The Effect of Inter-Pregnancy Interval on Primary Postpartum Hemorrhage in Urban South Ethiopia: A Community-Based Matched Nested Case Control Study

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Research Article

Keywords: Primary postpartum hemorrhage, Inter-pregnancy interval, Cohort, Nested Case Control, Urban South Ethiopia

Posted Date: March 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-345340/v1

Abstract

Background: Globally, postpartum hemorrhage remained a leading cause of maternal mortality, accounting for nearly one quarter of all pregnancy related deaths. To decrease postpartum hemorrhage related maternal mortalities to desired level, identifying its risk factors is very crucial to guide interventions. In this regard, little is known about the link between inter-pregnancy interval and primary postpartum hemorrhage in Ethiopia where maternal mortality is one of the highest in the world (412 per 100,000 live births). Therefore, we mainly aimed to assess the effect of inter-pregnancy interval on primary postpartum hemorrhage in urban South Ethiopia.

Methods: A community-based matched nested case control study was conducted among 365 women (73 cases and 292 controls). Cases were women with primary postpartum hemorrhage and controls were women without primary postpartum hemorrhage. Cases were individually matched with controls (1:4 ratio) for age group and location. A conditional logistic regression analysis was done using R version 4.0.3 software. Statistically significant association was declared at $P < 0.05$. Odds ratio and attributable fraction (AF) were used to report effect sizes from the adjusted model.

Results: The incidence of primary postpartum hemorrhage was 2.9%, 95%CI: (2.2%, 3.6%). More than half (56%) of primary postpartum hemorrhage was attributed to short inter-pregnancy interval <18 months (AF=56.1%, 95%CI: 6.5%, 79.5%). This could have been prevented if inter-pregnancy interval was increased to 24-36 months. Moreover, primary postpartum hemorrhage was attributed to presence of antepartum hemorrhage (AF=82.4%, 95% CI: 17.4%, 96.2%), prolonged labour (AF=71.8%, 95%CI: 31.5%, 88.4%) and late initiation of breast feeding (AF=78.2%, 95%CI: 47.4%, 90.9%).

Conclusions: In this study, inter-pregnancy interval was causally related with primary postpartum hemorrhage. More than half of primary postpartum hemorrhage can be prevented by spacing pregnancy for at least 18 months. Other risk factors for primary postpartum hemorrhage were antepartum hemorrhage, prolonged labour and late initiation of breast feeding. Increasing existing maternal health service utilization (family planning emphasizing on spacing, antenatal care, health facility delivery with early referrals and postnatal care) will contribute for reducing primary postpartum hemorrhage, as the risk factors identified were maternal health service related and modifiable.

Plain English Summary

Postpartum hemorrhage (PPH) is bleeding in excess amount than expected after delivery. Excess bleeding within 24 hours after delivery is termed as primary PPH. Primary PPH is a well-known cause of maternal death all over the world, mainly in developing countries. In this study, the effect of inter-pregnancy interval on primary PPH was estimated.

Inter-pregnancy interval (IPI) is defined as a time elapsed from a live birth to subsequent conception or women's last menstrual period. A total of 2546 pregnant women were followed until delivery. Information at the time of delivery was obtained for 2517 women. From these, 73 (2.9%) of them had primary PPH. To

estimate the effect of IPI on primary PPH, we selected 73 women who had primary PPH and 292 women who had no primary PPH.

About 56% of primary PPH was attributed to IPI <18 months. This means, more than half of primary PPH can be prevented by increasing IPI to at least 18 months after the preceding child birth. Additionally, this study took the opportunity to identify other factors that increase the risk of primary PPH. These include: antepartum hemorrhage (bleeding after 28 weeks of pregnancy), long duration of stay in labor (>12 hours from the beginning of contraction of uterus) and delayed initiation of breast feeding (≥ 1 hour after delivery). Therefore, family planning utilization emphasizing on spacing pregnancies, initiation of breast feeding within an hour and timely management of labor need to be improved.

Background

Primary postpartum hemorrhage (PPH) is generally defined as a loss of 500 ml or more amounts of blood within 24 hours after vaginal birth or 1000 ml or more blood following caesarean delivery (1). It is the commonest form of PPH, as more bleeding occurs within this time frame after delivery. It is a universal fact that bleeding during delivery in small amount is a natural phenomenon. But, it can be a massive life-threatening condition and causes maternal death when the bleeding is profuse or ongoing and cause changes in vital signs (2).

Globally, PPH is recognized as the leading cause of maternal mortality (1) which accounts for nearly one quarter (25%) of all maternal deaths annually (2), (3), (4) and affects about 18% of all deliveries (5). Specifically, primary PPH is a common one, contributing for 19.7% of all pregnancy-related maternal deaths worldwide (6). Those mothers who survived from death often face serious complications following immediate PPH such as shock, acute renal failure, respiratory distress syndrome, coagulopathy, myocardial ischemia, hysterectomy and anemia that has a long term clinical effects on the women and subsequent pregnancies and child births (7), (8). These acute and chronic complications of PPH causes considerable suffering for mothers who are the victims of bleeding and their families, especially the newborn who needs care and support from the mother such as breast feeding and good temperature from skin to skin contact. PPH disturbs these crucial cares for the newborn because mother herself needs life-saving cares during the condition. Moreover, the complications cause a heavy burden on health systems in general (9). Low and middle income countries such as Africa and Asia take the highest burden of PPH related morbidities and mortalities due to inadequate access and unavailability of quality obstetric services including lack of surgical management of atony in these settings (10). However, recent publications have reported that the rate and related maternal morbidities were increasing in high income countries such as United states, United Kingdom, Canada and Japan (7), (11).

Previously conducted studies attempted to identify factors that put mothers at a higher risk of developing PPH such as: a) antepartum risk factors: previous history of PPH (12), age ≥ 35 years (13), (14), uterine over-distention (due to multiple pregnancy (13), (15) fetal macrosomia (13), (16)), multiparty (14), (17), (18); b) labour risk factors: prolonged labour (17), (18), induced or augmented labour (17), (19), pre-eclampsia (15) and chorioamnionitis (20) and; c) surgical risk factors: caesarean section (13), (19) and episiotomy (2), (16). However, about 20% of PPH cases could present without known risk factors (2), (6). From these studies, we understood that the identified risk factors were mostly those conditions at the time of labour and delivery. But, less attention was given for inter-pregnancy interval as a risk factor for PPH in the literatures.

In Ethiopia, maternal mortality remains one of the highest in the world, 412 per 100,000 live births (21). Hemorrhage, specifically, PPH is the main direct cause of maternal death (22), (23), (24). The government of Ethiopia shared the global sustainable development goal (SDG), targeted to reduce maternal mortality to below 70 per 100,000 live births. At the end of 2030, no country is expected to exceed its double (140 per 100,000 live births) (24). In order to achieve this goal, the government has been implementing community and health facility based interventions by means of trained health extension workers, midwives and emergency caesarean section professionals that were working with mothers (25). These interventions, since millennium development goals set, have been contributed to decrease maternal mortality to current level, 412 per 100,000 live births. This figure is still highest and can be difficult to reduce to desired level unless PPH is substantially reduced. Due to low utilization of existing maternal health services, poor access and unavailability of quality obstetric care in most of health facilities, decreasing PPH and related maternal death remained a challenge in Ethiopia (26), (27), (28). Moreover, there was high rate of fertility (4.6), desire for additional child soon (18%) and half of second and higher pregnancies occur to women within short duration after preceding child birth (25). These circumstances may increase the burden of obstetric complications due to repeated exposures for pregnancy that put mother at risk of death. Having all these problems, adequate information is lacking, whether short interval between pregnancies could have impact on primary PPH or not.

Therefore, the main aim of this study was to estimate the effect of inter-pregnancy interval on primary PPH. It also designed to estimate the incidence and other risk factors of primary PPH. The results of this study could contributes for designing interventions to reduce maternal mortality caused by PPH at local and national level as well.

Methods

Study design and setting

A community-based nested case-control study design was used for this study. It is a part of community-based open prospective cohort study that was conducted among pregnant women in five urban settings, in Hadiya zone, South Ethiopia. For this open cohort, pregnant women were enrolled at the end of 1st trimester of confirmed pregnancy (after 12 weeks of gestation) via house to house identification and registration in every three months, for a total of nine months. An enrolment was done from July 08/2019 to March 30/2020 by trained midwives and followed until September 30/2020. A total of 2546 pregnant women were enrolled for the study.

The study was conducted in Hadiya zone which is located in Southern Nations, Nationalities and Peoples Region (SNNPR), Ethiopia. This region is known by its multiple ethnic (>56 ethnic groups), cultural and diverse geographic locations. Hadiya zone is one of the zones in SNNPR which is located at 232Km far from the capital city, Addis Ababa and 194 km from regional capital, Hawassa. The administrative center of Hadiya zone is Hossana town. Hadiya zone has a total population of 1,688,820, of these 836,979 (49.56%) are men and 851,841 (50.44%) women. Women of child bearing age (15-49 years) constituted 393,493 (23.3%). A total number of expected pregnancies are 57,094 (3.46%). In Hadiya zone there are one general hospital, three primary hospitals, 62 health centers and 311 health posts that offer health services for the community [Hadiya Zone Health Bureau report-Unpublished]. In this study, five urban settings (Hossana, Shone, Gimbichu, Jajura and Homecho) which consists a total of eighteen kebeles (lowest administrative units in Ethiopia) were included.

Participants

During the recruitment, study participants were included in the study based on the eligibility criteria for the main exposure variable (inter-pregnancy interval (IPI)). The inclusion criteria were women who: were pregnant at the time of recruitment, had a live birth during the most recent child birth and were able to recall date of last child birth. Exclusion criteria were women who: had recent stillbirth, had recent abortion, and did not show willingness to be followed. Except for the main exposure variable, all other covariate variables were assumed to be random in both exposed and unexposed groups. All primary PPH cases occurring during a follow up time (July 08/2019 to September 30/2020) were taken as cases. The controls were mothers included in the cohort who had no primary PPH. A 1:4 ratio was used because cases (primary PPH) were relatively small in size. Hence to increase the statistical power, four controls were selected for each case. For every primary PPH cases, four controls were randomly selected from the frame of the cohort by using a random numbers generator in open-Epi software. We matched a case with four controls each for age group and location (kebele). Individual matching approach was used. Age categorized in five years interval (as age is less accurately reported in most of people in Ethiopia due to absence of vital registration system so far). Location (kebele) was easily identifiable (objective) so that simply matched without recoding in to interval or groups. Thus, individual matching possibly makes the cases to be very similar with controls. Matching in location (kebele) also makes the cases and controls very similar for many unobserved source of heterogeneity. For example, it makes the distance to health facility, the health facility that they receive maternal health services (such as antenatal, delivery and postnatal cares), social, cultural and other neighborhood circumstances. Thus, reduce geographic disparities as this study was conducted in multiple (five) locations.

Variables

The dependent/outcome variable was primary PPH. The independent variables were: 1) socio-demographic and economic variables such as maternal age, marital status, education, occupation, family size and wealth status. 2) reproductive and related characteristics such as IPI, age at first child birth, parity, contraception, number of antenatal visit, receiving ferrous sulphate, type of pregnancy, antepartum hemorrhage (APH), pre-eclampsia/eclampsia, premature rupture of membrane (PROM), gestational age, progress of labour, failure of trial of vaginal birth after caesarean section (VBAC), prolonged/obstructed labour, mode of delivery, stillbirth, birth asphyxia, receiving oxytocin, weight of the new-born, time at initiation of breast feeding and sex of new-born. Definition of some technical variables was as follow: parity was defined as the number of times a woman gives birth, irrespective of the outcome (stillbirth or live birth). Inter-pregnancy interval (IPI) is defined as a time elapsed from a live birth to subsequent conception or woman's last menstrual period. Antepartum hemorrhage is defined as vaginal bleeding after 28 weeks of gestation. Pre-eclampsia is pregnancy-related high blood pressure and protein in the urine. Eclampsia is when mother with pre-eclampsia develops convulsion or comma. Premature rupture of membranes refers to rupture of membranes at any time before the onset of uterine contractions. Prolonged labour is defined as a duration of true labour that exceeds 12 hour, irrespective of the stages. Failure of trial of vaginal birth after caesarean section (VBAC) refers when a woman who had caesarean section during a preceding child birth and she faced difficulty to give birth vaginally for subsequent delivery. Stillbirth was defined as giving a dead birth (no sign of life such as crying, movement, breathing etc.) after 28 weeks of gestation including intra uterine fetal death and death throughout the course of labour and delivery. Birth asphyxia refers to the failure to initiate and sustain breathing at birth. Weight of new-born is the weight of the baby at birth. Time at initiation of breast feeding is the time at the start of breast feeding after delivery in minutes. If breast feeding was initiated within sixty minutes, it is termed as early initiation. If it was started at and after sixty minutes, it is termed as late initiation. Type of pregnancy refers to the number of babies born at the time of deliver (single or multiple). Gestational age refers to duration of pregnancy until delivery. Mode of delivery is whether a woman gives birth spontaneous vaginally, assisted vaginally with instruments (forceps and vacuum) or via caesarean section. Progress of labour is to mean whether labour was going on its natural course or assisted via augmentation or induction.

Data sources/measurement

Baseline data about sociodemographic and reproductive variables including main exposure variable (inter-pregnancy interval) were collected at household level during enrolment via face to face interview. Outcome (primary PPH) and other clinical data such as pre-eclampsia, PROM, prolonged labor, progress of labor, mode of delivery, date of delivery, weight of baby, etc. were collected from client chart, during the time of delivery before discharge made. Before baseline data collection, the questionnaire was prepared from existing related literatures (published articles and Ethiopia Demographic and Health Surveys) based on the study objectives (6), (25), (29), (30). English version was translated to Amharic version by two native speakers of Amharic language (one was public health and the other was English language and literatures in professions). Then back translation to English was done by another two individuals who could speak English (again one was from public health and the other from English language and literatures). Individuals involved in translations were those who knew local says for some expressions.

Final questionnaire was prepared by involving both groups (translators) after resolving inconsistences via discussion for some meanings and terminologies. The tool was piloted on 50 pregnant women in Durame town where actual study population are culturally related. Amendment was made by the investigators. Data was collected by ten trained midwives and supervised by five public health professionals. Data collectors were those who speak both Amharic and local languages (Hadiyisa) to clarify when difficulty in listening Amharic happened.The training was given for two days on the concepts of the questionnaire related to the objectives. Roleplay was made during training on how to approach study participants ethically and make interviews consistently without disrupting the concepts. Comments were given by data collectors, supervisors and principal investigator immediately upon completion of the roleplay. The data collectors at each health facilities were assigned and the list of participants was given for each of them. The birth attendants were informed to consult nearby gynaecologist in zonal hospital and emergency medicine specialist in district primary hospitals to make diagnosis of observed maternal complications in addition to their expertise.

The variables were measured as follow: In the study settings, there is no standardized tool to quantify the amount of blood loss to diagnose PPH. Visual estimation is commonly used in all health facilities supplemented with vital signs such as drop in blood pressure and increase in heart rate (tachycardia). Signs of hypovolemic shock and cases with blood transfusion were also used to diagnose PPH in addition to visual estimation in the health facilities. For this study in particular, we used clinically diagnosed PPH based on visual estimation plus vital signs and taken from clients' chart. Primary PPH was categorized as a binary variable (0=absent, 1=present). Other exposure/predictor variables were measures as follow: reported age at interview was measured in completed years and categorized in to five year interval according to WHO and EDHS. Educational status was measured as attending any formal schooling (grade one and above) or no formal schooling (both unable to read/write and able to read/write). Marital status was categorized as whether women are currently in marital union or not. Family size measured as the number of permanent families (parents and children only). Occupation measured by asking them the main occupation that they routinely do. Wealth index was measured using household assets for urban residence, which consists of the following items: owner of the house, number of rooms, material of roof, material of floor, material of exterior wall, source of drinking water, type of latrine, type of cooking materials (1=electricity, 0=wood/charcoal/biogas/natural gas, etc.), source of income, and presence or absence of; cell phone, refrigerator, radio, television, stove, chair, table, watch, modern bed, bicycle, bajaj, motor cycle, car, donkey/horse cart and bank account. Each item was categorised in to two (1=yes and 0=no). Latrine and water sources were categorized as improved and unimproved facility based on world food program and WHO recommendations. Principal component analysis was done to generate the components. Finally, ranking was done in to five categories (lowest, second, middle, fourth and highest) according to EDHS. Reproductive and related characteristics were measured as follow: we calculated IPI by subtracting date of last child birth from a woman's last menstrual period. In cases when the woman did not remember date of her cycle we have requested her for Ultrasound (free of charge) to estimate gestational age and then by deducing gestational age we could get date of her cycle and have calculated the interval. We categorized IPI as short if it is less than

24 months and normal if it is from 24-59 months based on World Health Organization (WHO) recommendation for minimum IPI of at least 24 months from date of a live birth to date of last menstrual period (31). To see the effect of various durations of IPIs we created a sub-cohort like <18, 18-24, 24-36 and 36-60 months as this help to make comparison with global literatures. Time at initiation of breast feeding was measured as early if it was initiated within one hour and late if it was initiated at and after one hour. Antepartum haemorrhage assessed for recent pregnancy in two ways: firstly from patient chart if data is available. Secondly, by interviewing the woman if she had any vaginal bleeding after seven months of gestation (after 28 weeks). If at least one data was obtained from the two sources, she would have been diagnosed as having APH. PROM, pre-eclampsia/eclampsia, failure of trial of VBAC, prolonged labour, birth asphyxia, stillbirth, management of third stage of labour and other clinical data were taken from clients' chart and categorized as 0=absent, 1= present.

The causes of primary PPH was diagnosed by gynaecologists in zonal referral hospital and emergency medicine specialist in district primary hospitals. The results were taken from the clients' charts. Those PPH cases with no reported cause on the clients' chart were reported as unidentified cause.

Bias

In this study, bias might be introduced while estimating blood loss, selection of participants during initial enrollment for the main cohort and data collection, and could be attempted to minimize by early recognizing potential sources during design stage and analysis.

Selection bias: In our study, determining gestational age by Ultrasound was not feasible for all study participants and also it was not available in most of health facilities in Ethiopia. Because of these reasons determining gestational age by LMP was an alternative option. On the other side, excluding women who did not remember LMP leads to selection bias. Thus, for those women who couldn't be able to recall LMP due to breast feeding, contraceptive method use, and other reasons, we used Ultrasound as a solution to minimize selection bias. For this study cases were individually matched for age group and location, and the controls were randomly selected from risk set (data frame). This might help in reducing bias in this study. We included all pregnant women during the nine months enrollment so that this population level study also helps to minimize selection bias. Due to cost constraints for laboratory tests, enrolment was made after first trimester because first trimester pregnancy was detected mainly via laboratory tests and some women might not know whether they are pregnant (another potential source of selection bias). Hence we enrolled pregnant women who had already confirmed pregnancy or visible pregnancy.

Recall bias: happened when the participants asked the date of preceding child birth and last menstrual period. In urban community, it is common to see birth date ceremonies, it was used in addition to verbal report. Immunization card was also used where available which help to see the date that immunization was initiated, usually initiated at 45 days of delivery in addition to those vaccines given at birth. Family members such as husband, mother in-law and others who exactly remember date of recent child birth were used to support the women in recalling. Furthermore, we limited time of the most recent child birth date, within the last five years from the date of data collection to minimize bias related to recalling.

Misclassification bias: might happen when some subjects having a primary PPH remain undiagnosed or some subjects might be diagnosed for PPH with minimal bleeding that occurs naturally since there is no clear-cut and accurate means to estimate blood loss in the study settings. Thus, cases and controls likely to be misclassified. This bias was attempted to minimize by consulting gynecologists and emergency medicine specialists in addition to those midwives who had a training on basic and comprehensive emergency obstetric care services.

Bias due to sparse data: occurs when sample size is small. We used a case to control ratio of 1:4 to increase sample size, power and precision. We used matched analysis (conditional logistic regression) which was developed as a remedy for the sparse data bias and it is a standard for analyzing matched case control data.

Study size

A sample size of 365 was obtained from the main cohort study by taking all clinically diagnosed cases (73 primary PPH) and controls which have no diagnosis of primary PPH (292) in 1:4 ratio (Figure 1).

Analysis

Collected data were edited and coded manually before entry. Data entry template was prepared in Epi-data version 3.1 software. Then, data were entered by individual who have experience in Epi-data and exported to SPSS version 20 software for further exploration using frequency tables and visualizing graphically to identify outliers, missing values, and transformation or recoding. After exporting, data consistency was checked by using the original questionnaire for the responses using participants' code numbers. Principal component analysis was done for wealth indices and ranked in five groups. After cleaning and making data ready for final analysis, the data were exported to R version 4.0.3 software and analyzed. Descriptive statistics such as mean and standard deviations were done for continuous variables. Frequencies and percentages were also calculated for categorical variables and discreet continuous variables. For missing data, a complete case analysis approach was used. We have fitted a conditional binary logistic regression analysis for matched data. A 'clogistic' algorism was used for the analysis. All independent variables which have shown significant association with primary PPH in bi-variable conditional logistic regression model at $P < 0.05$ were included in multivariable conditional logistic regression model (adjusted for confounding in addition to matching). In the multivariable model, interactions for possible effect modification were assessed. Finally, variables which have shown statistically significant association at $P < 0.05$ and confidence intervals for odds ratio did not include 1 were declared as risk factors for primary PPH. Fit statistics (Likelihood ratio test) was significant indicating the model fits the data better ($P<0.001$). The results were interpreted using attributable fraction (attributable risk percent) as an effect measure. Attributable fraction (AF) was calculated from adjusted odds ratio to estimate the impact of public health of the exposure and other risk factors (i.e. to what extent the occurrence of primary PPH could have been reduced if a particular risk factor was prevented).

Results

Source population profile and incidence of primary PPH

During the study period, a follow up was made for 2546 pregnant women. Of these, 29(1.14%) of them were lost to follow up (21 due to end of study period, 8 no information at all including via phone calling) and their pregnancy outcomes could not be ascertained. Of 29 lost to follow up, 14 were from exposed and 15 from unexposed groups. The pregnancy outcomes were ascertained for 2517 study participants. At the end of a follow up, 73(2.9%) women had primary PPH

In this study, missing data was not related to outcome (primary PPH). The missed variables were: age at first child birth 5(all were controls), modern contraception 2(both were controls), family size 2(1 in case and 1 in control), number of antenatal visit 2(1 in case and 1 in control), active management of third stage of labour 1(1 control), asphyxia 8(4 cases and 4 controls) and time at initiation of breast feeding 12(2 cases and 10 controls)

Socio-demographic and economic information of the participants

The mean age of both cases and controls was 27.1 years $\pm$ 3.1 and 27.5 years $\pm$ 3.5 respectively. More controls 231(79.1%) were attended formal education (1-12 grade or above) than the cases 55(75.3%). Higher proportion of the cases 58(79.5%) were housewife as compared to the controls 210(71.9%) (Table 1).

Reproductive and related characteristics of the participants

The mean age of women at first child birth for cases and controls was 21.9 $\pm$ 2.9 years and 21.3 $\pm$ 2.8 years respectively. For current pregnancy, more proportion of controls 264(90.4%) had given birth via spontaneous vaginal mode as compared to the cases 62(84.9%). More proportion of cases had given birth via caesarian section 4(5.5%) and instrumental delivery 7(9.6%) than controls. Higher proportion of the cases 4(5.5%) had stillbirths as compared to the controls 4(1.4%) during current pregnancy. Higher proportion of both the controls 268(92.1%) and the cases 64(87.7%) received oxytocin during third stage of labour. Nearly similar proportion of controls 3(1%) and cases 1(1.4%) had previous history of PPH (Table 2).

Determinants of primary postpartum hemorrhage

In bi-variable conditional logistic regression model, seven variables: IPI, APH, prolonged labour, birth asphyxia, birth weight, type of pregnancy and time at initiation of breast feeding were associated with primary PPH at $P < 0.05$. When these variables fitted in multivariable conditional logistic regression model, adjusted for potential confounding, four variables: IPI, APH, prolonged labour and time at initiation of breast feeding were found to be the independent determinants of primary PPH at $P < 0.05$.

In this study, more than half of primary PPH was attributed to short IPI <18 months (AF=56.1%, 95%CI: 6.5%, 79.5%) as compared to 24-36 months of IPI. Eighty-two percent of primary PPH was attributed to presence of APH (AF=82.4%, 95% CI: 17.4%, 96.3%). Nearly seventy-two percent of primary PPH was attributed to presence of prolonged labour (AF=71.8%, 95%CI: 31.5%, 88.4%). More than three-fourth of primary PPH was attributed to late initiation of breast feeding (AF=78.2%, 95%CI: 47.4%, 90.9%) (Table 3).

Causes of primary postpartum hemorrhage

Uterine atony is the main cause of primary PPH among the participants followed by retained placenta/tissues (Table 4).

Discussion

The observed incidence of primary PPH in the urban settings was 2.9%. More than half of primary PPH was attributed to short IPI of <18 months. The other risk factors of primary PPH identified include: APH, prolonged labour and late initiation of breast feeding.

Despite the attempts made to reduce this study might have the following limitations: firstly, some cases of PPH might be remain undiagnosed or misdiagnosed since bleeding in small amount during delivery is a natural phenomenon. The diagnosis of PPH might vary across the health facilities since there was no standardized estimating tool for blood loss in the facilities which often depends on clinical experience of the health professionals. Thus, the observed PPH might be underestimated and misclassified. Secondly, data for some covariates, specifically, those anthropometric variables that usually measured during antenatal visits such as hemoglobin concentration, body mass index, mid-upper arm circumference and weight gain during pregnancy were not obtained, incase if they have an effect on PPH. Despite the limitations, nested case control studies are efficient in elucidating temporal relationship, especially when supplemented with matching and stratification (conditional analysis). Readers are expected to interpret the results keeping these limitations in to consideration.

In this study, the incidence of primary PPH was 2.9%. This figure should not be regarded as low because any woman if she has PPH and left untreated may die due to ongoing blood loss. The incidence might also be underestimated due to the fact that the diagnosis and judgment of primary PPH depends on visual estimation and vital signs which are less accurate than others such as gravimetric and calibrated under-buttock tape estimations. However, there is no strong evidence for the estimation techniques and whether quantifying the amount of blood loss improves maternal outcomes remains unclear (1). Despite this, the result was similar with that of Kabul-Afghanistan (2.5%) (5) and France (3.36%) (32). The result was lower than the result from rural health facilities in Uganda (9%) (13). The variation could mainly be due to estimation procedure for blood loss between the two countries and respective health facilities. In Ugandan study, they have used calibrated under-buttock tape which is probably more accurate than visual estimation. The difference might also be due to the difference in study population and settings; our study was a community-based prospective cohort study in urban women. Health facility based studies usually overestimate the incidence as many referral cases visit the facilities. The occurrence of primary PPH might be vary between rural and urban women due to life style and health service utilization related factors. Women in urban settings generally have a better access to health services such as health information, early detection of risk factors and timely management as compared to rural women. The result of this study was also lower than that of high income countries such as Canada (6.2%) (7), Japan (8.7%) (33), and UK (13.8%) (34). The possible reason for the variation could be better estimation of blood loss as these countries have adequate resources for measuring PPH quantitatively and more accurately than low resource settings like ours. In countries like Ethiopia, quantitatively measuring the amount of blood loss could be impractical due to limited tools for estimation, lower trained midwives and crowded obstetric units due to high number of clients attending for deliveries in urban settings including referrals, and subsequent lack of adequate time to follow each mother. On the other side, recently published studies were reporting that the incidence of PPH being increasing in developed nations as well (7), (33). The observed incidence of primary PPH in our study was higher than that of Zimbabwe (1.6%) (4) and Nigeria (1.13%) (35). Variation in diagnosis or estimation of blood loss might be the possible reason in these settings too. Prevalence of primary PPH in Ethiopia ranges from 5.8% in Dessie (18) and 7.6% in Debre Tabor (36) to 16.6% in Southern region (6). These figures were larger as these were cross-sectional surveys and were health facility based studies, the findings might be over-represented due to referral cases from lower level health facilities. Generally, the observed incidence of primary PPH in our study settings can be reduced by improving maternal health services as PPH is mostly preventable (37). There is a need for further consideration of the estimation procedures for the amount of blood loss for more accurate diagnosis that reduce under-estimation.

In this study, IPI was found to be causally associated with primary PPH. This study revealed that spacing pregnancy for at least 18 months would have reduced the risk of experiencing primary PPH by 56%. This could probably be due to the hypothesis that adequately spacing pregnancy helps the uterine wall to recover from hormonal imbalance, nutritional depletion, abnormal process of remodeling of endometrial vessels and incomplete healing of uterine scars, and then make it ready for subsequent pregnancy (38), (39). Besides, when interval is adequate, uterine muscle will get adequate tone for contraction after delivery thereby reduce the risk of atonic uterus related PPH and subsequent risk of maternal death (38). Optimizing IPI by means of effective contraceptive methods will help mothers in reducing morbidities and mortalities related with PPH. It also avoid lactation stress and pregnancy-breast feeding overlaps that can potentially deplete maternal nutrition (such as folate, Iron, Vitamins) via breast feeding for the baby already born and trans-placental sharing for the fetus in the womb (38), (40). The result was supported by that of Tanzania (29) and Nigeria (41) where shortly spaced pregnancies were identified as risk factors for PPH. However, it opposes the latter study in Tanzania (39) which has reported IPI <24 months had no relation with PPH as compared to those 24-59 months. The difference might be explained by variation on the nature of data obtained, study design, sample size, analysis and categorization of IPI as well. Data obtained in Tanzanian study was 15 years retrospective data, from zonal referral hospital (single source) where higher number of referral cases could probably detected in excess (high detection rate) and the care providers could be hyper vigilant so that the result might be over-represented the maternal complications as explained by the authors in their limitation. Adequate information on the relationship between IPI and PPH is lacking which indicate a need for further prospective studies to reach a consensus. Some cases of PPH might be undiagnosed or misdiagnosed as bleeding after delivery is natural. Some might manage those potential PPH cases early so that no more PPH could occur even in the presence of known risk factor. It was also reported that no maternal complications due to short IPI could occur when women referred early and get appropriate care (40). We used both matching and stratification to control confounding and bias in our analysis. Nested case controls studies are efficient with matching and stratification. Therefore, we could not ignore IPI as risk factor for PPH. Rather we suggest family planning programs and organizations working on it to give due attention for spacing pregnancies. To benefit women, their families and country at large more, increasing contraceptive utilization rate via information, education and communication of the effects of shortly spaced pregnancies need to be underlined. This is due to the fact that contraception decrease the number of times a woman become pregnant there by decrease the number of times a woman becomes at risk of pregnancy related complications including PPH and subsequent risk of maternal death.

In this study, more than three quarter (82%) of primary PPH was attributed to APH. Women who experience APH need to be followed carefully during pregnancy, labour and delivery suspecting that they may develop subsequent PPH. The result was supported by other literatures which have reported that PPH is one of the complications of APH (4), (42).

Women who remained in labour for longer duration (>12 hours) had a higher risk of acquiring primary PPH than those with shorter duration. The result of this study suggested that timely interventions to reduce prolonged labour would have reduced the risk of developing primary PPH by 72%. Prolonged labour was recognized as one of the risk factor for PPH in the literatures (4), (5), (12), (14). Birth attendants are expected to monitor the duration and progress of labour and suggest appropriate intervention to reduce the risk of PPH and related burden from mothers and their families. More, early detection and appropriate management of prolonged labor saves the life of the mother, as it is one of the direct causes of maternal death (24), (22).

In this study, time at initiation of breast feeding was found to have a link with primary PPH. This study revealed that early initiation of breast feeding (within an hour) would have reduced the risk of primary PPH by 78%. This is due to the fact that lactation stimulates the release of oxytocin hormone that has a contraction effect on myometrium and subsequently promote the return of the uterus in to its normal state (invulsion). Thus, it decreases postpartum blood loss and help the mother recover more quickly. For this reason, timely initiation of breast feeding is referred as the final stage of labour (43). This result was supported by other studies (44), (45). Promoting early initiation of breast feeding starting from antenatal visits will contribute to reduce the risk of PPH. Special attention should be given for those mothers who lost their newborn during delivery as they cannot benefit from breast feeding in fact. Active management of third stage of labour using utero-tonic drugs together with early initiation of breast feeding jointly will contribute to reduce PPH (46).

Primary PPH can significantly be reduced by administering utero-tonic drugs during third stage of labour for all women since considerable proportion of women without any historical risk factor may present with PPH. Thus, birth attendants need to check every women after delivery for potential bleeding before making a discharge from health facility.

The findings of this study can be generalized for urban places in similar population and settings. However, it cannot be generalized for rural mothers where the incidence, risk factors and causes might be varied depending up on life style, access to health services, skill of care providers in lower health facilities and other socio-cultural contexts.

Conclusions

In this study, IPI was causally related with primary PPH. More than half of primary PPH can be prevented by spacing pregnancy for at least 18 months. Other risk factors for primary PPH were APH, prolonged labour and late initiation of breast feeding. Increasing maternal health service utilization (family planning emphasizing on spacing, antenatal care, health facility delivery with early referrals and postnatal care) will contribute for reducing primary PPH, as the risk factors identified were maternal health service related and modifiable. Whilst PPH is preventable when risk factors were known still ample number of PPH cases may present without known risk factors or causes. Thus, birth attendants have to be Extra vigilant, prepared and be skeptic for PPH for all deliveries.

List Of Abbreviations

APH: Antepartum hemorrhage; AF: Attributable Fraction; EDHS: Ethiopia Demographic and Health Survey; IPI: Inter-Pregnancy Interval; PPH: Postpartum hemorrhage; PROM: Premature Rupture Of Membranes; VBAC: Vaginal Birth After Caesarean section; WHO: World Health Organization

Declarations

Ethical approval and consent to participate

The study was conducted after the confirmation of national and international ethical guidelines for biomedical research involving human subjects (47). Before collection of data, ethical clearance was obtained from institutional review board (IRB) of University of Gondar. Then permission letter was received from regional, zonal and district health offices. Study participants were informed about how they were included in the study, the purpose of the study, their rights to withdraw or continue and potential benefits and harms of the study. Study participants were also told that the information they provide will be used only for the research purpose and will not be disclosed for anyone including during publication. Written consent form was prepared and attached together with each questionnaire to obtain approval from each study participant by signature.

Consent for publication

Not applicable

Availability of data and materials

The raw materials that support the conclusions of this research will be available to researchers, who need the data to use for non-commercial purposes through requesting the corresponding author.

Competing interests

The authors declare no competing interests exist.

Funding

This study was sponsored by University of Gondar and Wachemo University. The funders had no any contribution in collecting, analyzing or writing the paper except the financial support.

Authors' contributions

BH, GA, KA and YK contributed in designing proposal; BH, GA, KA and YK conducted the analysis; BH, GA, KA and YK contributed in writing and editing the paper; all authors have read and approved the manuscript.

Acknowledgment

We would like to thank University of Gondar and Wachemo University for financial support. We are very much thankful for study participants for cooperation and giving us data. Our gratitude also goes to supervisors and data collectors for their patience and collection of data for long duration. Individuals involved in language translation and pilot study are acknowledged for their immense contribution. We are grateful for Hadiya zone and district health office for supporting us in arranging transportation. Lastly, we thank very much, health professionals working in obstetric ward in each hospital for supporting data collection process.

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Tables

Table 1

Socio-demographic and economic variables of the participants in Hadiya zone towns, South Ethiopia, July 2019 to September 2020.

Variables	Cases (n=73)	Controls (n=292)	Total (n=365)
	Number (%)	Number (%)	Number (%)
Marital status			
Currently in marital union	72(98.6%)	290(99.3%)	362(99.2%)
Currently not in marital union	1(1.4%)	2(0.7%)	3(0.8%)
Religion			
Protestant	68(93.2%)	264(90.4%)	332(91%)
Orthodox	2(2.7%)	13(4.5%)	15(4.1%)
Catholic	1(1.4%)	6(2.1%)	7(1.9%)
Muslim/Apoplectics/Jova-witness	2(2.7%)	9(3.1%)	11(3%)
Ethnicity			
Hadiya	70(95.9%)	270(92.5%)	340(93.2%)
Kembata/Tembaro	2(2.7%)	9(3.1%)	11(3%)
Siltie/Guragie/Amhara/Oromo	1(1.4%)	13(4.4%)	14(3.8%)
Maternal educational status			
No formal education	18(24.7%)	61(20.9%)	79(21.6%)
Attended formal education	55(75.3%)	231(79.1%)	286(78.4%)
Husband educational status			
No formal education	16(21.9%)	45(15.4%)	61(16.7%)
Attended formal education	57(78.1%)	247(84.6%)	304(83.3%)
Maternal occupation			
House-wife	58(79.5%)	210(71.9%)	268(73.4%)
Employed	9(12.3%)	54(18.5%)	63(17.3%)
Merchant/daily laborer/farmer	6(8.2%)	28(9.6%)	33(9.3%)
Family size	N=72	N=291	N=363
1-3	31(43.1%)	103(35.4%)	134(36.9%)
4-5	28(38.9%)	127(43.6%)	155(42.7%)
≥ 6	13(18.1%)	61(21%)	74(20.4%)
Wealth status	N=73	N=291	N=364

Lowest	18 (24.7%)	55 (18.9%)	73(20.1%)
Second	11 (15.1%)	61 (21%)	72(19.8%)
Middle	10 (13.7%)	63 (21.6%)	73(20.1%)
Fourth	16 (21.9%)	57 (19.6%)	73(20.1%)
Highest	18 (24.7%)	55 (15.7%)	73(20.1%)

Table 2

Reproductive and related characteristics of the participants in Hadiya zone towns, South Ethiopia, July 2019 to September 2020.

Variables	Cases (n=73)	Controls (n=292)	Total (n=365)
	Number (%)	Number (%)	Number (%)
Parity			
1	31(42.5%)	99(33.9%)	130(35.6%)
2	19(26%)	89(30.5%)	108(29.6%)
≥ 3	23(35.1%)	104(35.6%)	127(34.8%)
Modern contraception after recent birth	N=73	N=290	N=363
Used	34(46.6%)	131(45.2%)	165(45.5%)
Not used	39(53.4%)	159(54.8%)	198(54.5%)
Ferrous Sulphate			
Received	57(78.1%)	241(82.5%)	298(81.6%)
Not received	16(21.9%)	51(17.5%)	67(18.4%)
PROM			
Present	9(12.3%)	24(8.2%)	33(9%)
Absent	64(87.7%)	268(91.8%)	332(91%)
Pre-eclampsia/eclampsia			
Present	3(4.1%)	7(2.4%)	10(2.7%)
Absent	70(95.9%)	285(97.6%)	355(97.3%)
Gestational age at birth			
< 37 weeks	13(17.8%)	36(12.3%)	49(13.4%)
≥ 37 weeks	60(82.2%)	256(87.7%)	316(86.6%)
Progress of labour			
Unassisted/normally progressed	66(90.4%)	260(89%)	326(89.3%)
Augmented/induced	7(9.6%)	32(11%)	39(10.7%)
Mode of delivery			
Spontaneous vaginally	62(84.9%)	264(90.4%)	326(89.3%)
Caesarean section	4(5.5%)	11(3.8%)	15(4.1%)
Instrumental	7(9.6%)	17(5.8%)	24(6.6%)
Failure of trial of VBAC			

Present	3(4.1%)	6(2.1%)	9(2.5%)
Absent	70(95.9%)	286(97.9%)	356(97.5%)
Sex of child (including twins)	N=81	N=300	N=381
Male	47(58%)	147(49%)	194(50.9%)
Female	34(42%)	153(51%)	187(49.1%)
Birth weight			
≤ 4000gm	64(87.7%)	284(97.3%)	348(95.3%)
> 4000gm	9(12.3%)	8(2.7%)	17(4.7%)

Table 3

Multivariable conditional logistic regression model for the risk factors of primary PPH in Hadiya zone towns, South Ethiopia, July 2019 to September 2020.

Variables	Cases (n=73)	Matched controls (n=292)	Total (n=365)	COR (95%CI)	AOR (95%CI)	AF (95%CI)
	Number (%)	Number (%)	Number (%)			
Inter-pregnancy interval (in months)						
<18	35(47.9%)	86(29.5%)	121(33.2%)	2.2(1.2, 4.2)*	2.3(1.1, 4.9)*	56.1% (6.5%, 79.5%)
18-24	19(26%)	58(19.9%)	77(21.1%)	1.8(0.9, 3.6)	2.1(0.9, 5.0)	
24-36	18(24.7%)	98(33.6%)	116(31.8%)	1	1	
36-60	1(1.4%)	50(17.1%)	51(14%)	0.11(0.01, 0.8)*	0.14(0.02, 1.1)	
Antepartum hemorrhage						
Present	11(15.1%)	7(2.4%)	18(4.9%)	6.9(2.6, 18.9)***	5.7(1.2, 26.7)*	82.4% (17.4%, 96.3%)
Absent	62(84.9%)	285(97.6%)	347(95.1%)	1	1	
Number of ANC visits	N=72	N=291	N=363			
<4	39(54.2%)	196(67.4%)	235(64.7%)	1	1	
≥ 4	33(45.8%)	95(32.6%)	128(35.3%)	1.9(1.1, 3.4)*	1.7(0.8, 3.4)	
Prolonged labour						
Present	20(27.4%)	20(6.8%)	40(11%)	4.8(2.4, 9.5)***	3.5(1.5, 8.6)**	71.8% (31.5%, 88.4%)
Absent	53(72.6%)	272(93.2%)	325(89%)	1	1	
Type of pregnancy						
Singleton	65(89%)	285(97.6%)	350(95.9%)	1	1	
Multiple (twins)	8(11%)	7(2.4%)	15(4.1%)	4.6(1.7, 12.6)**	2.1(0.6, 7.5)	
Time at initiation	N=71	N=282	N=353			

of breast feeding						
< 60 minutes (early)	43(60.6%)	235(83.3%)	278(78.8%)	1	1	
≥ 60 minutes (late)	28(39.4%)	47(16.7%)	75(21.2%)	4.9(2.4, 9.9)***	4.6(1.9, 11)***	78.2% (47.4%, 90.9%)
Birth asphyxia	N=69	N=288	N=357			
Present	8(11.6%)	11(3.8%)	19(5.3%)	2.9(1.2, 7.5)*	1.3(0.4, 4)	
Absent	61(88.4%)	277(96.2%)	338(94.7%)	1	1	
Keys: Significant *** = P<0.001, ** = P<0.01, * = P<0.05. COR: Crude Odds Ratio. AOR: Adjusted Odds Ratio. CI: Confidence Interval. 1 = reference category. AF: Attributable Fraction.						

Table 4

Causes of primary PPH in Hadiya zone towns, South Ethiopia, July 2019 to September 2020.

Causes of primary PPH	Frequency (%)
Uterine atony	42 (57%)
Retained placenta or tissues	17 (23.3%)
Cervical laceration	4 (5.5%)
Uterine rupture	3 (4.1%)
Placenta Previa	2 (2.7%)
Unidentified causes	5 (6.9%)
Total	**73 (100%)**

Figures

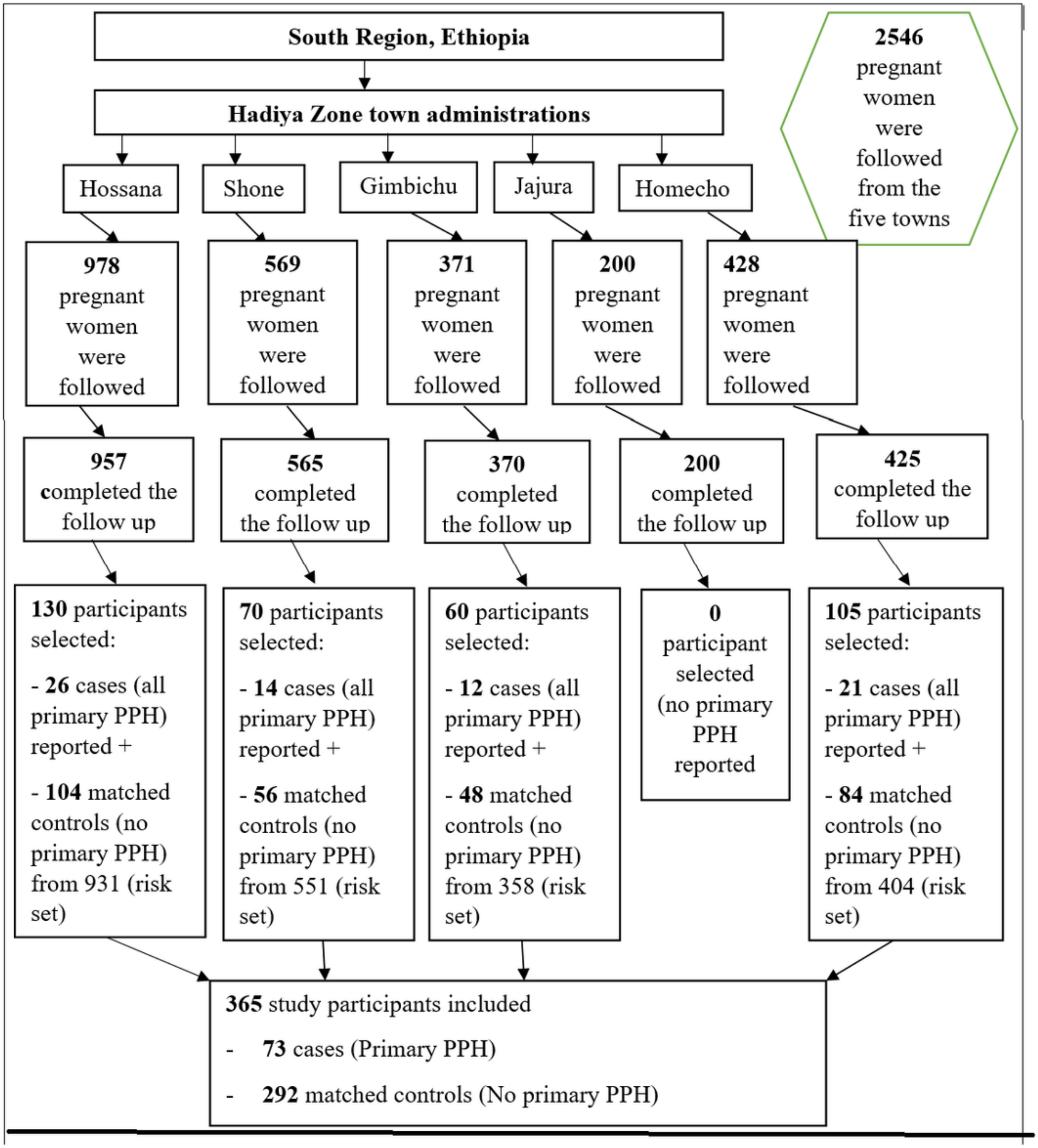

Figure 1

Schematic presentation of sampling procedure for the study of primary PPH in Hadiya zone towns, South Ethiopia, 2019-2020.