D-K: **A Systematic Review to Calculate Background Miscarriage Rates using Life Table Analysis**. *Birth Defects Research (Part A)* 2012, **94**(417).
7. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC: **Incidence of early loss of pregnancy**. *N Engl J Med* 1988, **319**(4):189-194.
8. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG: **Estimates of human fertility and pregnancy loss**. *Fertil Steril* 1996, **65**(3):503-509.
9. Ellish NJ, Saboda K, O'Connor J, Nasca PC, Stanek EJ, Boyle C: **A prospective study of early pregnancy loss**. *Hum Reprod* 1996, **11**(2):406-412.
10. Modvig J, Schmidt L, Damsgaard MT: **Measurement of total risk of spontaneous abortion: the virtue of conditional risk estimation**. *Am J Epidemiol* 1990, **132**(6):1021-1038.
11. Wang X, Chen C, Wang L, Chen D, Guang W, French J: **Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study**. *Fertil Steril* 2003, **79**(3):577-584.
12. Eskenazi B, Gold EB, Lasley BL, Samuels SJ, Hammond SK, Wight S, O'Neill Rasor M, Hines CJ, Schenker MB: **Prospective monitoring of early fetal loss and clinical spontaneous abortion among female semiconductor workers**. *American journal of industrial medicine* 1995, **28**(6):833-846.
13. Sweeney AM, Meyer MR, Aarons JH, Mills JL, LaPorte RE: **Evaluation of methods for the prospective identification of early fetal losses in environmental epidemiology studies**. *Am J Epidemiol* 1988, **127**(4):843-850.
14. Singh S, Sedgh G, Hussain R: **Unintended pregnancy: worldwide levels, trends, and outcomes**. *Studies in family planning* 2010, **41**(4):241-250.
15. Goldhaber MK, Fireman BH: **The fetal life table revisited: spontaneous abortion rates in three Kaiser Permanente cohorts**. *Epidemiology* 1991, **2**(1):33-39.

16. S. M: **Timing of gestational arrest prior to miscarriage.** Nashville, Tennessee: Vanderbilt University; 2014.
17. Central Statistical Agency [Ethiopia], ICF International: **Ethiopia Demographic and Health Survey 2011**. In. Addis Ababa, Ethiopia and Calverton, Maryland, USA: Central Statistical Agency and ICF International; 2012.
18. Ghana Statistical Service (GSS), Ghana Health Service (GHS), ICF Macro: **Ghana Demographic and Health Survey 2008**. In. Accra, Ghana: GSS, GHS, and ICF Macro; 2009.
19. Pell C, Menaca A, Were F, Afrah NA, Chatio S, Manda-Taylor L, Hamel MJ, Hodgson A, Tagbor H, Kalilani L *et al*: **Factors affecting antenatal care attendance: results from qualitative studies in Ghana, Kenya and Malawi**. *PLoS One* 2013, **8**(1):e53747.
20. Haws RA, Mashasi I, Mrisho M, Schellenberg JA, Darmstadt GL, Winch PJ: **"These are not good things for other people to know": how rural Tanzanian women's experiences of pregnancy loss and early neonatal death may impact survey data quality**. *Social science & medicine* 2010, **71**(10):1764-1772.
21. Stokes E, Dumbaya I, Owens S, Brabin L: **The right to remain silent: a qualitative study of the medical and social ramifications of pregnancy disclosure for Gambian women**. *BJOG : an international journal of obstetrics and gynaecology* 2008, **115**(13):1641-1647; discussion 1647.
22. Verhoeff FH, Milligan P, Brabin BJ, Mlanga S, Nakoma V: **Gestational age assessment by nurses in a developing country using the Ballard method, external criteria only**. *Annals of tropical paediatrics* 1997, **17**(4):333-342.
23. White LJ, Lee SJ, Stepniewska K, Simpson JA, Dwell SL, Arunjerdja R, Singhasivanon P, White NJ, Nosten F, McGready R: **Estimation of gestational age from fundal height: a solution for resource-poor settings**. *Journal of the Royal Society, Interface / the Royal Society* 2012, **9**(68):503-510.
24. Dellicour S, Desai M, Aol G, Oneko M, Ouma P, Bigogo G, Burton D, Breiman RF, Hamel M, Slutsker L *et al*: **Risks of miscarriage and inadvertent exposure to artemisinin derivatives in the first trimester of pregnancy: a prospective study in western Kenya**. *In preparation*.
25. Odhiambo FO, Laserson KF, Sewe M, Hamel MJ, Feikin DR, Adazu K, Ogwang S, Obor D, Amek N, Bayoh N *et al*: **Profile: the KEMRI/CDC Health and Demographic Surveillance System--Western Kenya**. *Int J Epidemiol* 2012, **41**(4):977-987.
26. Kenya National Bureau of Statistics (KNBS) and ICF Macro: **Kenya Demographic and Health Survey 2008-09**. Calverton, Maryland, USA. http://www.measuredhs.com/pubs/pdf/FR229/FR229.pdf; 2011.
27. Kenya National Bureau of Statistics (KNBS), Macro I: **Kenya Demographic and Health Survey 2008-09**. In. Edited by Macro KaI. Calverton, Maryland; 2010.
28. Dellicour S, Desai M, Mason L, Odidi B, Aol G, Phillips-Howard PA, Laserson KF, Ter Kuile FO: **Exploring risk perception and attitudes to miscarriage and congenital anomaly in rural Western kenya**. *PLoS One* 2013, **8**(11):e80551.
29. Mason L., Dellicour S., Ter Kuile F., Ouma P., Phillips-Howard P., Were F., K. L, M. D: **Barriers and facilitators to antenatal and delivery care in western Kenya: a qualitative study**. *BMC Pregnancy and Childbirth* 2015, **15**(26).
30. Bigogo G, Audi A, Aura B, Aol G, Breiman RF, Feikin DR: **Health-seeking patterns among participants of population-based morbidity surveillance in rural western Kenya: implications for calculating disease rates**. *Int J Infect Dis* 2010, **14**(11):e967-973.
31. Feikin DR, Audi A, Olack B, Bigogo GM, Polyak C, Burke H, Williamson J, Breiman RF: **Evaluation of the optimal recall period for disease symptoms in home-based morbidity surveillance in rural and urban Kenya**. *Int J Epidemiol* 2010, **39**(2):450-458.
32. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R: **New Ballard Score, expanded to include extremely premature infants**. *The Journal of pediatrics* 1991, **119**(3):417-423.

33. McKenzie D: **Measuring inequality with asset indicators**. *Journal of Population Economics* 2005, **18**(2):229.

34. World Health Organization: **Spontaneous and Induced Abortion: Report of a WHO scientific group**. In: *WHO Technical Report Series.* vol. 461. Geneva; 1970.

35. Regan L, Rai R: **Epidemiology and the medical causes of miscarriage**. *Bailliere's best practice & research Clinical obstetrics & gynaecology* 2000, **14**(5):839-854.

36. Howards PP, Hertz-Picciotto I, Poole C: **Conditions for bias from differential left truncation**. *Am J Epidemiol* 2007, **165**(4):444-452.

37. Margulis AV, Mittleman MA, Glynn RJ, Holmes LB, Hernandez-Diaz S: **Effects of gestational age at enrollment in pregnancy exposure registries**. *Pharmacoepidemiol Drug Saf* 2015, **24**(4):343-352.

38. Meister R, Schaefer C: **Statistical methods for estimating the probability of spontaneous abortion in observational studies--analyzing pregnancies exposed to coumarin derivatives**. *Reprod Toxicol* 2008, **26**(1):31-35.

39. McGready R, Lee SJ, Wiladphaingern J, Ashley EA, Rijken MJ, Boel M, Simpson JA, Paw MK, Pimanpanarak M, Mu O *et al*: **Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study**. *Lancet Infect Dis* 2012, **12**(5):388-396.

40. Smith KE, Buyalos RP: **The profound impact of patient age on pregnancy outcome after early detection of fetal cardiac activity**. *Fertil Steril* 1996, **65**(1):35-40.

41. Kline J: **I. An epidemiological review of the role of gravidity in spontaneous abortion**. *Early Hum Dev* 1978, **1**(4):337-344.

42. Regan L, Braude PR, Trembath PL: **Influence of past reproductive performance on risk of spontaneous abortion**. *BMJ* 1989, **299**(6698):541-545.

43. Brocklehurst P, French R: **The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis**. *Br J Obstet Gynaecol* 1998, **105**(8):836-848.

44. Temmerman M, Lopita MI, Sanghvi HC, Sinei SK, Plummer FA, Piot P: **The role of maternal syphilis, gonorrhoea and HIV-1 infections in spontaneous abortion**. *International journal of STD & AIDS* 1992, **3**(6):418-422.

45. Norsker FN, Espenhain L, S AR, Morgen CS, Andersen PK, Nybo Andersen AM: **Socioeconomic position and the risk of spontaneous abortion: a study within the Danish National Birth Cohort**. *BMJ open* 2012, **2**(3).

46. McCord GC, Liu A, Singh P: **Deployment of community health workers across rural sub-Saharan Africa: financial considerations and operational assumptions**. *Bulletin of the World Health Organization* 2013, **91**(4):244-253B.

47. African Population and Health Research Center, Ministry of Health Kenya, Ipas, Guttmacher Institute: **Incidence and Complications of Unsafe Abortion in Kenya: Key Findings of a National Study**. In. Nairobi, Kenya; 2013.

48. Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD: **Epidemiology and burden of malaria in pregnancy**. *Lancet Infect Dis* 2007, **7**(2):93-104.

Table 1. Participants' characteristics and risk factors for miscarriage

	Overall (N=1134)	Miscarriage (N=89)	Other Pregnancy Outcomes (n=1045)	Hazard Ratio (95%CI)	P-values
Gestational age at pregnancy detection in weeks (mean (SD))	13.3 (6.9; 0-27.9)	7.8 (4.4)	13.7 (6.9)	0.94 (0.88, 1.01)	0.094
Age in years (mean (SD))	26.1 (6.8)	29.5 (7.9)	25.8 (6.6)	1.08 (1.04, 1.11)	**<0.001**
Age categories					**<0.001**
15-20	285 (25.1)	14 (15.7)	271 (25.9)	1	
21-25	287 (25.3)	14 (15.7)	273 (26.1)	0.9 (0.42, 1.9)	
26-30	255 (22.5)	16 (18.0)	239 (22.9)	1.14 (0.57, 2.3)	
31-35	179 (15.8)	21 (23.6)	158 (15.1)	2.31 (1.2, 4.44)	
>35	128 (11.3)	24 (27.0)	104 (10.0)	4.02 (2.08, 7.76)	
Education level					0.713
None/ Primary not completed	495 (44.4)	38 (43.7)	457 (44.4)	1	
Primary completed	533 (47.8)	44 (50.6)	489 (47.5)	1.07 (0.69, 1.66)	
Secondary completed	88 (7.9)	5 (5.8)	83 (8.1)	0.69 (0.23, 2.04)	
Missing	18	2	16		
Occupation					**<0.001**
Not working	379 (34.4)	22 (25.6)	357 (35.1)	1	
Farming	369 (33.5)	39 (45.4)	330 (32.5)	1.47 (0.88, 2.45)	
Small business/Skilled Labour/Salaried	335 (30.4)	19 (22.1)	316 (31.1)	0.88 (0.48, 1.6)	
Other	20 (1.8)	6 (7.0)	14 (1.4)	5.15 (2.15, 12.34)	
Missing	31	2	16		
Marital Status					0.224

	Overall (N=1134)	Miscarriage (N=89)	Other Pregnancy Outcomes (n=1045)	Hazard Ratio (95%CI)	P-values
Single	240 (21.5)	22 (25.3)	218 (21.2)	1	
Married	876 (78.51)	65 (74.7)	811 (78.8)	0.74 (0.46, 1.2)	
Missing	18	2	16		
Household wealth quintiles					**0.024**
poorest	105 (9.7)	18 (20.5)	87 (8.8)	1	
very poor	158 (14.6)	9 (10.2)	149 (15.0)	0.33 (0.15, 0.75)	
poor	220 (20.4)	16 (18.2)	204 (25.6)	0.4 (0.2, 0.81)	
less poor	269 (24.9)	22 (25.0)	247 (24.9)	0.47 (0.25, 0.88)	
least poor	328 (30.4)	23 (26.1)	305 (30.8)	0.39 (0.21, 0.74)	
Missing	54	1	53		
Gravidity					**<0.001**
Primigravid	219 (19.6)	17 (19.3)	202 (19.6)	1	
1-3 pregnancies	525 (47.0)	23 (26.1)	502 (48.8)	0.49 (0.26, 0.91)	
4+ pregnancies	374 (33.5)	49 (55.1)	325 (31.6)	1.63 (0.95, 2.79)	
Missing	16	0	16		
Previous pregnancy loss	160 (14.3), *Missing n=17*	22 (25.0), *Missing n= 1*	138 (13.4) , *Missing n= 16*	2.23 (1.4, 3.56)	**0.001**
Antenatal Care Summary					
Gestational age at 1st ANC visit in weeks (mean (SD))	20.8 (7.8) Range: 1.7-41.0	10.4 (4.9), missing n=71	21.0 (7.7), missing n=227	0.85 (0.79, 0.91)	**<0.001**
Number of ANC visit					**<0.001**
none	89 (8.1)	66 (74.2)	23 (2.3)	1	
1	90 (8.2)	18 (20.2)	72 (7.2)	0.17 (0.1, 0.29)	
2	155 (14.2)	1 (1.1)	154 (15.3)	0 (0, 0.03)	
3	244 (22.3)	3 (3.4)	241 (24.0)	0.01 (0, 0.03)	
4+	517 (47.2)	1 (1.1)	516 (51.3)	0 (0, 0.01)	

	Overall (N=1134)	Miscarriage (N=89)	Other Pregnancy Outcomes (n=1045)	Hazard Ratio (95%CI)	P-values
Missing	39	0	39		
IPTp doses (HIV negative)					**<0.001**
none	242 (28.3)	73 (98.7)	169 (21.7)	1	
1	95 (11.1)	1 (1.4)	94 (12.1)	0.04 (0.01, 0.31)	
2	175 (20.5)	0	175 (22.4)	0 (0, 0)	
3	222 (26.0)	0	222 (28.5)	0 (0, 0)	
4	120 (14.1)	0	120 (15.4)	0 (0, 0)	
Missing	280	18	265	0 (0, 0)	
Vaginal Bleeding					**<0.001**
No	813 (97.3)	14 (77.8)	799 (97.7)	1	
Yes	23 (2.8)	4 (22.2)	19 (2.3)	11.57 (4, 33.46)	
Missing	298	71	227		
ANC Profile at 1st ANC visit					
HIV positive					**<0.001**
Negative	771 (68.0)	17 (19.0)	754 (72.2)	1	
Positive	262 (23.1)	27 (30.3)	235 (22.5)	4.83 (2.62, 8.9)	
Unknown	101 (8.9)	45 (50.6)	56 (5.4)	25.83 (14.7, 45.39)	
Haemoglobin (mean (SD; range))	11.2 (1.9; 4.3-17.2)	12.4 (1.9)	11.2 (1.9)	1.31 (1.05, 1.63)	**0.017**
	Missing n=309	*missing n=72*	*missing n=237*		
Anaemia (Hb<11g/dl)					0.184
No	476 (57.7)	13 (76.5)	463 (57.3)	1	
Yes	349 (42.3)	4 (23.5)	345 (42.7)	0.47 (0.15, 1.44)	
Missing	309	72	237		
Syphilis reactive test					0.750
Negative	838 (92.3)	20 (95.2)	818 (92.2)	1	

	Overall (N=1134)	Miscarriage (N=89)	Other Pregnancy Outcomes (n=1045)	Hazard Ratio (95%CI)	P-values
Positive	70 (7.7)	1 (4.8)	69 (7.8)	0.79 (0.18, 3.47)	
Missing	226	68	158		
Malaria slide positive at 1st ANC visit					0.651
Negative	712 (86.0)	16 (88.9)	696 (85.9)	1	
Positive	116 (14.0)	2 (11.1)	114 (14.1)	0.63 (0.09, 4.61)	
Missing	306	71	235		

Table 2. Table of weekly miscarriage rate, cumulative probabilities of survival and of miscarriage and remaining risk of miscarriage at each gestation week.

Gestational week	Pregnancies Detected during week	Pregnancy-Weeks at Risk	Miscarriage	Induced abortion	Loss to follow up & withdrawals	Weekly miscarriage rate per 1000 pregnancy-weeks (95%CI)	Probability of miscarriage per gestational week	Probability of survival per gestational week	Cumulative probability of survival	Cumulative probability of miscarriage	Remaining probability of miscarriage
<4	48	32.3	0	1	1	0	0.000	1.000	1.000	0.000	0.189
4	42	67.4	2	0	0	29.66 (7.42- 120)	0.029	0.971	0.971	0.029	0.189
5	77	127.6	2	0	0	15.68 (3.92- 62.69)	0.016	0.984	0.956	0.044	0.165
6	79	200.1	5	0	0	24.98 (10.4- 60.02)	0.025	0.975	0.932	0.068	0.152
7	69	276.9	2	3	0	7.22 (1.81- 28.88)	0.007	0.993	0.925	0.075	0.130
8	71	334.1	3	1	1	8.98 (2.9- 27.84)	0.009	0.991	0.917	0.083	0.124
9	63	397.7	6	0	0	15.09 (6.78- 33.58)	0.015	0.985	0.903	0.097	0.116
10	59	451	7	0	0	15.52 (7.4- 32.56)	0.015	0.985	0.889	0.111	0.103
11	57	502.6	6	1	1	11.94 (5.36- 26.57)	0.012	0.988	0.879	0.121	0.088
12	52	548.3	12	1	1	21.89 (12.43- 38.54)	0.022	0.978	0.860	0.140	0.078
13	41	583.4	3	1	0	5.14 (1.66- 15.94)	0.005	0.995	0.855	0.145	0.057
14	52	626.6	4	0	1	6.38 (2.4- 17.01)	0.006	0.994	0.850	0.150	0.052
15	40	667.9	9	0	0	13.47 (7.01- 25.9)	0.013	0.987	0.839	0.161	0.046
16	43	703.1	2	0	0	2.84 (0.71- 11.37)	0.003	0.997	0.836	0.164	0.033
17	44	739.9	5	1	0	6.76 (2.81- 16.24)	0.007	0.993	0.831	0.169	0.030
18	30	769.1	5	0	0	6.5 (2.71- 15.62)	0.006	0.994	0.825	0.175	0.024
19	33	796.4	2	0	0	2.51 (0.63- 10.04)	0.003	0.997	0.823	0.177	0.018
20	26	823.9	4	0	1	4.86 (1.82- 12.94)	0.005	0.995	0.819	0.181	0.015
21	33	852.1	1	0	1	1.17 (0.17- 8.33)	0.001	0.999	0.818	0.182	0.010
22	23	873.4	0	0	1	0	0.000	1.000	0.818	0.182	0.009
23	36	905.6	1	0	0	1.1 (0.16- 7.84)	0.001	0.999	0.817	0.183	0.009
24	30	937.3	0	0	0	0	0.000	1.000	0.817	0.183	0.008
25	20	960.1	2	0	0	2.08 (0.52- 8.33)	0.002	0.998	0.816	0.184	0.008
26	38	994.4	4	0	0	4.02 (1.51- 10.72)	0.004	0.996	0.812	0.188	0.006
27	28	1016.9	2	0	12	1.97 (0.49- 7.86)	0.002	0.998	0.811	0.189	0.002

Figures

Figure 1. Study participant flow diagram from screening to inclusion in data analysis for miscarriage.

Figure 2. Number of pregnancies detected according different recruitment strategies and mean gestational age at time of pregnancy detection over study period. Pregnancy detection strategies included: antenatal clinic at the designated study facility (ANC); enrolment in the pharmacovigilance cohort study (enrolment); participant seeking pregnancy tests from study staff (passive detection) or through 3-monthly home visits by study staff offering pregnancy tests (active detection).

Figure 3. Miscarriage rate per 1000 pregnancy-week by week of gestation with upper and lower estimates of 95% confidence interval.

Figure 4. Miscarriage Kaplan Meier survival curve by gestational week.

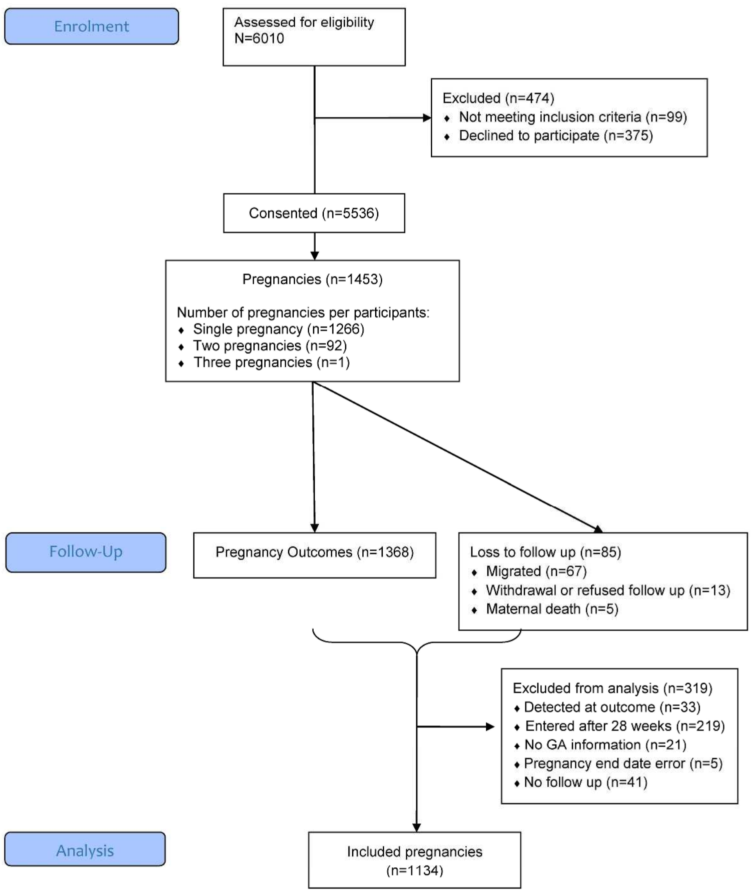
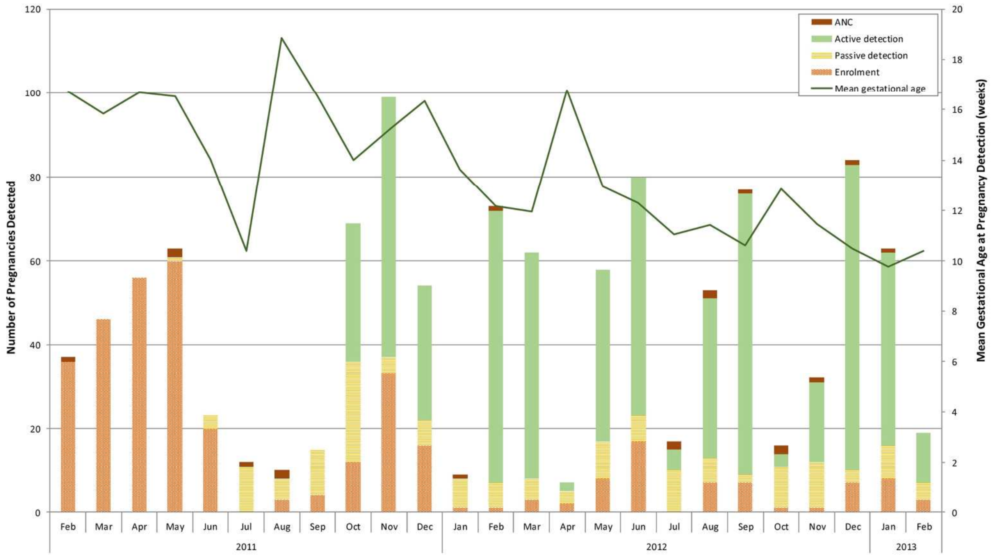
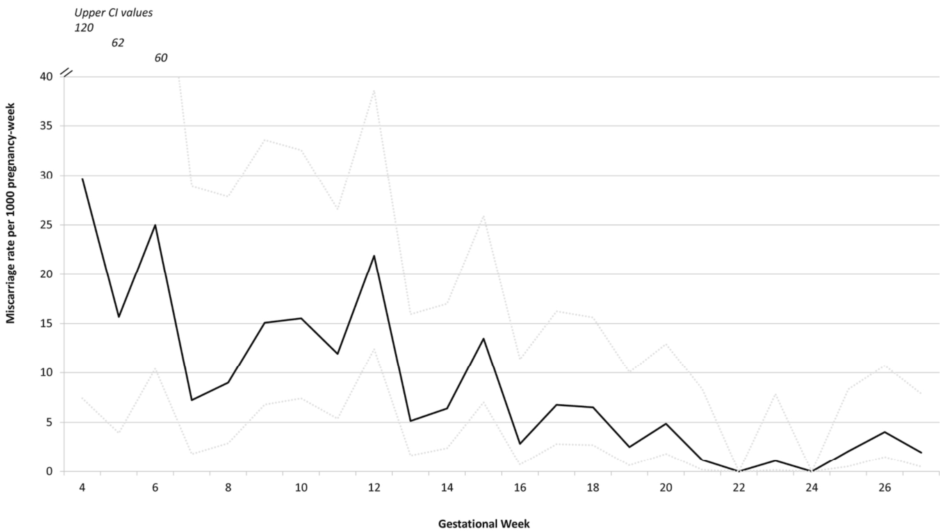


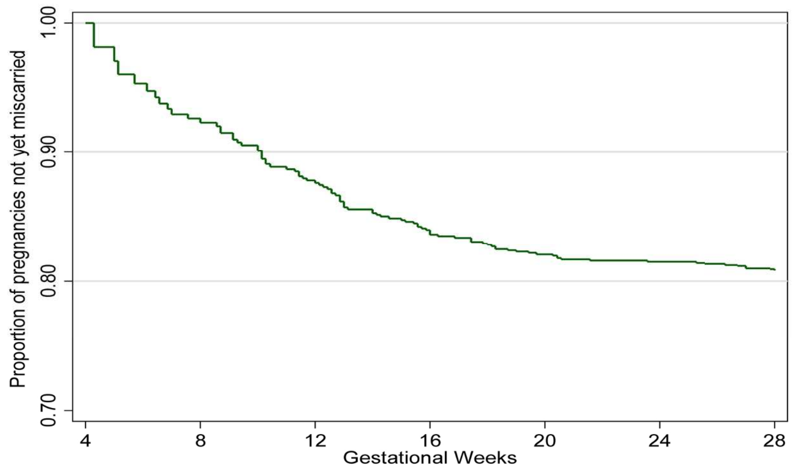
Figure 1. Study participant flow diagram from screening to inclusion in data analysis for miscarriage.
297x420mm (300 x 300 DPI)



Number of pregnancies detected according different recruitment strategies and mean gestational age at time of pregnancy detection over study period. Pregnancy detection strategies included: antenatal clinic at the designated study facility (ANC); enrolment in the pharmacovigilance cohort study (enrolment); participant seeking pregnancy tests from study staff (passive detection) or through 3-monthly home visits by study staff offering pregnancy tests (active detection).
190x107mm (300 x 300 DPI)



Miscarriage rate per 1000 pregnancy-week by week of gestation with upper and lower estimates of 95% confidence interval.
190x107mm (300 x 300 DPI)



Miscarriage Kaplan Meier survival curve by gestational week.
190x107mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	√ p.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	√ p.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√ p.4
Objectives	3	State specific objectives, including any prespecified hypotheses	NA
Methods			
Study design	4	Present key elements of study design early in the paper	√ p.4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	√ p.5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	√ p.5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√ p.6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√ p.6-7
Bias	9	Describe any efforts to address potential sources of bias	√ p.6-7
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	√ p.7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	√ p.7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	√ p.6-7
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	√ p.7 -8
		(b) Give reasons for non-participation at each stage	√ p.7-8
		(c) Consider use of a flow diagram	√ Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	√ p.8 & table 1
		(b) Indicate number of participants with missing data for each variable of interest	√ table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	√ p.8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	√ p.8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	√ p.9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	√ p.9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	√ p.10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	√ p.11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.