Anemia during different trimesters of pregnancy and hypertensive disorders are associated with adverse maternal and perinatal outcomes in Bekwai Municipality, Ghana: protocol for a prospective cohort study.

Kwabena Acheampong
Central South University Xiangya School of Public Health
Xiongfeng Pan
Central South University Xiangya School of Public Health
Aizhong Liu (lazroy@live.cn)
Central South University https://orcid.org/0000-0001-6890-1583

Study protocol

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Abstract

Background: Data examining whether anemia during different trimesters of pregnancy affects maternal and birth outcomes is lacking. Studies typically look at associations between risk factors and anemia or anemia and birth outcomes but have limited information as to whether birth outcomes differ with different trimesters of anemia. The main objective of this study is to determine whether anemia during different trimesters of pregnancy and hypertension disorders is associated with adverse maternal and perinatal outcomes in Ghana.

Methods: This will be a primary analysis of data from a hospital-based prospective cohort study in four selected hospitals in the Bekwai Municipality, Ghana from February 2020 to August 2020. All singleton pregnancy at less than 20 weeks to women with at least one hemoglobin measure during pregnancy will be included. The risk of maternal and perinatal outcomes will be measured. Descriptive statistics will be used to describe the baseline characteristics of our cohort. Baseline characteristics of the two groups will be compared using Pearson Chi-square (χ^2) test for categorical variables; the independent t-test and Mann–Whitney U test for parametric and nonparametric continuous variables, respectively. The risk associated with anemia and maternal and perinatal outcomes, using the history of anemia (Hb<11g/dL) in different trimesters will be calculated by logistic regression analysis, conditional on the baseline covariates. Possible confounding variables will be identified from background data, obstetric risk factors, and health behaviors. Multivariate analysis of significant effects ($p<0.05$) will be based on multiple logistic regression analysis. Confidence intervals will be evaluated at 95%. Data will be coded and examined using the SPSS program IBM version 20.

Discussion: The better understanding of whether anemia during different trimesters of pregnancy and hypertension disorders is associated with adverse maternal and perinatal outcomes in Bekwai Municipality of Ghana. This study will establish targets for early intervention and identify risk factors to save and improve the lives of pregnant women and inborn by developing solutions that promote the quality and accountability of health services for the most vulnerable. These findings will be served as a policy document to governments in designing effective programs to curb the increasing prevalence of anemia and its associated health consequences.

Background

Anemia is a global public health problem affecting 1.62 billion people worldwide[1]. It affects 32 million (38%) of pregnant women globally, of whom 750,000 had the lowest hemoglobin concentrations (Hb < 7.0 g/dL)[2], with the highest prevalence found in Southern Asian (52%), Central African and West African countries (56%)[3].However, there is a significant variation in the prevalence of anemia both within and between countries, necessitating a need for local data to help improve preventive programs. Anemia during pregnancy is associated with low birth weight, preterm delivery [4, 5] and a greater risk of maternal-perinatal morbidity and mortality [6-10]. Emerging evidence has suggested that anemia may be associated with perinatal outcomes. However, there are conflicting data as to whether anemia during

different trimesters of pregnancy increases adverse maternal and perinatal outcomes. Although, studies have reported an association between maternal anemia in the first trimester and low birth weight (OR=3.14, 95% CI: 1.35-7.28). However, the mid- and third-trimester anemia groups showed no significantly different outcomes when compared with the non-anemic women. [11, 12]. Again, Klebanoff and colleagues[13] observed a weak relationship between early third-trimester pregnancy anemia and preterm delivery. But, such association did not account for the substantial increase in preterm birth seen among black women and anemia after 30 weeks' gestation was not associated with preterm birth. Nevertheless, Kidanto and colleagues [14] indicated that the risk of preterm delivery increased significantly with the severity of the, with odds ratios of 1.4, 1.4 and 4.1 respectively for mild, moderate and severe anemia which is similar to LBW. Furthermore, epidemiological evidence suggest that maternal anemia increased the risk of low birth weight (odds ratio (OR), 1.65; 95% confidence interval (CI): 1.45–1.87), preterm birth (OR, 2.11; 95% CI: 1.76–2.53), perinatal mortality (OR, 3.01; 95% CI: 1.92–4.73), stillbirth (OR, 1.95; 95% CI: 1.15–3.31), and maternal mortality (OR, 3.20; 95% CI: 1.16–8.85) [15]. However, another study reported that anemia in later pregnancy was inversely associated with preterm birth and low birth weight. they even concluded that anemia during pregnancy does not increase the risk of poor birth outcomes[16].Nevertheless, other studies did not detect such a significant association between anemia and adverse pregnancy outcomes. [17, 18].

Beyond anemia, hypertensive(HDP) are the most common complications which occur in 10% of pregnancies [19] and are responsible for approximately 14% of maternal deaths globally[20]. The adverse perinatal outcomes are thought to be due to non-hypertensive etiologies, including infection, obstructed labor, and preterm or post-term pregnancy [21-25] and stillbirth [26-28], particularly in low and middle-income countries [29]. Although there have been reports on maternal and perinatal complications and outcomes elsewhere, no research has been carried out in the study area. Besides, anemia is one of the most prevalent nutritional deficiency problems affecting pregnant women, which differs significantly because of variations in socioeconomic conditions, lifestyles, and health-seeking behaviors across different cultures[30]. Physiologically, plasma volume expands by 25–80% of pre-pregnancy volumes between the second trimester and the middle of the third trimester of pregnancy[31]. This induces a modest decrease in hemoglobin levels during pregnancy. Previous studies show that the best time to investigate any risk factors associated with anemia may be up until 20 weeks of gestation [13]. However, studies focusing on anemia in different trimesters and pregnancy outcomes are scarce, and the findings are inconsistent due to a wide variation in study designs, sample sizes, and populations. Furthermore, not all studies reported adjustments for confounders which could affect the final outcome, such as the timing of hemoglobin assessment[32] and possibly over or underestimate risks. For instance, Rohilla and colleagues [33], conducted a study using a hemoglobin concentration of < 7 g/dl to determine the maternal and perinatal outcome in patients with severe anemia in pregnancy. They reported higher proportions of hypertensive disorders, adverse maternal and perinatal outcomes. Hemoglobin levels measurement is a standard during prenatal visit and it is used to evaluate the physical status and anemia [34]. According to the World Health Organization[35], anemia is diagnosed when a blood test shows a hemoglobin value of less than 11.0 g/dL in pregnant women. However, few studies to date have

assessed the effects of anemia during different trimesters and adverse maternal-perinatal outcomes. Therefore this study will seek to evaluate whether associations exist between anemia during different trimester, hypertensive disorders, and adverse maternal-perinatal outcomes in the study area.

Study Objective

The main objective of this study is to determine whether anemia during different trimesters of pregnancy and hypertension disorders is associated with adverse maternal and perinatal outcomes in Bekwai Municipality, Ghana

Specific objectives

- To determine whether anemia during different trimesters of pregnancy is associated with adverse maternal and perinatal outcomes in the study population.
- To determine whether hypertension disorders in pregnancy is associated with adverse maternal and perinatal outcomes in the study population.

Methods

Study Design

This study will be conducted using a hospital-based prospective cohort study aimed at enrolling pregnant women in the first trimester to identify anemia or no anemia at the baseline. The selected subjects will be followed up to delivery to determine whether anemia during different trimesters of pregnancy and hypertension disorders is associated with the risk of adverse maternal and perinatal outcomes in Bekwai Municipality, Ghana.

Study settings

This study will be conducted in four selected hospitals across the Bekwai municipality specifically, Bekwai Municipal hospital, Bekwai, Kotwia Hospital, Kotwia, Abenkyiman hospital, Anwiankwanta, and Adventist hospital, Dominate all in the Ashanti Region of Ghana between February and August 2020. The surveillance system will be established in March 2020 and covers the member hospitals, each of which manages more than 500-1800 deliveries annually. The population of Bekwai municipality, according to the 2010 Population and Housing Census, is 118,024 with the women aged 15-49 years representing 23.9%. The rural population constitutes 97,277 which represent 82.4 percent of the total population whiles the urban areas have a population of 20,747 (17.6%). The total number of live births in the Municipality for the last 12 months prior to the census night was 2,897. The data further indicates that the total fertility rate was approximate 3.5.

Sample size considerations

The sample size will be calculated using a PASS for determining proportions for the study population. Where N_1=the first sample size, Power (1-Beta)=0.90, Inspection performance is 90% Alpha (Significance Level)=0.05, Inspection level is 0.05N2 (Sample Size Group 2): Use R, Two groups of sample ratio coefficient R (Sample Allocation Ratio): 1, Two groups of cases Equivalent R_1 (Ratio|H_1=P_1/P_2)= 0.5, RR value is $2P_2$ (Control Group Proportion)=0.23, Control event rate is 23%, Alternative Hypothesis (H_1)= Two-Sided, Alternative Hypothesis (Two Sides Test)=Test Type= Z Test (Pooled). Then, the total sample size for exposed/unexposed will be 225 each for the group. Hence the total sample size for exposed/unexposed with a 10% continuity correction will be approximately 250 each for group and total of 500. Therefore, for a normally distributed continuous outcome, it is possible to detect with a type I error of 5%, two-sided significance level (1-alpha) of 95% confidence interval, and a type II error of 10% with 90% power (1-beta, % chance of detecting).

Eligibility criteria

Inclusion criteria

Pregnant women who had no bleeding at the time of recruitment will be included. All pregnant women aged 15-49 years who has given consent personally with anemia or without will be included, regardless of whether or not they had taken iron supplementation. Women under the age of 18, for whom a written permission to participate has been obtained from a parent or guardian , pregnant women who were not lately been given blood or transfused, who had no chronic medical diseases, who had no early bleeding at recruitment will be included in the study.

Exclusion criteria

Pregnant women with severe immunodepression and women who do not permanently reside in the study area (i.e., less than 6 months residency in the study area) will be excluded.

Selection and recruitment of study participants

The data will be collected at two stages: (i) prenatal data collection from pregnant women and (ii) post-delivery data collection.

Study population

Pregnant women, at the time they scheduled their initial antenatal care visit, which occurred between 6 to 12weeks of gestation will be recruited for the study. The exposed (history of anemia) and non-exposed (no anemia) will be identified as shown in figure 1, since about 88.3% of all pregnant women booked for antenatal care before 12 weeks, and seen at intervals in maternity units where hemoglobin concentrations are routinely measured in each trimester in the study area. Baseline data collection, anthropometric measurements, and blood investigations will be also collected.

Exposed and non-exposed definition

- **Exposed:** The prevalence of anemia will denote pregnant women with hemoglobin levels below 11 g/dL, i.e hemoglobin levels < 11g/dL will be stratified by trimester and women having anemia in more than one trimester will be allocated to that trimester in which their anemia was first recognized.
- **Non-Exposed:** Pregnant women without anemia will denote hemoglobin levels ≥11 g/dl, i.e. with three normal hemoglobin tests, one per trimester. For each exposed, the non-exposed will be recruited.

Follow-up period

The mid-pregnancy follow-up visits with pregnant women at the time of the routine antenatal care visit will be conducted between 20 to 24 weeks and 32 to 34weeks of gestation. Postnatal follow-up will be done with the mothers and newborn in the hospital during the birth admission at >37 to 42weeks of gestation. Participant's recruitments and followed-up periods will last for 26weeks to record maternal and perinatal outcomes.

Prenatal data collection and management

In prenatal data collection, a cross-sectional study will be conducted by using a semi-structured questionnaire. The questionnaire will be consisting of socio-demographic factors (age, marital status, religious belief, place of residence, ethnicity, education status, occupation and housing and household) about the participants. This will also include obstetric and gynecological factors (Gravidity, parity, abortions, stillbirth, inter-pregnancy interval, haemorrhage, type of delivery, birth interval, previous low birth weight, previous preterm, previous pregnancy complications, and all the related information for knowledge menstruation, contraceptives and its usage. This study will acquire behavioural factors (alcohol use, tobacco use, ITN usage, mosquito's prevention methods, food taboos, Geophagia, herbal usage weight and weight control, physical activity, psychosocial behaviour, adherence to folic acid and iron supplements). Information on medical history (hypertension, diabetes and etc (past and this pregnancy), genetic factors (sickling status, G6PD status and type of blood) infectious diseases (malaria, intestinal worms, HIV, hepatitis B, syphilis, and etc) will be also assessed. Anthropometric measurements (weight, height, body mass index, will be conducted from enrolled pregnant women. Furthermore, nutritional Adequacy and frequency of food consumption will be undertaken from enrolled pregnant women. This food frequency questionnaire will help to assess the die consumed by women in district Municipality. Besides, information of occupation and income status of the husband and be examined.

Hypertensive disorders in pregnancy

Following the course of the pregnancy, the following information will be collected from exposed and non-exposed. Blood pressure will be measured in each trimester with the validated Omron RCHS automated digital sphygmomanometer. All participants will be seated in an upright position with back support for 5 min. An appropriate cuff will be placed around the non-dominant upper arm, which will be supported at the level of the heart, with the bladder midline over the brachial artery pulsation. The mean value of two blood pressure readings will be documented over a 2min interval. Information on chronic hypertension

superimposed preeclampsia, preeclampsia or eclampsia, and gestational hypertension will be derived from maternal antenatal registries.

Post-delivery data collection

All participants will be followed-up and will be also contacted twice during their pregnancy over the telephone to enquire about their well-being. Post-delivery data will be collected involving in daily identification of all the women who had delivered during the previous 24 h in the hospital by the support of station nurse. Baseline data will be extracted from patients' folders, admission and discharge registers at the labor wards. After the initial daily baseline data extraction on all the parturient incomes (fetal distress, neonatal intensive care (NICU) admission, stillbirth, early neonatal death, low birth weight, small for gestation age, birth weight, macrosomia, preterm delivery, APGAR score < 7 at 1 min and APGAR score <7 at 5 min) and mothers outcomes (transfusion, hypertensive disorders, postpartum hemorrhage, gestational diabetes, and maternal mortality) will be identified and their folder numbers recorded. Post-delivery data collection will be completed by August 30, 2020.

Data management and quality control

The data collectors and key informants will be staff midwives nurses and one research assistant supervised by the principal investigator. Training and practical demonstrations on the interview techniques and measurement procedures will be given to data collectors for two consecutive days. A pilot study will be done on 20 ANC attendants over a period of 5days to determine the appropriateness and completeness of the questionnaire for the study. Information that will be retrieved from the ANC books will be confirmed by the principal investigator for its consistency. After informed consent has been obtained, eligible participants will be interviewed using a semi-structured questionnaire. Maternal records will be reviewed on specific items related to the study. Data collected will be then entered into a safe computerized database using a unique code to ensure data accuracy. The databases will have patient-identifiable information attached such as name and address, and each patient will have an anonymized study ID. A copy of the anonymized database (without a name, address) will be sent to SPSS for data analysis. The patient identity will be protected and only aggregate summary data will be released publically (e.g., in the form of a peer-reviewed publication),

Study endpoints and statistical analyses

Perinatal outcomes

Data will be available to performed analyses for the following perinatal outcomes: (1) stillbirth, (2) preterm birth (3), low birth weight (4), small for gestational age (5) perinatal mortality; and (6) NICU admission, (7) APGAR score < 7 at 1 min, (8) APGAR score <7 at 5 min, (9) macrosomia (10) neonatal mortality. The results for these outcomes will be presented by (1) time period: first, second, and third trimesters anemia; (2) cutoff: ≤7.0 g/dL, 7.0-9.9 g/dL, 10-10.9 g/dL, and ≥11.0 g/dL (3) overall estimate

of anemia throughout pregnancy will be analyzed. The results of the association between maternal anemia and perinatal outcomes will be summarized in tables.

Maternal health outcomes

Data will be available to performed analyses for the following selected maternal health outcomes: (1) transfusion, (2) hypertensive disorders, (3) postpartum hemorrhage, (4) and gestational diabetes and (5) maternal mortality. The results for these outcomes will be presented by (1) time period: first, second, and third trimesters anemia; (2) cutoff: ≤7.0 g/dL, 7.0-9.9 g/dL, 10-10.9 g/dL, and ≥11.0 g/dL (3) overall estimate of anemia throughout pregnancy will be analyzed. Results of the association between prenatal anemia and maternal outcomes will be summarized in tables.

Data analysis

Statistical analysis

The distribution of the study variables such as sociodemographic factors, nutritional factors, genetic factors, behavioral factors and obstetric factors of exposed and non-exposed will be calculated using means with standard deviations for normal continuous variables and frequencies and percent for categorical variables. Univariate comparisons will be performed using the Pearson Chi-square (χ^2) for categorical variables; the independent t-test and Mann–Whitney U test for parametric and nonparametric continuous variables, respectively when the quality of variances is satisfied. Binary logistic regression analysis will be used to evaluate the risk associated between anemia and adverse maternal and perinatal outcomes, using history of anemia (Hb<11g/dL) in different trimester by calculating the odds of different exposures and non-exposed, taking into account, when the interaction terms are observed followed by multiple logistic regression and adjusting for potential confounders. Similar models will be used to examine the associations between hypertensive disorders and adverse maternal and perinatal outcomes. The variables for which p-value turns out to be less than 0.2 will be included in the multivariable analysis. In multivariate analysis of significant effects ($p<0.05$) will be based on multiple logistic regression analysis. Confidence intervals will be evaluated at 95%. During this analysis interaction between the variables will be assessed. This analysis will also be helpful in identifying the potential confounders such as sociodemographic factors, nutritional factors, genetic factors, behavioral factors and obstetric factors related to the study. In addition, we will also explore the role of first-trimester anemia only, second-trimester anemia only, third-trimester anemia only, first-trimester anemia and second-trimester anemia only, first-trimester anemia and third-trimester anemia on, second-trimester anemia and third-trimester anemia and adverse maternal and perinatal outcomes. Data will be coded and examined using the SPSS program IBM version 20.

Discussion

The better understanding of whether anemia during different trimesters of pregnancy and hypertension disorders is associated with adverse maternal and perinatal outcomes in the Bekwai Municipality of

Ghana. This will, in turn, decrease the chances of adverse maternal and perinatal outcomes associated with anemia. This study will establish targets for early intervention and identify risk factors to save and improve the lives of pregnant women and inborn by developing solutions that promote the quality and accountability of health services for the most vulnerable population of Ghana. These findings will be served as a policy document to governments in designing effective programs to curb the increasing prevalence of anemia and its associated health consequences.

Strengths And Weaknesses Of The Study

The primary strength of this study will be the in-person collection of exposure and outcome measures using research standard procedures that will be conducted by trained and expert staff. Another is the wealth of covariate information that will be collected, which will helps to minimize confounding. Weaknesses may include the loss to follow-up over time to miscarriages, maternal transfers from the study area and other others reasons not specified.

Declarations

Ethical approval and Consent to participant

There will be no major ethical issues in this study as it will be carried out within the confines of routine antenatal care. Those found to be anemic will follow the routine protocol for anemia treatment. Approval is given by institutional review board (IRB), human subjects committee of Central South University, China. Administrative permission will be granted from the Bekwai Municipal District Health Management Team. Informed consent will be obtained from the mothers before participating in this study. Informed consent will be obtained from all new antenatal women who will consent to the study.. The objective of the study will be explained and each study participant will be informed that her participation is voluntary and that she will be free without needing to justify herself, withdraw at any time without consequences. Women who are unable to read and write will be informed in detail about the study and thumb printing will be taken from them.

Consent for publication

Not applicable

Availability of data and materials

Not applicable in this section

Competing interest

The authors declare that they have no competing interests.

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Authors’ contributions

The study was conceptualized by AK prepared the first draft of the manuscript. AK, XP, and AL reviewed the manuscript several times and provided feedback. All authors have contributed to this manuscript, and reviewed and approved the final version of the paper.

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None

Author Details

[1] Department of Epidemiology & Health Statistics

School of Public Health Central South University

110 Xiangya Rd, Changsha, Hunan, P.R. of China 410078

Abbreviations

ANC: Antenatal Care; NICU: neonatal intensive care; WHO: World Health Organization

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Figures

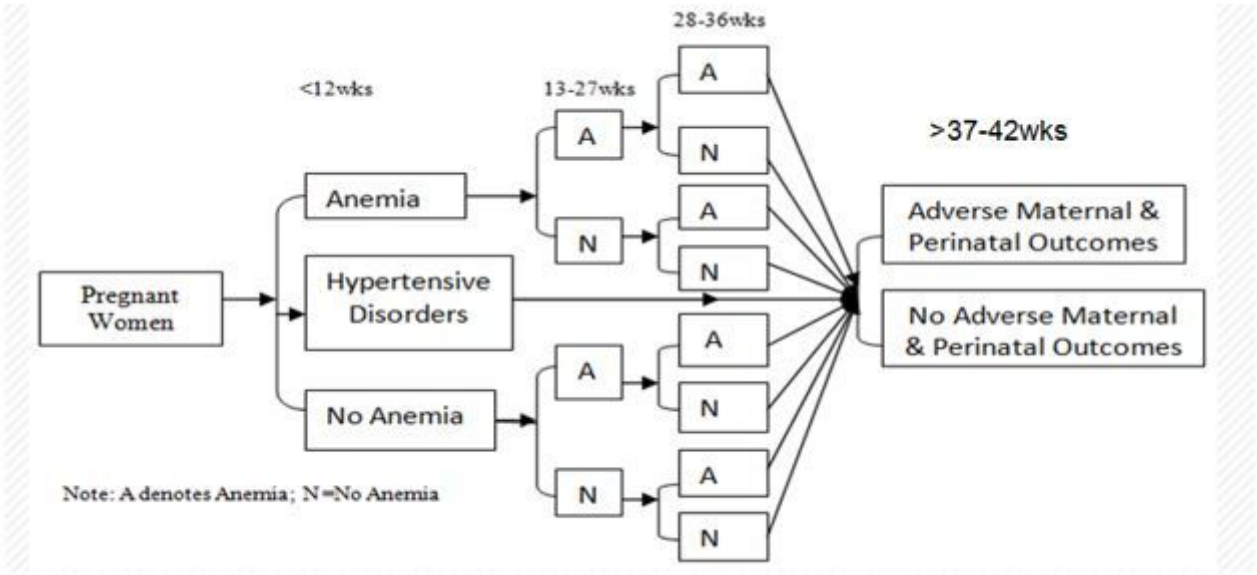

Figure 1

Design of different stages of Anemia, Hypertensive Disorder with Adverse Maternal and Perinatal Outcomes

Supplementary Files

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